PROCTOR AND HUGHES'
CHEMICAL HAZARDS of the WORKPLACE

Fifth Edition

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TOXICOLOGICAL CONCEPTS—SETTING EXPOSURE LIMITS

Nick H. Proctor, Ph.D.

DEFINITIONS

In occupational health practice, the following terms describe the states of matter in which chemical atmospheres may occur:

Gas: A formless fluid that completely occupies the space of an enclosure at 25°C and 760 torr (1 atmosphere) pressure.

Vapor: The gaseous phase of a material that is liquid or solid at 25°C and 760 torr (1 atmosphere) pressure.

Aerosol: A dispersion of particles of microscopic size in a gaseous medium; may be solid particles (dust, fume, smoke) or liquid particles (mist, fog).

Dust: Airborne solid particles (an aerosol) that range in size from 0.1 to 50 μm and larger in diameter. A person with normal eyesight can see dust particles as small as 50 μm in diameter. Smaller airborne particles cannot be seen unless strong light is reflected from the particles. Dust of respirable size (below 10 μm) cannot be seen without the aid of a microscope.

Fume: An aerosol of solid particles generated by condensation from the gaseous state, generally after volatilization from molten metals. The solid particles that make up a fume are extremely fine, usually less than 1.0 μm in diameter. In most cases, the volatilized solid reacts with oxygen in the air to form an oxide. A common example is cadmium oxide fume.

Smoke: An aerosol of carbon or soot particles less than 0.1 μm in diameter that results from the incomplete combustion of carbonaceous materials such as coal or oil. Smoke generally contains droplets as well as dry particles.

Mist: An aerosol of suspended liquid droplets generated by condensation from the gaseous to the liquid state or by the breaking up of a liquid into a dispersed state, such as by splashing, foaming, or atomizing. Examples are the oil mist produced during cutting and grinding operations, acid mists from electroplating, acid or alkali mists from pickling operations, and paint spray mist from spraying procedures.

Fog: A visible liquid aerosol formed by condensation.

The following terms of measurement are commonly used in toxicological testing and in industrial hygiene practice:

ppm: Parts of vapor or gas per million parts of air by volume

mg/m^3: Milligrams of a substance per cubic meter of air

mg/l: Milligrams of a substance per liter of air

TOXICOLOGICAL CONCEPTS

Routes of Entry of Chemicals into the Body

In the occupational setting, inhalation is the most important route of entry of chemical agents into the body, followed by contact with skin and subsequent cutaneous absorption. Although the gastrointestinal tract is a potential site of absorption, the ingestion of significant amounts of chemicals is rare in the occupational setting.

Inhalation

The respiratory tract is exposed to chemicals in the inspired air. The two main factors that determine the tissue responses to chemicals are the functional anatomy of the respiratory tract and the physicochemical nature of the material.[1–3]

The respiratory tract may be divided into three major regions: the nasopharyngeal (upper airways), the tracheobronchial tree (lower airways), and the pulmonary (alveoli).

The *nasopharynx* begins with the anterior nares and extends down to the larynx. The nasal passages are lined with vascular mucous epithelium composed of ciliated epithelium and scattered mucous glands. The nasopharynx filters out large inhaled particles and is where the relative humidity is increased and the temperature of the air is moderated.

The airways (trachea, bronchi, and bronchioles or tracheobronchial tree) serve as conducting airways between the nasopharynx and alveoli. They are lined with ciliated epithelium and coated with a thin layer of mucus secreted primarily by goblet cells in the upper airways and primarily by Clara cells at the bronchiolar level. This mucous covering terminates at the film covering the alveolar membrane. The surface of the airways serves as a *mucociliary escalator*, moving particles up to the oral cavity, where they are swallowed and excreted or expectorated.

The ciliated cells are most vulnerable to damage. The most frequent degenerative changes in these cells are loss of cilia, necrosis, and sloughing of cells into the airway lumen. Necrosis and desquamation of nonciliated and secretory cells are less frequently observed.

After acute mild insult the nonciliated cells proliferate and the epithelium regenerates to normal. In the airways, nonciliated basal cells are the main proliferating population. In the bronchioles, the Clara cell is the main precursor cell for regeneration. Because of the delicate nature of the respiratory tract epithelium and the close proximity of subepithelial blood vessels, an inflammatory response occurs to all but the mildest form of injury. Many lesions are therefore diagnosed as rhinitis, tracheitis, and bronchiolitis and qualified as acute, subacute, and chronic depending on the stage of the response.

If the insult persists, hyperplasia (cell proliferation) proceeds and leads to an abnormal epithelium. Injury produced by chronic exposure to irritants such as SO_2, NO_2, O_3, formaldehyde, and tobacco smoke includes undifferentiated basal cells (hyperplasia), squamous metaplasia, and goblet cell metaplasia. In practice, many irritants produce responses between mild and severe, and various combinations of degeneration, inflammation, and proliferation may be observed.

The lower respiratory tract (pulmonary region or alveolar ducts and sacs) is the area where gas exchange occurs. Alveolar sacs, clusters of two or more alveoli, branch from alveolar ducts. It is generally considered that there is a total of approximately 300 million alveoli in the lungs of adult humans.[4] The total alveolar surface area in the lungs of adult humans is

about 35 m^2 during expiration, 70–80 m^2 at three-fourths total lung capacity, and 100 m^2 during deep inspiration.[5]

The alveoli are lined by two main types of epithelial cells. Type I cells (squamous pneumonocytes) have flattened nuclei and thin but very extensive cytoplasm covering most of the alveolar wall. Because this cell has a very large surface area it is very susceptible to injury.

Type II cells (granular pneumonocytes) are distributed throughout the alveoli between Type I cells. Although they are more numerous than Type I cells, they are cuboidal in shape and occupy far less of the alveolar surface area. The prime function of this cell is the production of pulmonary surfactant, and it is generally less susceptible to injury than the Type I cell.

The other main cell type in the alveoli is the alveolar macrophage, which plays an important role by phagocytizing particulates and removing them from the alveoli. Phagocytosis of toxic particulates may injure macrophages, and the discharge of their contents may cause alveolar damage. Stromal cells such as fibroblasts are infrequent but may increase sufficiently in number during chronic inflammatory reactions to interfere with gaseous exchange and compromise lung function.

Most direct toxins entering the alveoli primarily affect Type I cells and their associated capillary endothelial cells. After acute injury, the epithelium and/or underlying capillary endothelial cells may swell and disrupt, distort, or lose their connections with others, leaving large areas of basement membrane uncovered. This allows fluid to move into the alveolar lumen from capillaries, with subsequent pulmonary edema.

The sequel to acute injury depends on the potency and concentration of the toxic agent and the duration of exposure. Potent gases produce a severe vascular reaction and alveolar flooding. The fluid prevents gaseous exchange, and death of the human or animal ensues. After acute mild nonlethal damage, excess fluid is removed and the resistant Type II cells proliferate and reline the alveoli. The cells subsequently differentiate into Type I cells.

If the chemical is a moderate irritant and causes significant damage to the basement membrane and stroma as well to the epithelial cells, fibroblastic repair and fibrous scarring result in the alveoli. These fibrotic alveoli are generally lined by atypical Type II cells. The lining of alveoli by Type II cells, either in the early phases of repair of mild damage or as an end stage of more severe damage, is often referred to as *alveolar epithelialization*. Occasionally, the alveoli may be relined by a proliferation of bronchiolar epithelium. This is termed *alveolar bronchiolization*. Intra-alveolar accumulation of macrophages is also a prominent feature.

Gases

The rate of removal of gases from the airstream during inhalation depends mostly on the water solubility of the gas. Highly water-soluble gases such as ammonia, hydrogen chloride, and hydrogen fluoride dissolve readily in the moisture associated with the mucous coating of the nasopharyngeal region, causing irritation at those sites. At high atmospheric concentrations, some of the gas will not be absorbed at the upper respiratory sites, and amounts sufficient to reach the alveoli can cause severe irritation and pulmonary edema.

Comparatively insoluble gases such as nitrogen dioxide and phosgene are not removed by the moisture in the upper respiratory tract and can easily reach the alveoli. Substances of intermediate solubility such as chlorine can cause irritation at points all along the respiratory tract.

Bronchoconstriction is one of the most common immediate responses observed on inhalation of a number of reactive gases. The constriction may be caused by a direct action on the airway smooth muscles or indirectly through the release of histamine and other mediators.

Particulates

The chief factor that determines the site of deposition of particulate matter in the respiratory tract is its size.[3,6] Particles having an aerodynamic diameter of 5–30 μm are primarily

deposited in the nasopharyngeal region by impaction with nose hairs and the angular walls of the nasopharyngeal passages.

Particles with an aerodynamic diameter of 1–5 μ are deposited in the airways (tracheobronchial regions) by sedimentation under gravitational forces. As the alveolar regions are approached, the velocity of the airflow decreases significantly, allowing more time for sedimentation. The very small particles, generally less than 1 μ, that penetrate to the alveoli are deposited there mainly by diffusion.

In extrapolating results from rodents to humans, it is important to understand the differences in deposition that occur.[7,8] Small rodents usually have lower fractional deposition of inhaled particles in the lung than humans, but rodents inhale more air per unit of lung mass or lung surface than humans. The most important interspecies differences in deposition are associated with particles larger than about 5 μ in aerodynamic diameter because these larger particles cannot readily reach the pulmonary region in small nose-breathing rodents.

In contrast, a decreasing proportion of particles from 1 μ (100%) up to 10 μ (1%) reaches the pulmonary region in the human lung during normal breathing via the nose.[9] Once there, maximum pulmonary deposition occurs for particle sizes of 1–4 μ: about 25% of 1 μ, 35% of 2 μ, 30% of 3 μ, and 25% of 4 μ.[10]

Mouth breathing by humans during exertion may result in deposition that is distinctly different from that associated with nasal breathing, with increased deposition of the larger particles up to about 15 μ in both the tracheobronchial and pulmonary regions.[8]

Particle Clearance

Particles deposited in the nasopharyngeal region are moved to the pharynx by the ciliated cells and mucus and expectorated or swallowed.[10] The clearance rate is relatively rapid with a half-life of 12–24 hours.

Particles deposited on or in the lung parenchyma are cleared primarily by alveolar macrophages. These phagocytized particles migrate to the ciliated epithelium or to the lymphatic system at times ranging from 2 to 6 weeks. However, for some materials, this time is longer, such that half-lives of many months occur.

Certain chemicals such as silicon dioxide have a cytotoxic effect on the alveolar macrophage, which results in the accumulation of particles in a given area. As the macrophages lose their activity, these particles become less subject to removal, leading to the development of masses containing dead cells and particles.

Fibers

When using animal inhalation studies for assessment of the risk to human health of airborne fibers, it is critical to demonstrate that the characteristics and concentrations of the experimental fiber aerosols are comparable to those in human exposure situations.[11] NIOSH has two criteria for defining fibers: "A" rules (total fibers) and "B" rules (respirable fibers).[12]

> NIOSH "A" rules count fibers with a length-to-diameter ratio ≥3 : 1, length ≥5 μ.
>
> NIOSH "B" rules count fibers with a length-to-diameter ratio >5 : 1, length ≥5 μ, and diameter <3 μ.

Skin Contact

Skin structure varies widely in different regions, from the delicate and relatively permeable skin of the scrotum, to the rough, thick covering of the palms and soles.[13] The skin of the scrotum has a relatively thin layer of keratin, whereas the palms and soles have a thick layer.

The skin consists of a thin outer layer (epidermis) and a relatively thicker inner layer (dermis). The epidermis is approximately 0.1 mm in thickness, whereas the dermis is generally 2–4 mm thick. Dermoepidermal ridges provide a large interface area between the epidermis and dermis. This is of great importance in that the epidermis, which is not vascularized, receives all its nutrients from the blood supply of the dermis.

The epidermis consists of several types of cells. The epidermal cell type apposed to the dermis is the stratum germinativum (basal cell layer), over which are the stratum spinosum, stratum granulosum, stratum ludicum, and the outermost layer or stratum corneum. The basal cell layer consists of one layer of columnar epithelial cells. On division, the basal cells are pushed up and become the stratum spinosum, which consists of several layers of cells. As these cells approach the surface of the skin they become larger and form the stratum granulosum.

At this point the nuclei are broken up, resulting in the death of the cell. The next layer, stratum ludicum, is ill defined except in areas of thick skin, and is said to contain eleidin, a transformation product of the keratohyalin present in the stratum granulosum.

In the outermost layer, the stratum corneum, the eleidin has been converted into keratin, which represents the ultimate fate of the epidermal cell. Keratin, continuously sloughed off or worn away, is replaced by the cells beneath it. The time required for a basal cell to migrate from the stratum germinativum to the outer part of the stratum corneum is estimated at 26–28 days.

The dermis is a thick fibrous network of collagen and elastin and is composed of two layers. The outer, thinner layer is the papillary layer, which has prominent papillae that merge with the thick reticular layer. The papillae are well supplied with blood by the capillaries that are prominent in them, which serves the basal cell layer in the dermis with nutrients.

The dermis contains several types of cells, including fibroblasts, fat cells, macrophages, histiocytes, mast cells, and cells associated with the blood vessels and nerves of the skin. The predominant cell is the fibroblast, which is associated with biosynthesis of the fibrous proteins and ground substances such as hyaluronic acid, chondroitin sulfates, and mucopolysaccharides.

The appendages of skin are hair follicles, sebaceous glands, eccrine and apocrine sweat glands, hair, nails, and arrector pili muscles.

When a substance contacts the skin, various actions are possible:

The skin and its associated film of lipid and sweat may act as an effective barrier that the substance cannot penetrate

The substance may react with the skin surface and cause primary irritation (acids, alkalies, many organic solvents)

The substance may penetrate the skin and cause allergic contact dermatitis (formaldehyde, nickel, phthalic anhydride)

The agent may penetrate the skin, enter the blood, and act systemically (aniline, parathion)

To pass into the skin, the substance must enter through one or more of the following routes: the epidermal cells, the sweat glands, the sebaceous glands, or the hair follicles. The pathway through the stratum corneum and the epidermal cells is the main avenue of penetration, as this tissue constitutes the majority of the surface area of the skin.

The stratum corneum plays a critical role in determining cutaneous permeability. Absorption is faster through skin that is abraded or inflamed. Chemicals that are not normally considered hazardous may be dangerous to individuals suffering from active inflammatory dermatoses.

The skin not only is a barrier to restrict diffusion of chemicals into the body, it is also an organ that can metabolize a variety of topically applied substances before they become systemically available.[14] The skin has many of the same enzymes as the liver. The activities of several cutaneous enzymes in whole skin homogenates have been measured and compared to hepatic activity in the mouse.[15] The activities of the enzymes in the whole skin homogenates were typically 2–6% of the hepatic values. However, there is evidence that the enzymes are present primarily in the epidermis. Because the epidermis makes up only 2–3% of the total skin, the real activities may range from 80% to 240% of those in the liver. Enzyme systems present include a cytochrome P-450 system and a mixed-function oxidase system.

Dose and Response

Toxicology is the study of the noxious effects of chemical and physical agents. The most fundamental concept in toxicology states that there is a relationship between the dose of an agent and the response that is produced in a biological system. The concept was first formalized by Paracelsus (1493–1541 A.D.).

Initial toxicity data on an uncharacterized agent usually are obtained by oral, intraperitoneal, or dermal administration to laboratory animals. This provides an estimate of the lethal potency of the material. Observation of the animals after administration of the material often provides valuable information concerning the effects that may occur in humans. Autopsy of the animals will show the likely target organs in humans.

Toxicity and Hazard

Toxicity is the ability of a substance to cause injury to biological tissue. The hazard or risk of a substance is the probability that it will cause injury in a given environment or situation. The hazard of a substance depends on several factors, including its toxicity; how it is absorbed, metabolized, and excreted; how rapidly it acts; its warning properties; and its potential for fire and explosion.

Exposure

Exposure to chemicals in toxicological tests of animals is classified according to frequency and duration, as follows:

- *Acute* exposure is exposure for up to 24 hours.
- *Subacute* exposure is repeated exposure for 1 month or less.
- *Subchronic* exposure is repeated exposure for 1–3 months.
- *Chronic* exposure is repeated exposure that lasts for more than 3 months, and often for 24 months or the lifetime of rodent species.

In the occupational setting, acute human exposure generally refers to exposure that causes an effect within 24 hours, whereas the term chronic exposure is applied to repeated exposures over time.

THE STANDARDS SETTING PROCESS

Threshold Limit Value (TLV)

The American Conference of Governmental Industrial Hygienists (ACGIH) has prepared a list of the threshold limit values (TLVs) for approximately 800 substances. The following three categories of TLVs are specified.[16]

Threshold Limit Value-Time-Weighted Average (TLV-TWA): The time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

Threshold Limit Value-Short Term Exposure Limit (TLV-STEL): The concentration to which workers can be exposed continuously for a short period of time without suffering from 1) irritation, 2) chronic or irreversible tissue damage, or 3) narcosis of sufficient degree to increase the likelihood of accidental injury, impair self-rescue, or materially reduce work efficiency, and provided that the daily TLV-TWA is not exceeded. It is not a separate independent exposure limit; rather, it supplements the time-weighted average (TWA) limit where there are recognized acute effects from a substance whose toxic effects are primarily of a chronic nature. STELs are recommended only where toxic effects have been reported from high short-term exposures in either humans or animals.

A STEL is defined as a 15-minute TWA exposure that should not be exceeded at any time during a workday even if the 8-hour TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 minutes and should not occur more than four times per day. There should be at least 60 minutes between successive expo-

sures in this range. An averaging period other than 15 minutes may be recommended when this is warranted by observed biological effects.

Threshold Limit Value-Ceiling (TLV-C): The concentration that should not be exceeded during any part of the working exposure.

In the absence of a STEL, excursions in worker exposure levels may exceed three times the TLV-TWA for no more than a total of 30 minutes during a workday, and under no circumstances should they exceed five times the TLV-TWA, provided that the TLV-TWA is not exceeded.

"Skin" Notation. Substances on the list followed by the designation "Skin" refer to the potential significant contribution to the overall exposure by the skin route, including mucous membranes and the eyes, either by contact with vapors or, of probable greater significance, by direct skin contact with the substance.

TLVs are revised by the ACGIH annually as new information becomes available. Each year, additional substances of interest are added to the TLV list. Certain compounds that are proven or suspected carcinogens in humans such as benzidine, 4-aminodiphenyl, and 4-nitrodiphenyl have no TLV value, and human exposure to these agents should be avoided. Note: For a detailed discussion of carcinogenic risks to humans, the publications of the IARC should be consulted.[17]

OSHA Standards

The first occupational safety and health standards were set when, with only minor changes, the 1968 ACGIH list of nearly 400 TLVs, as well as certain standards of the American National Standards Institute (ANSI), were incorporated into the Walsh–Healey Public Contracts Act. They thereby became limits of exposure for employees of federal government contractors.

Subsequently, under the authority of the Occupational Safety and Health Act of 1970, these same 1968 TLVs and ANSI standards were promulgated by the Occupational Safety and Health Administration (OSHA) as the start-up Permissible Exposure Limits (PEL) for all workers covered by the Act.

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Part

II

THE CHEMICAL HAZARDS

ACETALDEHYDE
CAS: 75-07-0

CH_3CHO

Synonyms: Ethanal; acetic aldehyde; ethyl-aldehyde; methyl formaldehyde

Physical Form. Colorless liquid

Uses. As a chemical intermediate in synthesis of acetic acid, pentaerythritol, and pyridine; in the production of perfumes, polyester resins, and dyes and as a food preservative and flavoring agent

Exposure. Inhalation

Toxicology. Acetaldehyde is an irritant of the eyes, skin, and respiratory tract; at high concentrations it causes narcosis; it is carcinogenic in experimental animals.

Nausea, loss of consciousness, and pulmonary edema have been reported with heavy exposure.[1] At 134 ppm for 30 minutes there was mild upper respiratory irritation, whereas 15 minutes at 50 ppm produced mild eye irritation.[2] Sensitive subjects have noted eye irritation after 15-minute exposures at 25 ppm.[3] Splashed in the eyes, the liquid causes a burning sensation, lacrimation, blurred vision, and corneal injury.[1] On the skin for a prolonged period of time, the liquid causes erythema and burns.

In animal studies the 4-hour inhalation LC_{50} was 17,000 ppm for hamsters and 13,300 ppm for rats.[4] Exposure to 5000 ppm for 10 minutes produced a 50% decrease in respiration rate in mice; in anesthetized rats significant increases in blood pressure were observed at 1700 ppm and concentrations above 6000 ppm significantly increased heart rate.[5,6]

Hamsters repeatedly exposed to 4500 ppm for 3 months had growth retardation, ocular and nasal irritation, increased erythrocyte counts, and severe histopathological changes in the respiratory tract.[7]

Chronic inhalation of acetaldehyde produced tumors of the respiratory tract in rats and hamsters.[8] The incidence of laryngeal carcinomas was increased in hamsters exposed for 1 year to 1500 ppm.[9] In a lifetime inhalation study (52 weeks, with recovery for 26 or 52 weeks), rats exposed at 750, 1500, or 3000 ppm had exposure-related increases in adenocarcinomas and squamous cell carcinomas of the nasal mucosa.[10] Associated changes included growth retardation, degenerative changes of the olfactory epithelium, and metaplasia of the respiratory epithelium, frequently accompanied by keratinization.[10,11]

The IARC has determined that there is sufficient evidence for carcinogenicity of acetaldehyde to experimental animals. One limited epidemiological study that found an increased relative frequency of bronchial and oral cavity tumors among nine cancer cases in aldehyde-exposed workers provided inadequate evidence for human carcinogenicity.[4,8]

Acetaldehyde is considered to be possibly carcinogenic to humans.[8]

Acetaldehyde has demonstrated genotoxicity in a variety of cell culture systems.[12] There is indirect evidence from *in vitro* and *in vivo* studies to suggest that acetaldehyde can induce protein-DNA and DNA-DNA cross-links.[13]

In several studies, parenteral exposure of pregnant rats and mice has produced embryotoxic, fetotoxic, and teratogenic effects; however, maternal toxicity was not adequately evaluated, and the selective developmental effects of acetaldehyde cannot be evaluated.[13]

The 2003 ACGIH ceiling threshold limit value (C-TLV) for acetaldehyde is 25 ppm (45 mg/m^3) with an A3-animal carcinogen designation.

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ACETAMIDE
CAS: 60-35-5

CH_3CONH_2

Synonyms: Acetic acid amide; ethanamide

Physical Form. Deliquescent crystals

Uses. Cryoscopy; organic synthesis; general solvent; lacquers; explosives, soldering flux; wetting agent; plasticizer

Exposure. Ingestion; inhalation; skin absorption

Toxicology. Acetamide is a mucous membrane irritant, a liver toxin, and a carcinogen in animals.

There are no data regarding the toxicity of acetamide to humans.

In animals, acetamide was stated to be a mild irritant to skin and eyes, although experimental details were not available. Oral administration of acetamide to rodents produced lethality with doses of 1–7 g/kg.[1] In another report, single oral dose LD_{50} values for male rats and male mice were 10.3 and 10.1 g/kg, respectively.[2] Minor changes in liver histology occur after acute exposures in rats.[1]

Oral doses of 0.3 g/kg acetamide administered on days 6 through 18 of gestation produced no toxicity or terata in rabbits. No maternal toxicity was seen at 1 g/kg, although one rabbit aborted; fetal numbers and body weights were lowered, with no terata. At 3 g/kg, maternal toxicity was encountered, fetal numbers and weights were reduced, the number of dead implants was elevated, and cleft palate was seen.[1] No reproductive, embryotoxic, or teratogenic effects were observed in rats.[1]

Acetamide produced benign and malignant liver tumors in rats after oral administration. In male mice, an increased incidence of malignant lymphomas also was observed.[2]

Acetamide was mutagenic in *Escherichia coli* and *Salmonella typhimurium*; this effect was independent of dose. Acetamide produced morphological transformation in Syrian hamster embryo cells in the absence of metabolic activation. However, acetamide did not induce reversions in several *Salmonella typhimurium* strains.[1]

The IARC has determined that there is sufficient evidence of carcinogenicity for acetamide in experimental animals and that it is possibly carcinogenic to humans.[3]

ACGIH has not established a threshold limit value for acetamide.

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ACETIC ACID
CAS: 64-19-7

CH_3COOH

Synonyms: Ethanoic acid; ethylic acid; methane carboxylic acid; vinegar (4–6% solution in water)

Physical Form. Liquid

Uses. Production of cellulose and vinyl acetate; dyeing; pharmaceuticals and food processing

Exposure. Inhalation

Toxicology. Acetic acid vapor is a severe irritant of the eyes, mucous membranes, and skin; chronic exposure may cause bronchitis and cracking and darkening of exposed skin.

Exposure to 50 ppm or more is intolerable to most persons and results in intensive lacrimation and irritation of the eyes, nose, and throat, with pharyngeal edema and chronic bronchitis.[1] Unacclimatized humans experience extreme eye and nasal irritation at concentrations in excess of 25 ppm; conjunctivitis from concentrations below 10 ppm has been reported.[1]

In one case report a 37-year-old male maintenance fitter was accidentally exposed to a large cloud of hot acetic acid while disconnecting a pressurized pump.[2] The patient suffered first-degree burns on the hands and face and developed progressive dyspnea. At 3 months there were persistent extensive crackles in the basal area of the lungs, widespread bronchial inflammatory changes, and diffuse moderate interstitial pneumonitis that promptly improved after treatment with corticosteroids and bronchodilators.

In a study of five workers exposed for 7–12 years to concentrations of 80–200 ppm at peaks, the principal findings were blackening and hyperkeratosis of the skin of the hands, conjunctivitis (but no corneal damage), bronchitis and pharyngitis, and erosion of the exposed teeth (incisors and canines).[3] Digestive disorders with pyrosis and constipation have also been reported at unspecified prolonged exposures.[4]

Chronic exposure to fumes of heated glacial acetic acid in a canning factory has been associated with a late airway response resulting in chronic inflammation and severe bronchial asthma. Inhalation challenge induced a late asthmatic response, confirming sensitization.[5]

A study of cancer mortality among 1359 workers involved in the production of acetic acid and acetic anhydride found that mortality from all causes decreased but mortality from prostate cancer was significantly increased, based on six deaths. Measurements of acetic acid levels were not made for most of the study period, but recent monitoring found exposures ranging between 0.1 and 1.2 ppm.[6]

Glacial (100%) acetic acid caused severe injury when applied to the eyes of rabbits; in humans it has caused permanent corneal opacification.[7] A splash of vinegar (4–10% acetic acid solution) in the human eye causes immediate pain and conjunctival hyperemia, sometimes with injury of the corneal epithelium.[7]

On the guinea pig skin, the liquid in concentrations in excess of 80% produced severe burns; concentrations of 50–80% produced moderate to severe burns; solutions below 50% caused relatively mild injury; no injury was produced by 5–10% solutions.[3]

Although ingestion is unlikely to occur in industrial use, as little as 1.0 ml of glacial acetic acid has resulted in perforation of the esophagus.[1]

Acetic acid was not clastogenic in Chinese hamster ovary (CHO) cells *in vitro* when the pH of the culture medium was neutralized.[8]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for acetic acid is 10 ppm (25 mg/m^3) with a short-term exposure limit of 15 ppm (37 mg/m^3).

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ACETIC ANHYDRIDE

CAS: 108-24-7

$(CH_3CO)_2O$

Synonyms: Acetic oxide; acetyl oxide; ethanoic anhydrate; acetic acid anhydride

Physical Form. Colorless liquid

Uses. Manufacture of cellulose esters, plastics, pharmaceuticals, photographic films, cigarette filters, and magnetic tape; inorganic synthesis as an acetylating agent, bleaching agent, and dehydrating agent

Exposure. Inhalation

Toxicology. Acetic anhydride vapor is a severe irritant of the eyes, mucous membranes, and skin.

Humans exposed to undetermined but high vapor concentrations complained immediately of severe conjunctival and nasopharyngeal irritation, harsh cough, and dyspnea.[1] Workers exposed to vapors from a boiling mixture complained of severe eye irritation and lacrimation.[1] The immediate effect of exposure to vapor concentrations above 5 ppm is acute irritation of the eyes and upper respiratory tract; inhalation of high vapor concentrations may produce ulceration of the nasal mucosa and, in some instances, bronchospasm.[2] Delayed deaths due to acetic anhydride exposure have been reported. In one case, a worker sustained burns to 35% of his body after the explosion of a drum of acetic anhydride; death occurred after 67 days from progressive lung damage that included pneumothoraces and bronchopulmonary fistulae.[3] Autopsy revealed extensive fibrous adhesions within the pleural cavity.

Both the liquid and the vapor can cause severe damage to the human eye; this is characterized by immediate burning, followed some hours later by an increasing severity of reaction with corneal and conjunctival edema.[1] Interstitial corneal opacity may develop over a period

of several days because of progression of tissue infiltration; in mild cases, this condition is reversible, but permanent opacification with loss of vision may also occur. Workers exposed to acetic anhydride vapor may show evidence of conjunctivitis with associated photophobia.[1]

Prolonged dermal contact with the liquid may cause the skin to redden and subsequently turn white and wrinkled but may not be immediately painful.[4] Skin burns may appear later. Repeated skin exposure to the liquid or vapor may cause irritation.

Generalized skin reactions in guinea pigs sensitized to acetic anhydride have been demonstrated, and skin sensitization in humans occasionally occurs.[2]

Although ingestion of the liquid is unlikely in ordinary industrial use, the highly corrosive nature of the substance may be expected to produce serious burns of the mouth and esophagus.

Acetic anhydride has good warning properties.

The 2003 ACGIH threshold limit value-time-weighted value (TLV-TWA) is 5 ppm (21 mg/m^3).

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ACETONE
CAS: 67-64-1

$(CH_3)_2CO$

Synonyms: Dimethyl ketone; 2-propanone; β-ketopropane

Physical Form. Colorless liquid

Uses. Solvent for fats, oils, waxes, rubber, plastics; in the production of lubricating oils; in the dyeing and celluloid industries; as a chemical intermediate; paint and varnish remover; major component of nail polish remover

Exposure. Inhalation; skin absorption

Toxicology. Acetone is an irritant of the eyes and mucous membranes; at very high concentrations it is a central nervous system depressant.

Acetone is considered to be of low risk to health because few adverse effects have been reported despite widespread use for many years.[1] One early study, often quoted, reports eye, nose, and throat irritation in volunteers exposed to 500 ppm.[2]

In more recent studies, subjects exposed to 500 ppm were aware of odor but exhibited no effects.[3] Mild eye irritation occurred around 1000 ppm.[4] Higher concentrations produced headache, light-headedness, and nose and throat irritation.[4] Concentrations above 12,000 ppm depressed the central nervous system (CNS), causing dizziness, weakness, and loss of consciousness.[5]

Neurobehavioral tests have found slight, but statistically significant, performance decrements after 4-hour exposure to 250 ppm, suggesting mild CNS depression at this level.[6]

In a retrospective mortality study of over 900 workers exposed from 3 months to 23 years to median time-weighted acetone concentrations up to 1070 ppm there was no significant risk of death from any cause (all causes, malignant neoplasm, circulatory system disease, ischemic heart disease) compared with rates for the general population.[7]

Topical application of 1 ml of acetone for 90 minutes produced reversible skin damage to humans.[8]

Acetone is metabolized mainly in the liver by three separate pathways, leading to the production of glucose with the subsequent liberation of carbon dioxide.[7] None of the intermediate metabolites appears to be toxic, with the possible exception of formate. Acetone and acetone-derived carbon dioxide are excreted in expired air and have little tendency to accumulate in the body.

High concentrations of acetone were required to produce death in animals; the 4-hour inhalation LC_{50} value is 32,000 ppm for rats.[9] Administered in the drinking water for 13 weeks, the minimal toxic doses were 20,000 ppm for male rats and mice and 50,000 ppm for female mice.[10] The kidney, hematopoietic system, and testis were target organs in male rats, and the liver was the target organ for mice.

In animal studies acetone has been found to potentiate the toxicity of other solvents by altering their metabolism through induction of microsomal enzymes, particularly cytochrome P-450. Reported effects include: enhancement of the ethanol-induced loss of righting reflex in mice by reduction of the elimination rate of ethanol; increased hepatotoxicity of compounds such as carbon tetrachloride and trichloroethylene in the rat; potentiation of acrylonitrile toxicity by altering the rate at which it is metabolized to cyanide; and potentiation of the neurotoxicity of *n*-hexane by altering the toxicokinetics of its 2,4-hexanedione metabolite.[11–14] Because occupationally exposed workers are most often exposed to a mixture of solvents, use of the rule of additivity may underestimate the effect of combined exposures.[15]

Significant developmental toxicity as determined by increased incidences of resorptions occurred in mice at levels of 6600 ppm, which also caused maternal toxicity.[16] Depressed sperm motility and epididymal weight and elevated evidence of abnormal sperm were observed in male rats receiving 50,000 ppm acetone in their drinking water for 13 weeks.[10]

Acetone may be weakly genotoxic, but the majority of assays were negative.[7] It was not tumorigenic in skin painting studies in mice.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for acetone is 750 ppm (1780 mg/m^3) with a short-term excursion level of 1000 ppm (2380 mg/m^3).

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ACETONITRILE
CAS: 75-05-8

CH_3CN

Synonyms: Methyl cyanide; cyanomethane; ethanenitrile

Physical Form. Colorless volatile liquid with sweetish odor

Uses. Chemical intermediate; solvent; extractant for animal and vegetable oils

Exposure. Inhalation; skin absorption

Toxicology. Acetonitrile causes headache, dizziness, and nausea; at extremely high concentrations it can cause convulsions, coma, and death.

Of 15 painters exposed to the vapor of a mixture containing 30–40% acetonitrile for 2 consecutive workdays, 10 developed symptoms ranging in severity from nausea, headache, and lassitude among the lesser exposed to vomiting, respiratory depression, extreme weakness, and stupor in the more heavily exposed. Five cases required hospitalization and one died; this worker experienced the onset of chest pain 4 hours after leaving the job on the second day of exposure, followed shortly by massive hematemesis, convulsions, shock. and coma, with death occurring 14 hours after cessation of exposure.[1] At autopsy, cyanide ion concentrations (in µg%) were: blood 796, urine 215, kidney 204, spleen 318, and lung 128; cyanide ion was not detected in the liver.[1]

Two human subjects inhaled 160 ppm for 4 hours; one of them experienced a slight flushing of the face 2 hours later and a slight feeling of bronchial tightness 5 hours later. A week before this, the same two subjects had inhaled 80 ppm with no effects.[2] Blood cyanide and urine thiocyanate levels did not correlate with exposure and, therefore, are not reliable indicators of brief exposure to low concentrations.

In male rats the LC_{50} was 7500 ppm for a single 8-hour exposure; there was prostration followed by convulsive seizures; at autopsy there was pulmonary hemorrhage.[2] Rats exposed 6 hours/day, 5 days/week for 4 weeks to concentrations greater than 600 ppm had respiratory and ocular irritation and anemia.[3] In another study rats repeatedly exposed to 665 ppm for 7 hours daily developed pulmonary inflammation, and there were minor changes in the liver and kidneys in some animals.[2]

All mice and some rats receiving 1600 ppm by inhalation 6 hours/day for up to 13 weeks died.[4] Clinical findings included hypoactivity, abnormal posture, and, in rats, clonic convulsions. Male mice administered 400 ppm and females given 200 ppm, also for 13 weeks, had focal epithelial hyperplasia and ulceration of the forestomach.

In chronic studies, mice exposed 6

hours/day, 5 days/week for 2 years to concentrations of up to 200 ppm had no increases in the incidences of neoplasms.[4] High-dose females had a significantly increased incidence of squamous hyperplasia of the epithelium of the forestomach. In male rats receiving up to 400 ppm for the same duration there was a slight increase in the combined incidence of hepatocellular adenoma and carcinoma. There were no exposure-related liver lesions in female rats.

Acetonitrile was not mutagenic in *Salmonella typhimurium* assays, with or without metabolic activation.[4] Positive results were obtained in a micronucleus assay, and weakly positive responses for sister chromatid exchanges and chromosomal aberrations occurred in Chinese hamster ovary cells.[4]

No malformations related to acetonitrile exposure were observed in the offspring of rats orally exposed at maternally toxic levels.[5,6] Inhalation of 5000 or 8000 ppm for 60 minutes by pregnant hamsters on day 8 of gestation was associated with production of severe axial skeletal disorders; maternal toxicity including irritation, respiratory difficulty, lethargy, ataxia, hypothermia, and increased mortality was noted.[7] At lower doses there were no signs of maternal toxicity and offspring were normal.[7]

In the rabbit eye, a drop of the liquid caused superficial injury.[8] The liquid on the belly of a rabbit caused a faint erythema of short duration.[9] The toxic effects of acetonitrile are attributed to the metabolic release of cyanide via hepatic metabolism; cyanide in turn acts by inhibiting cytochrome oxidase and thus impairs cellular respiration.[10] Evidence of the cyanide effect is supported by the reported effectiveness of specific cyanide antidotes in acetonitrile poisonings.[10]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for acetonitrile is 40 ppm (67 mg/m^3) with a short-term excursion level of 60 ppm (101 mg/m^3).

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2-ACETYLAMINOFLUORENE
CAS: 53-96-3

$C_{15}H_{13}NO$

Synonyms: *N*-2-fluorenylacetamide; 2-acetaminofluorene; *N*-acetylaminophenanthrene; AAF

Physical Form. Light tan crystals

Uses. As a laboratory reagent for research

purposes (specifically, a positive control for carcinogenicity and mutagenicity studies)

Exposure. Inhalation

Toxicology. 2-Acetylaminofluorene (AAF) is a potent carcinogen in dogs, hamsters, and rats.

There is no toxicity information on humans.[1]

Four of five dogs developed tumors of the liver and urinary bladder after ingestion of 0.6–1.2 g AAF/kg diet for up to 91 months.[2] Animals developing tumors received a total of 90–198 g AAF, whereas the animal with no tumor formation ingested 45 g; another group of four dogs receiving 32–37 g over 2.25 years did not develop tumors.[2] The extent of tumor formation was directly related to the amount of AAF consumed, being most marked in those animals that received nearly 200 g during the feeding period.[2] Liver tumors of varied types were observed. Multiple papillomas were produced in the urinary bladder, and in one dog there was invasion of the submucosa and muscle by the tumor cells.

Intratracheal administration of 5–15 mg AAF one to two times per week for 17 months in hamsters (total dose 1100 mg) caused bladder tumors in 10 of 23 animals; all tumors were transitional cell carcinomas with or without focal squamous cell carcinomas.[3]

In rats, AAF had no demonstrable acute toxicity in quantities up to 50 mg/kg subcutaneously and 1 g/kg gastrically; however, AAF was very toxic when administered in the diet.[4] Incorporation of 0.031% AAF or higher for at least 95 days led to epithelial hyperplasia of the bladder, renal pelvis, liver, pancreas, and lung; 19 of 39 rats developed malignant tumors, 16 of which were carcinomas.[4]

Animal studies have indicated that *N*-hydroxy-2-acetylaminofluorene (*N*-hydroxy-AAF) is a proximate carcinogenic metabolite of AAF.[5] AAF is not carcinogenic in the guinea pig, and no *N*-hydroxylation of AAF has been detected *in vivo* or *in vitro* in this species; however, administration of *N*-hydroxy-AAF causes tumors in guinea pigs.[5] In addition, *N*-hydroxy-AAF has proved to be a carcinogen of much greater potency than AAF in rats, mice, hamsters, and rabbits at sites of local application.[5] Recent toxicological studies suggest that both initiating (genotoxic) as well as promoting properties (nongenotoxic interference with mitochondrial respiration and oxidative phosphorylation) of AAF contribute to the formation of tumors in animals.[6]

AAF is classified as a cytotoxic teratogen.[1] Because of demonstrated carcinogenicity in animals, contact by all routes should be avoided. In recent years this compound has been used only in laboratories as a model of tumorigenic activity in animals.[7] It is of little occupational health importance.

The ACGIH has not established a threshold limit value for AAF.

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ACETYLENE TETRABROMIDE
CAS: 79-27-6

$CHBr_2CHBr_2$

Synonyms: Tetrabromoethane; Muthmann's liquid; 1,1,2,2-tetrabromoethane

Physical Form. Colorless to yellow liquid

Uses. Gauge fluid; solvent; refractive index liquid in microscopy

Exposure. Inhalation

Toxicology. Acetylene tetrabromide is an eye and nasal irritant, central nervous system depressant, and hepatotoxin.

A chemist working with the substance for 7.5 hours with no local exhaust ventilation developed severe, nearly fatal, liver damage and was hospitalized for 9 weeks; his estimated exposure during most of the work shift before the onset of symptoms was 1–2 ppm, although he had a single 10-minute exposure to approximately 16 ppm.[1] He complained first of headache, anorexia, and nausea within hours of the exposure, and within 5 days he developed abdominal pain with bilirubinuria and a monocytosis of 17%. In this case, exposure to higher concentrations or significant skin absorption might have occurred. The similarity of the symptoms to viral hepatitis is also noted. Other workers in the same laboratory complained only of slight eye and nose irritation, with headache and lassitude.

Rats exposed to a saturated atmosphere for 7 hours exhibited slight eye and nose irritation.[2] Guinea pigs exposed for 90 minutes to a saturated vapor became comatose, seemed to recover, but died after several days; the same exposure for up to 3 hours was not lethal to rats and rabbits.[3] No mortality was observed in rats, guinea pigs, rabbits, mice, and a monkey exposed 7 hours/day to 14 ppm for 100 days; findings at 14 ppm did include edema of the lungs and slight fatty degeneration of the liver in all species except guinea pigs, which only showed growth depression.[2] Repeated exposure to 4 ppm for 180 days caused slight histopathologic changes in the liver and lungs of some animals, but no effects were observed at 1 ppm.

Repeated application of 15 mg to the skin of mice caused a statistically significant increase in the incidence of forestomach papillomas.[4]

The liquid instilled in the rabbit eye caused slight to moderate pain, conjunctival irritation, and corneal injury that disappeared after 24 hours.[1] When bandaged onto the shaved abdomen of the rabbit for 72 hours, moderate redness, edema, and blistering were observed.[1]

Acetylene tetrabromide has a sweetish, unpleasant odor that is readily apparent and objectionable to most persons at concentrations greater than 1–2 ppm.[1,2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for acetylene tetrabromide is 1 ppm.

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ACROLEIN
CAS: 107-02-8

C_3H_4O

Synonyms: Acrylaldehyde; 2-propenal; allyl aldehyde; propylene aldehyde; Aqualin

Physical Form. Colorless or yellowish liquid

Uses. Intermediate in the manufacture of acrylic acid; herbicide; algicide; in pharmaceuticals, perfumes, food supplements, and resins; as a warning agent in methyl chloride refrigerating systems

Exposure. Inhalation

Toxicology. Acrolein is an intense irritant of the upper respiratory tract, eyes, and skin.

Exposure to high concentrations may cause tracheobronchitis and pulmonary edema.[1] The irritation threshold in humans is 0.25–0.5 ppm, and concentrations above 1 ppm are extremely irritating to all mucous membranes within 5 minutes.[1] Fatalities have been reported at levels as low as 10 ppm, and 150 ppm was lethal after 10 minutes.[2,3] The violent irritant effect usually prevents chronic toxicity in humans.[1] Skin contact causes irritation, burns, and epidermal necrosis.[4] Eye splashes cause corneal damage, palpebral edema, blepharoconjunctivitis, and fibrinous or purulent discharge.[5]

In experimental animals the respiratory system is a primary target of acrolein exposure after inhalation, and there is an inverse relationship between the exposure concentration and the time it takes for death to occur.[4] Inhalation LC_{50} values of 327 ppm for 10 minutes and 130 ppm for 30 minutes have been reported in rats.[4] Of 57 male rats, 32 died after exposure to 4 ppm for 6 hours/day for up to 62 days.[6] Desquamation of the respiratory epithelium followed by airway occlusion and asphyxiation is the primary mechanism for acrolein-induced mortality in animals.[4] Sublethal acrolein exposure in mice at 3 and 6 ppm suppressed pulmonary antibacterial defense mechanisms.[7] A combination of epithelial cell injury and inhibition of macrophage function may be responsible for acrolein-induced suppression of pulmonary host defense.[8]

Intra-amniotic administration of acrolein in rats induced a significant number of fetal malformations, whereas intravenous administration was embryo lethal.[9] Pregnant rabbits given 4.0 and 6.0 mg/kg/day on days 7 through 19 of gestation had high incidences of maternal mortality, spontaneous abortion, resorptions, clinical signs, gastric ulceration, and sloughing of the gastric mucosa.[10] Acrolein did not cause statistically significant embryo-fetal effects at lower doses and was not considered to be a developmental toxicant at doses that did not cause severe maternal toxicity. Similar results were reported in two generations of rats administered up to 6 mg/kg; reduced pup weight occurred at levels that also produced significant maternal deaths.[11]

The carcinogenic potential of acrolein has been examined in a number of studies. Hamsters exposed to 4.0 ppm, 7 hours/day, for 52 weeks showed no evidence of respiratory tract tumors or tumors in other tissues and organs.[12] Rats exposed for 10–18 months to 8 ppm 1 hour/day also showed no evidence of a tumorigenic response.[4]

Extensive histopathologic examination did not reveal any carcinogenic effects in rats, mice, or dogs after oral exposure to 2.5, 4.5, or 2 mg/kg/day acrolein, respectively, for 12–24 months.[4] In the one study that reported positive findings, 20 female rats given acrolein in the drinking water (625 mg/liter water, equivalent to daily doses approaching 40 mg/kg body weight) for 104–124 weeks had an increased incidence of adrenal cortex neoplasms compared with controls.[13] The small numbers of animals used in this study make it unsuitable for evaluating the carcinogenic potential of acrolein. Furthermore, reevaluation of this study by an independent pathology group failed to confirm the original findings.[14] (The working group determined that the slightly elevated incidence of pheochromocytomas in the treated females was within limits for historical controls and was of no biological significance.)

A 2-year study of rats treated by daily gavage with 0, 0.05, 0.5, or 2.5 mg/kg for 102 weeks found no evidence of a neoplastic response.[14] Chronic gavage studies in mice for 18 months and capsular administration to dogs for 1 year also revealed no indication of a carcinogenic response.[15] The IARC has determined that there is inadequate evidence in both animals and humans for the carcinogenicity of acrolein.[16] Acrolein has been found to be muta-

genic to bacteria and to induce sister chromatid exchanges *in vitro*.[16]

The 2003 threshold limit value-time-weighted average (TLV-TWA) is 0.1 ppm (0.23 mg/m^3) with a short-term excursion level of 0.3 ppm (0.69 mg/m^3).

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ACRYLAMIDE
CAS: 79-06-1

C_3H_5NO

Synonyms: Acrylic amide; propenamide; ethylenecarboxamide; vinyl amide

Physical Form. White crystalline powder

Uses. In the production of polyacrylamides, which are used in water and waste treatment, paper and pulp processing, cosmetic additives, and textile processing; in adhesives and grouts; as cross-linking agents in vinyl polymers

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Acrylamide causes central-peripheral axonopathy; in laboratory animals it is carcinogenic and causes male reproductive toxicity.

A variety of signs and symptoms have been described in cases of acrylamide poisoning sug-

gesting involvement of the central, peripheral, and autonomic nervous systems.[1] Effects on the central nervous system are characterized by abnormal fatigue, memory difficulties, and dizziness. With severe poisoning, confusion, disorientation, and hallucinations occur. Truncal ataxia, nystagmus, and slurred speech have also been observed. Peripheral neuropathy symptoms can include muscular weakness, paresthesia, numbness in hands, feet, lower legs, and lower arms, unsteadiness, and difficulties in walking and standing. Clinical signs are loss of peripheral tendon reflexes, impairment of vibration sense, and muscular wasting in the extremities. Nerve biopsy shows loss of large-diameter nerve fibers as well as regenerating fibers. Autonomic nervous system involvement is indicated by excessive sweating, peripheral vasodilation, and difficulties in micturation and defecation.

Central nervous system effects predominate in acute exposures at massive doses, whereas peripheral neuropathy is more common with lower doses.[1,2] After cessation of exposure to acrylamide, most cases recover, although the course of improvement can extend over months to years and depends on the severity of exposure.[1,2] Because peripheral neurons can regenerate and central axons cannot, severely affected individuals may still experience residual ataxia, distal weakness, reflex loss, or sensory disturbance.

Because most cases of human poisoning have included skin absorption, the dose-response relationship has not been determined. On the skin acrylamide causes local irritation characterized by blistering and desquamation of the palms and soles combined with blueness of the hands and feet.[1]

For a number of species the oral LD_{50} was approximately 150–180 mg/kg body weight. In cats a total cumulative dose of 70–130 mg/kg was characterized by delayed onset of ataxia.[3] Cats fed 10 mg/kg diet/day developed definite hind limb weakness after 26 days; at 3 mg/kg/day there was twitching in the hindquarters after 26 days and signs of hind limb weakness after 68 days.[4] The underlying lesion involves distal retrograde degeneration of long and large-diameter axons.[5]

Teratogenic effects were not observed in the offspring of rats given up to 50 mg/kg diet for 2 weeks before mating and for 19 days during gestation.[1] In mice, high doses produced decreased sperm count and an increase in abnormal sperm morphology.[6]

Acrylamide produced dominant lethal reproductive effects in males as evidenced by reduced numbers of live pups and increased resorptions at exposure levels (30 ppm in drinking water) below those that caused neurotoxicity.[7] In another report, acrylamide caused a dose-dependent increase in the frequency of morphologic abnormalities in preimplantation embryos (single-cell eggs, growth retardation, and blastomere lysis) after paternal treatment (10–50 mg/kg, for 5 days).[8] These more recent findings indicate a potential risk to the offspring of men exposed to acrylamide.

A statistically significant increase in mesothelioma of the scrotal cavity was observed in rats given drinking water formulated to provide 0.5 mg/kg body weight/day for 2 years; in females there were significant increases in the number of neoplasms of the central nervous system, thyroid, mammary gland, oral cavity, clitoral gland, and uterus.[9]

Acrylamide has also been reported to act as a skin tumor initiator in mice by three exposure routes and to increase the yield of lung adenomas in another strain of mice.[10]

In a human mortality study of 371 workers no increase in total malignant neoplasms or any specific cancers attributable to acrylamide exposure were found.[11] Exposure levels reached 1.0 mg/m^3 before 1957 and were between 0.1 and 0.6 mg/m^3 after 1970. However, this study was of such a limited sample size that only large excesses could have been detected.

A much larger cohort of 8854 men, 2293 of whom were exposed to acrylamide, from 1925 to 1983 was examined for mortality.[12] This cohort consisted of four chemical plant populations. No statistically significant excess of all-cause or cause-specific mortality was found among acrylamide workers. Analysis by acrylamide exposure levels showed no trend of increased risk of mortality from several cancer sites. Although the authors concluded that the results do not support the hypothesis that acry-

lamide is a human carcinogen, this view was challenged on the basis that the comparison group included individuals from one of the four plants who had a small but significant excess of lung cancer (standardized mortality ratio = 1.32), which had been attributed by the authors to another occupational exposure in the production of muriatic acid.[13] The most recent update of this cohort through 1994 corroborated the original findings showing little evidence for a causal relation between exposure to acrylamide and cancer mortality.[14] Although an increase in pancreatic cancer was noted, there was no consistent exposure-response relationship.

The IARC has determined that there is sufficient evidence in experimental animals for the carcinogenicity of acrylamide and inadequate evidence for carcinogenicity to humans. Overall it is considered "probably carcinogenic to humans."[15]

Acrylamide is genotoxic in a number of test systems.[15] It induces gene mutation, structural chromosomal aberrations, sister chromatid exchange, and cell transformation. Furthermore, acrylamide forms covalent adducts with DNA in rodents and covalent adducts with hemoglobin in humans. Hemoglobin adducts have been used for biomonitoring of acrylamide. Studies indicate that the adducts are useful predictors of acrylamide-induced peripheral neuropathy.[16]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for acrylamide is 0.03 mg/m^3 with a notation for skin absorption and an A3, confirmed animal carcinogen with unknown relevance to humans designation.

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ACRYLIC ACID
CAS: 79-10-7

$C_3H_4O_2$

Synonyms: 2-Propenoic acid; acroleic acid; ethylenecarboxylic acid; vinylformic acid

Physical Form. Colorless, fuming liquid

Uses. Starting material for acrylates and polyacrylates used in plastics, water purification, paper and cloth coatings, and medical and dental materials

Exposure. Inhalation; ingestion

Toxicology. Acrylic acid is a severe irritant of the eyes, nose, and skin. The major route of absorption is ingestion of inhaled vapors.

Medical reports of acute human exposures (concentration unspecified) include moderate and severe skin burns, moderate eye burns and mild inhalation effects.[1] Although acrylic acid is acutely irritating at sites of initial contact, it causes little systemic toxicity. The low systemic toxicity of acrylic acid is likely a consequence of its rapid and extensive metabolism to CO_2.[2]

There is a great variability in the reported values for the oral LD_{50} in rats, ranging from 350 to 3200 mg/kg.[3,4] The dermal LD_{50} in rabbits was 750 mg/kg.[5]

Rats exposed to 1500 ppm for four 6-hour periods exhibited nasal discharge, weight loss, lethargy, and kidney congestion.[6] At 300 ppm, twenty 6-hour exposures produced all but the latter effect. No toxic signs resulted from exposure to 80 ppm for twenty 6-hour periods.

Exposure to 0, 5, 25, or 75 ppm 6 hours/day, 5 days/week, for 13 weeks produced slight degenerative lesions of the nasal mucosa in rats at the high dose but none at 25 ppm.[7] In contrast, lesions of the nasal mucosa appeared in at least some of the mice at all dose levels but not in the control.

There were no indications of systemic toxicity and/or carcinogenicity in rats administered 0, 120, 400, or 1200 ppm in the drinking water for over 2 years.[8]

The application of 0.1 ml of a 4% acrylic acid solution in acetone to the skin of mice three times per week for 13 weeks led to distinct skin irritation from 1 week on. Only minimal proliferative processes were observed when 0.1 ml of a 1% acrylic acid solution was applied.[9]

In 2-week studies preliminary to a lifetime dermal carcinogenicity study in mice, a concentration of 5% in acetone caused peeling and flaking of the skin.[10] A 1% solution in acetone applied to the skin of 40 C3H/HEJ male mice 3 days/week for 1.5 years caused no treatment-related tumors or effects on mortality.

A 1% solution in the eye of a rabbit caused significant injury.[5]

Acrylic acid is not a selective reproductive toxin or teratogen when administered by inhalation or in the diet.[11] Pregnant rabbits exposed to 25, 75, or 225 ppm of vapor on gestation days 6 to 18 exhibited reductions in food consumption and body weight gain and lesions in the nasal epithelium that were concentration dependent. There was no evidence of developmental toxicity.[12] Similar effects were seen in rat studies. In one study, pregnant rats were exposed from day 6 to day 15 to 0, 40, 120, or 360 ppm.[13] Marked effects were observed in the dams at 360 ppm, including reduced weight gain, decreased food intake, and clinical signs of an irritant effect on mucous membranes. There were no signs, however, of embryotoxicity or teratogenicity at any of the doses tested.

Acrylic acid was not mutagenic in five strains of *Salmonella typhimurium* with or without metabolic activation by liver microsomes.[14] Results were also negative (nonmutagenic) in an number of *in vivo* assays in both somatic and germ cells.[15]

α, β-Diacryloxypropionic acid has been found to be a sensitizing impurity in commercial acrylic acid.[16]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for acrylic acid is 2 ppm (5.9 mg/m^3) with a notation for skin.

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ACRYLONITRILE
CAS: 107-13-1

C_3H_3N

Synonyms: ACN; cyanoethylene; propenenitrile; vinyl cyanide

Physical Form. Colorless liquid

Uses. Manufacture of acrylic fibers; synthesis of rubberlike materials; pesticide fumigant

Exposure. Inhalation; skin absorption

Toxicology. Acrylonitrile is an eye, skin, and upper respiratory tract irritant; systemic effects are nonspecific but may include the central nervous, hepatic, renal, cardiovascular, and gastrointestinal systems. It is carcinogenic in experimental animals.

Most cases of intoxication from industrial exposure have been mild, with rapid onset of eye irritation, headache, sneezing, and nausea; weakness, light-headedness, and vomiting may also occur.[1] Acute exposure to high concentrations may produce profound weakness, asphyxia, and death.[1] Acrylonitrile is metabolized to cyanide by hepatic microsomal reactions. Deaths from acute poisoning result from inhibition of mitochondrial cytochrome oxidase activity by metabolically liberated cyanide. Inhalation of more moderate concentrations for a longer period of time leads to damage to the liver tissues in addition to central nervous system (CNS) effects.[2]

Prolonged skin contact with the liquid results in both systemic toxicity and the formation of large vesicles after a latent period of several hours.[1] The affected skin may resemble a second-degree thermal burn.

Administration of 65 mg/kg/day by gavage to rats on days 6 to 15 of gestation produced significant maternal toxicity and an increased incidence of malformation in the offspring.[3] Inhalation of 80 ppm 6 hours/day by the dams resulted in a significant increase of fetal malformations including short tail, missing vertebrae, short trunk, omphalocele, and hemivertebra; maternal toxicity consisted of decreased weight gain.[3] Oral administration of 10 mg/kg/day for 60 days to male mice induced histopathologic changes in the testis and reduced sperm counts compared with controls. These changes were not observed at a dosage level of 1 mg/kg/day.[4] A recent review of reproductive and developmental toxicity data suggested that acrylonitrile does not produce clear adverse effects on fertility, reproduction or development at doses below those causing parental toxicity.[5]

In a number of chronic bioassays in rats, administration of acrylonitrile by gavage, by inhalation, and in the drinking water produced tumors of the mammary gland, the gastrointestinal tract, the zymbal glands, and the CNS.[6–8] Administration of 500 ppm in drinking water caused a statistically significant increase in microscopically detectable primary brain tumors.[9] Neurological signs were observed in 29 of 400 rats within 18 months, and brain tumors occurred in 49 of 215 animals that died or were killed in the first 18 months. Gavage administration of up to 20 mg/kg, 5 days/week for 104 weeks caused increased incidences of forestomach and harderian gland neoplasms in mice.[10]

In an epidemiological study of 1345 workers potentially exposed to acrylonitrile and followed for 10 or more years there was a greater than expected incidence of lung cancer (8 obs. vs. 4.4 exp.).[11] A trend toward increased risks of cancer of all sites was also observed with increased duration of exposure and with higher severity of exposure. However, in a follow-up of this cohort through 1983 the only statistically significant excess was for prostate cancer (5 obs. vs. 1.9 exp.).[12] An excess number of lung cancer cases remained (10 obs. vs. 7.2 exp.) but was not as marked.[12,13] A study of 1774 workers, potentially exposed to acrylonitrile and followed for 32 years, reported no significant excess of all-site or site-specific cancer mortality rates.[14] Other epidemiological studies reported excess cancer deaths but lacked statistical significance because of small cohort size, low exposures, and insufficient follow-up times.

The IARC has determined that there is sufficient evidence of carcinogenicity of acrylonitrile in animals and that it is probably carcinogenic to humans.[15]

In vitro genotoxic studies have given positive results for gene mutations, chromosomal aberrations, DNA damage, and cell transformation in the presence of metabolic activation; *in vivo* assays have generally been negative.[16]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for acrylonitrile is 2 ppm (4.3 mg/m^3) with an A3-confirmed animal carcinogen with unknown relevance to humans designation and a notation for skin absorption.

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ALDRIN
CAS: 309-00-2

$C_{12}H_8Cl_6$

Synonyms: 1,2,3,4,10,10-Hexachloro-1,4,4*a*,5,8,8*a*-hexahydro-1,4,5,8-dimethanonaphthalene; HHDN(ISO); aldrine

Physical Form. White, crystalline, odorless solid

Uses. Insecticide

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Aldrin is a convulsant; in animals it causes liver and kidney damage and hepatocellular tumors.

In humans, early symptoms of intoxication may include headache, dizziness, nausea, vomiting, malaise, and myoclonic jerks of the limbs; clonic and tonic convulsions and sometimes coma follow and may occur without the premonitory symptoms.[1,2] A suicidal person who ingested 25.6 mg/kg developed convulsions within 20 minutes that persisted recurrently until large amounts of barbiturates had been administered. Hematuria and azotemia occurred the day after ingestion and continued for 18 days. Liver function studies were within normal limits except for an elevated icterus index; an electroencephalogram revealed generalized cerebral dysrhythmia, which returned to normal after 5 months.[3]

Once aldrin is absorbed, it is rapidly metabolized to dieldrin.[4] In a study of five workers exposed to concentrations of aldrin of up to 8.5 mg/m^3 who had suffered convulsive seizures or myoclonic limb movements, the probable concentration of dieldrin in the blood during intoxication ranged from 16 to 62 µg/100 g of blood; in healthy workers the concentration of dieldrin ranged up to 22 µg/100 g of blood.[4]

Aldrin is reported to have caused erythematobullous dermatitis in a single case. Minor

erythema may be observed from skin contact, but dermatitis associated with aldrin is unusual.[5]

In animal studies aldrin induced an increased incidence of hepatocellular carcinoma at two dietary doses in male mice; the tumors showed a significant dose-response trend and were statistically significant at the high dose.[6] Follicular cell tumors of the thyroid and adrenal cortical cell adenomas were increased in female rats in the low-dose group but not in the high-dose group; the results could not be clearly associated with treatment.[6]

In contrast to animal studies, epidemiological studies of workers employed in the manufacture of aldrin provide no conclusive evidence of carcinogenicity in humans.[7,8] One study of a cohort having mixed exposure to aldrin, dieldrin, and endrin found 9 deaths from cancer versus 12 expected. The workers had been exposed to the pesticides for a mean of 11 years and followed a mean of 24 years.[9] A more recent examination of 2384 manufacturing workers, employed between 1952 and 1982, with exposure to a number of pesticides including aldrin found no excess mortality rates attributable to occupational exposures.[10] Similarly, a 23-year follow-up of 570 aldrin- and dieldrin-exposed workers found no increase in overall mortality rates or mortality from liver cancer.[11]

Genotoxic assays have yielded primarily negative results, and aldrin does not appear to react directly with the DNA molecule.[7]

Accumulating evidence suggests that aldrin is "not a likely human carcinogen" and that it acts as a species-specific hepatocarcinogen in mice through nongenotoxic mechanisms.[7,8]

Single high doses of aldrin (50 mg/kg) administered orally to hamsters during the period of organogenesis caused a high incidence of fetal deaths, congenital anomalies, and growth retardation.[12] No information on the health status of maternal animals was provided, but this dose is in the range of reported LD_{50} values. Decreased postnatal survival has been observed in laboratory animals after in utero exposure.[7] Intraperitoneal injection of aldrin has caused adverse effects on the male reproductive system including decreased sperm count and degeneration of germ cells. Decreased fertility has been noted in some, but not all, studies after oral exposure.[7]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for aldrin is 0.25 mg/m^3 with a notation for skin absorption.

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ALLYL ALCOHOL
CAS: 107-18-6

C_3H_6O

Synonyms: 2-Propen-1-ol; 1-propenol-3; vinyl carbinol

Physical Form. Colorless liquid

Uses. In manufacture of allyl compounds, resins, plasticizers; fungicide and herbicide

Exposure. Inhalation; skin absorption

Toxicology. Allyl alcohol is a potent lacrimator and is an irritant of the mucous membranes and skin.

In humans, severe eye irritation occurs at 25 ppm and irritation of the nose is moderate at 12.5 ppm.[1] In workers exposed to a "moderate" vapor level there was a syndrome of lacrimation, retrobulbar pain, photophobia, and blurring of vision.[1] The symptoms persisted for up to 48 hours. Skin contact with the liquid has a delayed effect, causing aching that begins several hours after contact, followed by the formation of vesicles. Splashes of the liquid in human eyes have caused moderately severe reactions.[2]

In rats the 1-, 4-, and 8-hour LC_{50} values are 1060, 165, and 76 ppm, respectively.[1] Signs of toxicity included lethargy, excitability, tremors, convulsions, diarrhea, coma, pulmonary and visceral congestion, and varying degrees of liver injury. Repeated 7 hour/day exposure at 60 ppm caused gasping during the first few exposures, persistent eye irritation, and death of 1 of 10 rats.[1] In several species of animals exposed to 7 ppm for 7 hours/day for 6 months, observed effects were minimal; at autopsy, findings were focal necrosis of the liver and necrosis of the convoluted tubules of the kidneys.[3]

Allyl alcohol was not carcinogenic in limited oral studies in rats and hamsters. It was mutagenic in bacterial assays and in mammalian cells in culture.[4]

The warning properties are thought to be adequate to prevent voluntary exposure to acutely dangerous concentrations but inadequate for chronic exposure.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for allyl alcohol is 2 ppm (4.8 mg/m^3) with a short-term excursion limit of 4 ppm (9.5 mg/m^3) and a notation for skin absorption.

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ALLYL CHLORIDE
CAS: 107-05-1

C_3H_5Cl

Synonyms: Chlorallylene; 3-chloropropene; 3-chloroprene; 1-chloro-2-propene; 3-chloropropylene; 2-propenyl chloride

Physical Form. Liquid

Uses. Manufacture of epichlorohydrin, epoxy resin, glycerin pesticides, and sodium allyl sulfonate

Exposure. Inhalation; skin absorption

Toxicology. Allyl chloride is an irritant of the eyes, mucous membranes, and skin; chronic exposure may cause toxic polyneuropathy. In animals it causes renal, hepatic, and pulmonary damage and, at high concentrations, central nervous system depression.

The most frequent effects in humans from overexposure have been conjunctival irritation and eye pain with photophobia; eye irritation occurs at levels between 50 and 100 ppm.[1] Irritation of the nose occurs at levels below 25 ppm.

In one report from China 26 factory workers exposed to allyl chloride ranging from 0.8 ppm to 2100 ppm complained of lacrimation and sneezing, which gradually diminished.[2] After 2.5 months to 5 years exposure, most had developed weakness, paresthesia, cramping pain, and numbness in the extremities with sensory impairment in the glove-stocking distribution as well as diminished ankle reflexes. Electroneuromyography showed neurogenic abnormalities in 10 of 19 subjects. Similar but much milder symptoms appeared in other workers exposed at 0.06–8 ppm for 1–4.5 years. Diagnostic findings suggested mild neuropathy in 13 of 27 of these subjects.

The liquid is a skin irritant and may be absorbed through the skin, causing deep-seated pain.[1] If splashed in the eye, severe irritation would be expected.

Rats survived 15 minutes at 32,000 ppm, 1 hour at 3,200 ppm, or 3 hours at 320 ppm, but 0.5-, 3-, and 8-hour exposures, respectively, were lethal to all within the following 24 hours.[3] Exposure to 16,000 ppm for up to 2 hours in rats or 1 hour in guinea pigs caused eye and nose irritation, drowsiness, weakness, instability, labored breathing, and ultimately death. Postmortem findings were severe kidney injury, alveolar hemorrhage in the lungs, and slight liver damage. No significant effects were found in rats exposed at 200 ppm for 6 hours; renal toxicity appeared at 300 ppm, but mortality was not affected until 1,000 ppm was reached.[4] Several species exposed to 8 ppm for 7 hours daily for 1 month showed no apparent ill effects, but histopathologic examination revealed focal necrosis in the liver and necrosis of the convoluted tubules of the kidneys. Exposed at 3 ppm for 6 months, rats showed slight centrilobular degeneration in the liver.[5]

In other reports, rats and mice showed no effects at 20 ppm 7 hours/day for 90 days, but adverse effects were found following the 50 ppm regime.[4] In a limited inhalation study, rabbits exposed at 206 mg/m^3 for 6 hours/day for 2 months developed unsteady gait and flaccid paralysis, whereas rabbits exposed at 17 mg/m^3 for 5 months showed no evidence of toxic effects.[6]

Rats given 2 mmol/kg allyl chloride by subcutaneous injection 5 days/week for 3 months showed clinical signs of neurotoxicity after the treatment period and biochemical evidence of neurofilament protein accumulation in both the central and peripheral nervous systems.[7] However, no evidence of neurofilament protein cross-linking was found, suggesting that allyl chloride may not share a common mechanism for the accumulation of neurofilaments with other neurotoxins such as 2, 5-hexanedione.

Allyl chloride was fetotoxic to rats exposed during gestation to 300 ppm, which also caused considerable maternal toxicity in the form of kidney and liver injury.[8] It was a testicular toxicant in mice, causing decreased testes weight, reduced numbers of spermatids, and increased frequency of abnormal sperm after a single subcutaneous injection to male mice at one-fifth the LD_{50}.[9]

Administered by gavage for 1.5 years, allyl chloride was not carcinogenic to rats but caused a low incidence of squamous cell carcinomas of the forestomach in mice.[10] It is genotoxic in a number of *in vitro* assays and is a direct alkylating agent.[11] The IARC has determined that there is inadequate evidence in experimental animals for the carcinogenicity of allyl chloride and that it is not classifiable as to its carcinogenicity to humans.[12]

Although allyl chloride is detectable below 3 ppm, the warning properties are insufficient to prevent exposure to concentrations that may be hazardous with chronic exposure.[4]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for allyl chloride is 1 ppm (3 mg/m^3) with a short-term excursion limit of 2 ppm (6 mg/m^3).

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ALLYL GLYCIDYL ETHER
CAS: 106-92-3

$C_6H_{10}O_2$

Synonyms: AGE; allyl 2, 3-epoxypropyl ether

Physical Form. Liquid

Uses. Reactive diluent in epoxy resin systems; stabilizer of chlorinated compounds; manufacture of rubber

Exposure. Inhalation; skin absorption

Toxicology. Allyl glycidyl ether (AGE) causes skin, eye, and upper respiratory tract irritation and contact dermatitis; high concentrations cause pulmonary edema and narcosis, whereas chronic exposures induce nasal lesions in animals.

Workers exposed to the vapor and/or liquid complained of dermatitis with itching, swelling, and blister formation.[1] Skin sensitization has occurred; cross sensitization probably can occur with other epoxy agents.[2]

Three workers applying an epoxy-based waterproofing paint containing glycidyl ether inside an underground water tank died in the tank of asphyxia. Constituents of epoxy resin will displace oxygen in a confined space and may have an independent narcotic effect on exposed workers. Strict precautionary measures are recommended under these conditions.[3]

In rats, the LC_{50} for 8 hours was 670 ppm; effects were lacrimation, nasal discharge, dyspnea, and narcosis.[1] In rats repeatedly exposed to 600 ppm for 8 hours daily, effects were pronounced irritation of the eyes and respiratory tract; more than half of the rats developed corneal opacity; at necropsy, after 25 exposures, pulmonary findings were inflammation, bronchiectasis, and bronchopneumonia.[1]

Inhalation of 7 ppm for 6 hours/day caused necrosis and complete erosion of nasal mucosa after 4 days; squamous metaplasia of the respiratory epithelium and focal erosion of the olfactory epithelium with evidence of regeneration of some epithelial surface occurred in mice after 9–14 days at this exposure level.[4] Rats and mice exposed to concentrations as low as 4 ppm for 13 weeks had squamous metaplasia, hyperplasia, and inflammation of the nasal mucosa.[5]

Chronic 24-month inhalation exposure to 5 or 10 ppm AGE induced nasal lesions in rats and mice.[6] Inflammation, degeneration, regeneration, metaplasia, hyperplasia, and neoplasia were observed in the nasal mucosa. Although the incidence of primary nasal tumors was not statistically significant compared with the incidence in concurrent controls, the relative rarity of primary nasal tumors occurring spontaneously and the presence of other nonneoplastic lesions suggests that the tumors observed may be related to AGE exposure. It was concluded that there was some evidence of carcinogenicity of inhaled AGE for male mice, equivocal evidence of carcinogenicity for female mice and male rats, and no evidence of carcinogenicity for female rats.[5]

AGE was mutagenic in some strains of bacteria with or without metabolic activation. It also induced sister chromatid exchanges and chromosomal aberrations in cultured cells.[5]

Percutaneous absorption has been documented in rabbits.[2] The liquid dropped into the eye of a rabbit caused severe but reversible conjunctivitis, iritis, and corneal opacity.[1] Cytotoxic effects on rat bone marrow cells, with reduction in leukocyte counts, and testicular degeneration were observed after intramuscular injections at 400 mg/kg/day.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for allyl glycidyl ether is 1 ppm (4.7 mg/m^3).

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ALLYL PROPYL DISULFIDE
CAS: 2179-59-1

$C_6H_{12}S_2$

Synonyms: Disulfide, allyl propyl; onion oil

Physical Form. Pale yellow oil

Source. Onions

Exposure. Inhalation

Toxicology. Allyl propyl disulfide vapor is a mucous membrane irritant.

No systemic effects have been reported from industrial exposure. At an average concentration of 3.4 ppm in an onion dehydrating plant there was irritation of eyes, nose, and throat in some workers.[1]

Allyl propyl disulfide was not mutagenic in *Salmonella typhimurium* assays with or without activation.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for allyl propyl disulfide is 2 ppm (12 mg/m^3) with a short-term excursion limit of 3 ppm (18 mg/m^3).

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ALUMINUM
CAS: 7429-90-5

Al

Physical Form. Metal dusts, pyro powders, welding fumes: When exposed to air, an aluminum surface becomes oxidized to form a thin coating of aluminum oxide, which protects against ordinary corrosion. Powder and flake aluminum are flammable and can form explosive mixtures in air, especially when treated to reduce surface oxidation (pyro powders).

Uses. Structural material in construction, automotive, and aircraft industries; in the production of metal alloys; in cookware, cans, food packaging, and dental materials; pyro powders are used in fireworks and aluminum paint.

Exposure. Inhalation

Toxicology. Exposure to aluminum may cause subtle neurological effects, and massive inhalation of aluminum dusts may cause pulmonary effects.

In humans, the symptoms of long-term overexposure to fine powders of aluminum may include dyspnea, cough, and weakness. It has been noted that these workers are usually exposed to a number of other toxicants that could cause similar symptoms. Typically, there may be radiographic evidence of fibrosis and occasional pneumothorax. At autopsy, there is generalized interstitial fibrosis, predominantly in the upper lobes, with pleural thickening and adhesions. Particles of aluminum are found in the fibrotic tissue. A rare fatal case of pulmonary fibrosis from inhalation of a heavy concentration of fine aluminum dust was reported in a 22-year-old British worker; autopsy revealed a generalized nonnodular fibrosis and interstitial emphysema with right ventricular hypertrophy. There had been work exposure to varying concentrations of a wide range of particle sizes, but the quantity of dust in the atmosphere below 5 μ was of the order of 19 mg/m^3.[1]

Of 27 workers with heavy exposures to aluminum powder in the same plant as the above-mentioned case, 6 were found to have evidence of pulmonary fibrosis. The finer dust was more dangerous than the coarse dust: Of the 12 men exposed to fine aluminum powder, 2 died and 2 others were affected, and of 15 men who worked exclusively with coarser powder, 2 had radiological changes but no symptoms.[2]

Fine metallic aluminum powders inhaled by hamsters and guinea pigs caused no pulmonary fibrosis; in rats that inhaled the dust, small scars resulted from foci of lipid pneumonitis. Alveolar proteinosis developed in all three species; it resolved spontaneously, and the accumulated dust deposits cleared rapidly from the lungs after cessation of the exposure. The failure of inhaled aluminum powder to cause pulmonary fibrosis in experimental animals parallels the clinical experience in the United States, where pulmonary fibrosis has not been observed in aluminum workers.[3]

It has been suggested that the explanation of pulmonary disease among powder workers in other countries may lie in the duration of exposure, the size of the particles, the density of the dust, and especially the fact that all reported cases have been associated with exposure to a submicron-sized aluminum pyrotechnic flake (powder), which has been lubricated with a nonpolar aliphatic oil rather than the usually employed stearic acid.[2,4]

Evidence of the relatively benign nature of aluminum dust in measured concentrations lies in the 27-year experience of administration of freshly milled metal particles to workers exposed to silica as a suggested means of inhibiting the development of silicosis. Inhalation of aluminum powder of particle size of 1.2 μ (96%), over 10- or 20-minute periods several times weekly, resulted in no adverse health effects among thousands of workers over several years.

The etiologic role of aluminum in neurological disorders has been of increasing interest in recent years. Subtle neurological effects (altered performance on neurobehavioral tests and increased reporting of subjective symptoms) have been detected in workers exposed to large amounts of aluminum dusts in factories.[5]

Several mortality studies of aluminum reduction plant workers, in which the study cohorts totaled nearly 28,000 long-term employees, recorded no excess deaths due to organic brain disorders of dementia type, and an analysis of the occupational mortality experience of nearly 430,000 men who died in Washington state during the years 1950 through 1979 showed no excess deaths from this cause among the 1238 former aluminum workers included in the study.[6–8] However, three cases of a progressive neurological disorder, characterized by incoordination, intention tremor, and cognitive deficit, in workers at an aluminum reduction plant have been reported, and the investigators postulated that they may have been related to occupational exposure to aluminum in some form.[9]

People on renal dialysis who have received high doses of aluminum in medications and in dialysate fluid for a number of years are at increased risk of developing encephalopathy or "dialysis dementia."[5] The disease is characterized by altered speech, personality changes, seizures, and motor dysfunction. Symptoms have been reversed when aluminum exposures were lowered.

A possible association between aluminum ingestion and Alzheimer disease, which has clinical and histopathologic features distinct from dialysis encephalopathy, has also been proposed. Alzheimer disease is pathologically characterized by the formation of neurofibrillary tangles and senile plaques; these tangles in the cerebral cortex and hippocampus have been reported to contain aluminum. It is not known whether aluminum is a causal agent or whether the neurodegenerative disease just allows more aluminum to accumulate in the brain. It has been noted that Alzheimer disease may largely be a genetic disorder.[5]

One study suggested a possible link of aluminum in public water supplies with the occurrence of Alzheimer disease in 88 county districts of England and Wales.[10] In districts in which the mean aluminum concentration in water exceeded 0.11 mg/l, rates were 1.5 times higher than in districts in which the mean levels were less than 0.01 mg/l. The results have been challenged on the basis of study design and on the interpretation of the relative significance of the dose of aluminum from water as a fraction of total dietary intake.[11]

Ingested aluminum is poorly absorbed, and there appears to be no retention of aluminum from nutritional sources in individuals with normal kidneys. Dusts of metallic aluminum and aluminum oxide are not significantly absorbed systemically, although fume from welding aluminum is absorbed through the lungs, producing a rise in aluminum levels in plasma and urine.[12]

Aluminum does not appear to be a potential carcinogen. It has not been shown to be carcinogenic in human epidemiological studies or in animal studies after oral or inhalation exposure.

Aerosols of the soluble salts of aluminum, such as the chloride and sulfate, are irritants of little occupational importance. Although the aluminum alkyls may also be irritants, there is

inadequate toxicity information on these compounds.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for aluminum is 10 mg/m^3 for the metal dust, 5 mg/m^3 for pyro powders and welding fumes, as Al, and 2 mg/m^3 for the soluble salts and alkyls, as Al.

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ALUMINUM OXIDES
Chemical Compound: Aluminum oxide (Al_2O_3)
Mineral Name: Corundum
Synonym: α-Alumina
CAS: 1344-28-1

Chemical Compound: Aluminum oxyhydroxide (AlO_2H)
Mineral Name: Boehmite, Diaspore
Synonym: Alumina monohydrate
CAS: 24623-77-6

Chemical Compound: Alumina trihydroxide ($Al(OH)_3$)
Mineral Name: Gibbsite, bayerite, nordstrandite
Synonym: Alumina trihydrate, aluminum hydroxide
CAS: 21645-51-2

Uses. Production of aluminum; synthetic abrasives; refractory material

Exposure. Inhalation

Toxicology. The aluminas are considered to be nuisance dusts; their role in fibrogenic lung disease remains unclear.

Assessment of the toxicity of aluminas has been complicated by the chemical and physical variants of the compounds and inconsistencies in the nomenclature used to describe them.[1] The group of compounds referred to as aluminas is composed of various structural forms of aluminum oxide, trihydroxide, and oxyhydroxide.[2] As these aluminas are heated, dehydration occurs, producing a variety of transitional forms; temperatures between 200 and 500°C result in low-temperature-range transitional

aluminas characterized by increased catalytic activity and larger surface area.[2] (Transitional aluminas include χ, η, and γ forms, which, taken together, were formerly termed "γ.")[2]

Despite the problems in defining precise exposures (in terms of structure and form) population studies of potentially exposed workers have shown minimal evidence for pulmonary fibrosis or pneumoconiosis.

A report from an aluminum production facility found that 7–8% of potentially exposed alumina workers had small, irregular opacities as determined by chest radiograph.[2] The prevalence of opacities was increased among smokers and among nonsmokers with high cumulative dust exposures. The pulmonary pathologic changes occurring that are responsible for the opacities are not clear.[2] A slight but significant decrement in ventilatory function among nonsmoking workers was also observed in this population.[3] The findings were consistent with a minor degree of nonspecific chronic industrial bronchitis associated with excessive protracted nuisance dust exposure (i.e., 100 mg-years for more than 20 years).[1]

A number of epidemiological studies of aluminum smelter workers have confirmed either minimal or absent fibronodular disease and no excess mortality associated with pneumoconiosis.[4–6] A report of 4 subjects exposed for many years to alumina dust found a correlation between radiographic opacities and apparent pulmonary burden of aluminum as determined by neutron activation analysis.[7] A recent study of nine aluminum oxide workers with abnormal chest roentgenograms found histologic evidence of interstitial lung fibrosis in three of the most severely affected workers who underwent lung biopsy.[8] The absence of asbestos bodies and silicotic nodules, although there was concurrent exposure to these substances, and the large number of aluminum-containing particles in lung tissue indicated to the investigators that aluminum oxide was the common exposure. The role of smoking in altering the host response in these cases is unknown. In other case reports of lung fibrosis, the exposure to aluminum oxide was not well quantified and there was concurrent exposure to other dust and fumes.[9]

Animal experiments with alumina have shown that the type of reaction in lung tissue is dependent on the form of alumina and its particle size, the species of animal used, and the route of administration. For example, intratracheal administration into rats of γ-alumina of 2-μ average size caused only a mild fibrous reaction of loose reticulin.[10] However, intratracheal administration of γ-alumina of 0.02- to 0.04-μ size into rats produced reticulin nodules that later developed into areas of dense collagenous fibrosis.[11] The latter alumina by the same route in mice and guinea pigs caused development of a reticulin network with occasional collagen, whereas in rabbits only a slight reticulin network was observed.[10] Intratracheal administration of another form of alumina in rats, corundum of particle size less than 1 μ, caused the development of compact nodules of reticulin.

In rats, inhalation of massive levels of γ-alumina with an average particle size of 0.0005–0.04 μ for up to 285 days caused heavy desquamation of alveolar cells and secondary inflammation, but only slight evidence of fibrosis.[12] The dust concentration in the exposure chamber was described as so high that visibility was reduced; a few breaths of the atmosphere by the investigators caused bronchial irritation and persistent cough.

A review of the animal studies concluded that a fibronodular response has resulted only from intratracheal insufflation of catalytically active, low-temperature-range transitional aluminas and high-surface-area aluminas.[1] In general, alumina is efficiently eliminated from the lung and has a low degree of fibrogenicity.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for aluminum oxide is 10 mg/m^3 for total dust containing no asbestos and <1% crystalline silica.

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4-AMINODIPHENYL

CAS: 92-67-1

$C_{12}H_{11}N$

Synonyms: 4-ADP; *para*-aminodiphenyl; 4-aminobiphenyl; biphenylamine; *p*-xenylamine

Physical Form. Colorless, crystalline compound; darkens on oxidation

Uses. Previously used as a rubber antioxidant; no longer produced on a commercial scale

Exposure. Inhalation; skin absorption

Toxicology. 4-Aminodiphenyl exposure is associated with a high incidence of bladder cancer in humans.

Of 171 workers exposed to 4-aminodiphenyl for 1.5–19 years, 11% had bladder tumors; the tumors appeared 5–19 years after initial exposure.[1]

In a study of 503 exposed workers, there were 35 histologically confirmed bladder carcinomas and an additional 24 men with positive cytology.[2]

Two bladder papillomas and three bladder carcinomas were observed in six dogs fed a total of 5.5–7 g (1.0 mg/kg, 5 days/week for life).[3] In another study, each of four dogs developed urinary bladder carcinomas with predominantly squamous differentiation in 21–34 months after ingestion of 0.3 g of 4-aminodiphenyl three times per week (total dose 87.5–144 g/dog); hematuria, salivation, loss of body weight, and vomiting were also noted, and all animals died within 13 months of the first appearance of a tumor.[4]

Rats injected subcutaneously with a total dose of 3.6–5.8 g/kg had an abnormally high incidence of mammary gland and intestinal tumors.[5] Nineteen of 20 newborn male mice and 6 of 23 newborn female mice developed hepatomas in 48–52 weeks after three subcutaneous injections of 200 µg of 4-aminodiphenyl;

in control animals, 5 of 41 males and 2 of 47 females had hepatomas.[6]

The IARC has determined that there is sufficient evidence for carcinogenicity to humans and animals.[7] Furthermore, the accumulated experimental and epidemiological evidence has demonstrated that 4-aminodiphenyl may be the most hazardous of the aromatic amines regarding carcinogenic potential.[8] Because of demonstrated carcinogenicity, contact by all routes should be avoided.[9]

ACGIH has designated 4-aminodiphenyl as an A1 human carcinogen with no assigned threshold limit value and a notation for skin absorption.

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p-AMINOPHENOL

CAS: 123-30-8

$NH_2C_6H_4OH$

Synonyms: Activol; 4-amino-1-hydroxybenzene; 4-hydroxyaniline; PAP

Physical Form. White or reddish-yellow crystals; discolors to lavender when exposed to air

Uses. Oxidative dye; developing agent for photographic processes; precursor for pharmaceuticals; used in hair dyes

Exposure. Inhalation; skin absorption

Toxicology. *p*-Aminophenol is of moderately low toxicity but has caused dermal sensitization and kidney injury; the potential for producing methemoglobin is of relatively minor importance.

The oral LD_{50} in rats was 671 mg/kg.[1] Effects included central nervous system depression. A solution of 2.5% applied to abraded skin of rabbits was a mild irritant.[1] *p*-Aminophenol caused dermal sensitization in guinea pigs, and skin sensitization has been reported in humans.[2,3] The dermal LD_{50} in rabbits was greater than 8 g/kg, which strongly suggests that absorption through the skin is minimal.[4] Single nonlethal acute doses in rats produced proximal renal tubular necrosis of the pars recta.[5,6]

Early animal studies of *p*-aminophenol administered in the diet and topical studies of oxidative hair dyes containing *p*-aminophenol have not shown definitive carcinogenic

effects.[7–9] *p*-Aminophenol has shown variable results in a wide variety of genotoxic assays.[3]

Studies of the teratogenic effects of *p*-aminophenol indicated both positive and negative effects depending on the route of administration. Hamsters given intravenous or intraperitoneal injections of *p*-aminophenol at 100–250 mg/kg showed significant increases in malformed fetuses and resorptions in a dose-dependent manner.[10] However, oral studies using hamsters and topical application of hair dyes containing *p*-aminophenol on rats showed no teratogenic effects.[11]

The ACGIH has not assigned a threshold limit value to *p*-aminophenol.

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2-AMINOPYRIDINE

CAS: 504-29-0

$(NH_2)C_5H_4N$

Synonyms: α-Aminopyridine; α-pyridylamine

Physical Form. Crystalline solid

Uses. Manufacture of pharmaceuticals, especially antihistamines

Exposure. Inhalation; skin absorption

Toxicology. 2-Aminopyridine causes central nervous system effects.

In industrial experience, intoxication has occurred from inhalation of the dust or vapor or by skin absorption after direct contact.[1] Fatal intoxication occurred in a chemical worker who spilled a solution of 2-aminopyridine on his clothing during a distillation; he continued to work in contaminated clothing for 1.5 hours. Two hours later, he developed dizziness, headache, respiratory distress, and convulsions that progressed to respiratory failure and death; it is probable that skin absorption was a major factor in this case.

A nonfatal intoxication from exposure to an undetermined concentration of 2-aminopyridine in air resulted in severe headache, weakness, convulsions, and a stuporous state that lasted several days. A chemical worker exposed to an estimated air concentration of 20 mg/m^3 (5.2 ppm) for approximately 5 hours developed

severe, pounding headache, nausea, flushing of the extremities, and elevated blood pressure, but he recovered fully within 24 hours.

The LD_{50} in mice by intraperitoneal injection was 35 mg/kg; lethal doses in animals also produced excitement, tremors, convulsions and tetany.[1] Fatal doses were readily absorbed through the skin. A 0.2 M aqueous solution dropped in a rabbit's eye was only mildly irritating.[2]

2-Aminopyridine was not mutagenic in a variety of *Salmonella* tester strains with or without metabolic activation.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for aminopyridine is 0.5 ppm (1.9 mg/m^3).

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AMITROLE
CAS: 61-82-5

$C_2H_4N_4$

Synonyms: Aminotriazole; Amitrole-T; Amizol; Azolan; 3-amino-1,2,4-triazole; ATA; Cytrol; Weedazol

Physical Form. White crystalline powder

Uses. Herbicide

Exposure. Inhalation; ingestion

Toxicology. Amitrole has low acute toxicity; in experimental animal studies subchronic exposures were associated with changes in the thyroid and chronic exposures were carcinogenic.

Intentional ingestion of a mixture that contained 20 mg/kg amitrole did not cause any signs of intoxication.[1] In one reported case study, inhalation of a large amount of amitrole-containing herbicide was associated with acute toxic reaction of the lungs.[2] Lung injury was thought to be secondary to direct toxic damage to the alveolar lining cells. The remarkable lack of any other reports describing pulmonary toxicity of this herbicide was noted, in addition to the presence of other chemicals in the herbicide solution.

The LD_{50} values in animal studies are high, indicating very low acute toxicity but varying considerably according to species.[3] The oral LD_{50} in mice was 11,000 mg/kg, whereas 4000 mg/kg was fatal to sheep. No detectable signs of toxicity were noted in rats at 4080 mg/kg.[4] Poisoning in animals is characterized by increased intestinal peristalsis, pulmonary edema, and hemorrhages in various organs.[3]

At a level of 1000 ppm in the diet of rats, significant enlargement of the thyroid could be detected as early as 3 days.[5] At a dietary level of 60 or 120 ppm, there was enlargement of the thyroid within 2 weeks.[6] Morphologic changes were noted in the thyroid of rats fed 10 or 50 mg/kg amitrole for 11–13 weeks.[7] Amitrole is thought to interfere with the formation of thyroxine by inhibiting the peroxidase-dependent iodide oxidation in the thyroid.[1] Suppression of thyroid function leads to further stimulation by the pituitary, with resultant hyperplasia and tumor formation.

Like other antithyroid compounds, or like diets that are low in iodine, continuous exposure for long periods produces adenomatous changes in the thyroid glands of rats.[3] Male and female rats fed diets containing 10 or 100 mg/kg amitrole for life had marked increases in the incidence of thyroid tumors in the high-dose group: benign thyroid tumors in males (45/75 high dose; 5/75 controls) and females (44/75 high dose; 7/74 controls); for

malignant thyroid tumors, the incidence was 18/75 high dose versus 3/75 for controls in males, and females had 28/75 versus none in controls.[8] (The high-dose female group also had an increased incidence of benign pituitary tumors.) Early studies, although limited, also found increased incidence of thyroid tumors in rats chronically fed amitrole.[3,9]

In mice, thyroid and liver tumors were produced after oral administration. Mice administered 1000 mg/kg amitrole by gavage for 4 weeks, followed by diets containing 2192 mg/kg for up to 60 weeks, had an incidence of 64/72 for thyroid tumors and 67/72 for liver tumors.[10] Among 55 male mice, 9 hepatocellular adenomas and 11 hepatocellular carcinomas were observed after a continuous diet of 500 mg/kg for 90 weeks; among the 49 females, there were 5 hepatocellular adenomas and 4 hepatocellular carcinomas. The untreated controls had one hepatocellular adenoma and no carcinomas in the males and females combined.[11] There was no indication of a carcinogenic effect in mice (or hamsters) fed up to 100 mg/kg for life.[8] No skin tumor was observed after weekly topical applications of up to 10 mg amitrole for life.[9]

Very few human data are available to assess the long-term effects of amitrole. In a small-cohort study of Swedish railroad workers, there was a statistically significant excess of all cancers among those exposed to both amitrole and chlorophenoxy herbicides (6 deaths vs. 2.9 expected) but not among those exposed primarily to amitrole (5 deaths vs. 3.3 expected).[12]

The IARC has determined that there is sufficient evidence for the carcinogenicity of amitrole to experimental animals and inadequate evidence for carcinogenicity to humans.[1] It was noted that amitrole produces thyroid tumors in rodents by a nongenotoxic mechanism that involves interference with the functioning of the thyroid peroxidase, resulting in a reduction in circulating thyroid hormone concentration and an increase secretion of thyroid-stimulating hormone.[1] Amitrole would not be expected to produce thyroid cancer in humans exposed to concentrations that do not alter thyroid hormone homeostasis.

No effect on offspring growth or viability was observed in rats given up to 100 mg/kg in the diet for two generations; litter size and weight, as well as postnatal viability, were reduced in the offspring of breeding pairs exposed to 500 mg/kg in the diet.[3]

Amitrole was not genotoxic in bacterial assays and cultured mammalian cells or in rodents exposed *in vivo*; it did induce transformation of Syrian hamster embryo cells *in vitro*.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for amitrole is 0.2 mg/m^3.

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AMMONIA
CAS: 7664-41-7

NH_3

Synonym: Ammonia gas

Physical Form. Colorless gas

Uses. Fertilizer; refrigeration; petroleum refining; blue printing machines; manufacture of fertilizers, nitric acid, explosives, plastics, and other chemicals

Exposure. Inhalation

Toxicology. Ammonia is a severe irritant of the eyes, respiratory tract, and skin.

Exposure to and inhalation of concentrations of 2500–6500 ppm, as might result from accidents with liquid anhydrous ammonia, cause severe corneal irritation, dyspnea, bronchospasm, chest pain, and pulmonary edema that may be fatal. Upper airway obstruction due to laryngeal/pharyngeal edema and desquamation of mucous membranes may occur early in the course and require endotracheal intubation or tracheostomy.[1–3] Case reports have documented chronic airway hyperreactivity and asthma, with associated obstructive pulmonary function changes after massive ammonia exposures.[3,4]

In a human experimental study that exposed 10 subjects to various vapor concentrations for 5 minutes, 134 ppm caused irritation of the eyes, nose, and throat in most subjects and one person complained of chest irritation; at 72 ppm several reported the same symptoms; at 50 ppm two subjects reported nasal dryness; and at 32 ppm only one reported nasal dryness.[2] Surveys of workers have generally found that the maximum concentration not resulting in significant complaints is 20–25 ppm.[2]

Tolerance to usually irritating concentrations of ammonia may be acquired by adaptation, a phenomenon frequently observed among workers who become inured to the effects of exposure; no data are available on concentrations that are irritating to workers who are regularly exposed to ammonia and who presumably have a higher irritation threshold.

Cytogenetic evaluation of workers exposed to ammonia showed increased frequency of chromosome aberrations and sister chromatid exchanges.[5]

In animal studies, pigs exposed at 25, 50, and 100 ppm continuously for 6 days exhibited lethargy and a concentration-related depression of body weight gain.[6] Concentrations greater than 50 ppm altered the pulmonary vascular response to endotoxins.

Liquid anhydrous ammonia in contact with the eyes may cause serious injury to the cornea and deeper structures and sometimes blindness; on the skin it causes first- and second-degree burns that are often severe and, if extensive, may be fatal. Vapor concentrations of 10,000 ppm are mildly irritating to the moist skin, whereas 30,000 ppm or greater causes a stinging sensation and may produce skin burns and vesiculation.[2] With skin and mucous membrane contact, burns are of three types: cryogenic (from the liquid ammonia), thermal (from the exothermic dissociation of ammonium hydroxide), and chemical (alkaline).[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA for ammonia is 25 ppm (17 mg/m^3) with a short-term excursion limit of 35 ppm (24 mg/m^3).

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AMMONIUM CHLORIDE FUME

CAS: 12125-02-9

NH_4Cl

Synonym: Ammonium muriate fume

Physical Form. Odorless fume

Uses. Manufacture of dry cell batteries; component of fluxes in zinc and tin plating; fume is evolved in galvanizing operations; mordant in dyeing and printing; fertilizer; hardener for formaldehyde-based adhesives

Exposure. Inhalation

Toxicology. Ammonium chloride fume is a mild irritant of the eyes and respiratory tract, and repeated inhalation exposure of the fume has been associated with pulmonary sensitization.

Two cases of occupational asthma caused by exposure to soft, corrosive soldering fluxes have been reported.[1] The first case involved a 56-year-old man who developed chest tightness and wheeze 18 months after beginning work making tins. He was using a flux containing ammonium chloride and zinc chloride. A work-related deterioration in mean daily peak expiratory flow was noted that improved when the man was away from work. The second case involved an 18-year-old man who had cough, wheeze, chest tightness, and sneezing while working in a small firm that made and repaired car and truck radiators. Symptoms developed 1 year after he started work at the shop. He also was using a flux containing ammonium chloride and zinc chloride.

The fume (concentrations unspecified) is reported to cause irritation of the eyes, nose, throat, lungs, and skin.[2] No reports are available from animal studies on the toxic effects of fume inhalation. Administered into rabbit eyes, the liquid caused mild to severe irritation.

The 2003 threshold limit value-time-weighted average (TLV-TWA) is 10 mg/m^3 with a short-term excursion level of 20 mg/m^3.

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AMMONIUM PERFLUOROOCTANOATE

CAS: 3825-26-1

$C_8F_{15}O_2H_4N$

Synonyms: Octanoic acid, pentadecafluoroammonium salt; ammonium pentadecafluorooctanoate; ammonium perfluorocaprylate; FC-143

Physical Form. White powder

Uses. Polymerization of fluorinated monomers; surfactant

Exposure. Inhalation

Toxicology. Ammonium perfluorooctanoate is an hepatotoxin in rats; there are no reports of adverse effects in humans.

In workers exposed to airborne levels up to 7.6 mg/m^3, blood levels of organic fluoride were higher than background but there were no adverse health effects attributable to the exposure.[1]

In rats ammonium perfluorooctanoate induced hepatomegaly that was more pronounced in the male than in the female.[2–5] Male rats are thought to be more sensitive to the toxic effects of ammonium perfluorooctanoate because of their slower excretion rate. The rapid excretion by female rats is due to active renal tubular secretion, which is considered to be hormonally controlled by estradiol and testosterone levels. The hepatomegaly was hypertrophic rather than hyperplastic and involved proliferation of peroxisomes.

The LC_{50} for 4 hours in male rats was 980 mg/m^3; this exposure caused an increase in liver size and corneal opacity that diminished over time in survivors.[6] Exposure of male rats to 8 mg/m^3 6 hours/day for 10 of 12 days produced reversible liver weight changes, reversible increases in serum enzyme activities, and liver necrosis. No ocular changes occurred. No observable effects occurred at 1 mg/m^3.

In a 90-day oral study in rhesus monkeys at levels ranging from 3 to 100 mg/kg/day, the gastrointestinal tract and reticuloendothelial system were the sites of toxic effects at 30 and 100 mg/kg/day.[2] Histopathologic effects were seen in the gastrointestinal tract, spleen, lymph nodes, and bone marrow. Unlike rats, sex-related differences were not evident in the monkeys. No tissue changes were observed at 3 or 10 mg/kg/day.

Dermal application of 500 mg for 24 hours to rabbit skin produced mild skin irritation.[7] The dermal LD_{50} was 4300 mg/kg. Dermal application of 200 mg/kg/day to rats for 10 of 12 days caused mild decrease in body weights and increases in serum enzyme activities indicating hepatic effects. The effects were more obvious in males than females, and all findings resolved during a 42-day recovery period.

In a teratology study, rats were exposed from days 6 through 15 of gestation by inhalation 6 hours/day to levels of 0. 0.1, 10, and 25 mg/m^3 and by gavage at 100 mg/kg/day in corn oil.[8] Maternal deaths occurred in the groups given the highest level by each route, and overt toxicity in dams was evident at 10 mg/m^3. A teratogenic response was not demonstrated.

Rats fed diets containing 30 or 300 ppm ammonium perfluorooctanoate for 2 years had increased liver weights with occasional necrosis and an apparent dose-dependent increase in Leydig cell adenomas, but there was no evidence of an increased incidence of hepatocellular carcinoma.[9] In a follow-up study in male mice, 300 ppm in the diet for 2 years caused increases in liver, Leydig cell, and pancreatic acinar cell tumors that may have been associated with the peroxisome-proliferating capabilities of the compound. Ammonium perfluorooctanoate also produced sustained increases in serum estradiol concentrations.[10]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for ammonium perfluorooctanoate is 0.01 mg/m^3 with an A3 animal carcinogen designation and a notation for skin absorption.

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Repeated application of a 4% solution to the anterior surface of one arm of each of five human subjects for 5 days caused no skin irritation.[1]

The oral LD_{50} values were 3900 mg/kg for rats and 5760 mg/kg for mice.[2]

In rats, the intraperitoneal injection of 0.8 g/kg caused the death of 6 of 10 animals; effects were stimulation of respiration and then prostration.[1]

Continuous feeding of 1% (10,000 ppm) in the diet of rats for 105 days caused no effect; 2% in the diet caused growth inhibition, but no histologic effects were observed.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for ammonium sulfamate is 10 mg/m^3.

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AMMONIUM SULFAMATE

CAS: 7773-06-0

$NH_4SO_3NH_2$

Synonyms: Ammate; Amicide

Physical Form. White crystals

Uses. Manufacture of weed-killing compounds and fire-retardant compositions

Exposure. Inhalation

Toxicology. Ammonium sulfamate is of low toxicity; there are no reports of systemic effects in humans.

n-AMYL ACETATE

CAS: 628-63-7

$CH_3COOC_5H_{11}$

Synonyms: Amyl acetic ether; pentyl acetate

Physical Form. Liquid

Uses. As a solvent in lacquers, paints, leather polishes, inks, adhesives, degreasers, and cosmetics

Exposure. Inhalation; minor skin absorption

Toxicology. *n*-Amyl acetate is an irritant of mucous membranes; at high concentrations it

causes narcosis in animals, and it is expected that severe exposure would produce the same effect in humans.

Several grades of technical amyl acetate are known; isoamyl acetate is the major component of some grades, whereas *n*-amyl acetate predominates in others.[1]

In humans exposure to amyl acetate vapor for 3–5 minutes at 200 ppm caused mild eye and nose irritation and severe throat irritation; at 100 ppm slight throat discomfort has been reported.[2]

Inhalation of excessive concentrations may also cause headache, fatigue, excessive salivation, "oppression in the chest and occasional vague nervousness."[3]

Air saturated with 5200 ppm of technical amyl acetate (*n*-amyl acetate the principal component) was fatal to 6 of 6 rats in 8 hours but caused no deaths in 4 hours.[4]

Male mice exposed for 20 minutes to up to 4000 ppm showed changes in posture, decreased arousal, increased tonic/clonic movements, disturbances in gait, delayed righting reflexes, and increased sensorimotor reactivity.[5] On removal from exposure recovery was rapid.

In standardized testing on rabbit eyes, amyl acetate was graded as only slightly injurious.[6] No evidence of delayed contact hypersensitivity due to 20% amyl acetate was observed in repeat-insult skin patch tests of 211 human subjects.[3]

Amyl acetates may be recognized at concentrations of 7 ppm by the fruitlike odor characteristic of esters; the mean olfactory detection threshold is 0.2 ppm.[1,3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for *n*-amyl acetate is 100 ppm (532 mg/m^3).

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***sec*-AMYL ACETATE**
CAS: 626-38-0

$C_7H_{14}O_2$

Synonyms: α-Methyl butyl acetate; 2-pentyl acetate; banana oil

Physical Form. Liquid

Uses. Manufacture of lacquers, artificial leather, photographic film, artificial glass, celluloid, artificial silk, and furniture polish

Exposure. Inhalation

Toxicology. *sec*-Amyl acetate is an irritant of the eyes, mucous membranes, and skin; high concentrations cause narcosis in animals, and severe exposure is expected to produce the same effect in humans.

In humans, exposure to 5000–10,000 ppm for short periods of time caused irritation of the eyes and nasal passages.[1] Exposure to 1000 ppm for 1 hour is expected to produce serious toxic effects.

In guinea pigs, 2000 ppm for 13.5 hours produced no abnormal signs except irritation of the eyes and nose; at 5000 ppm, there was lacrimation after 5 minutes, incoordination in 90 minutes, and narcosis within 9 hours, from which animals recovered. A concentration of 10,000 ppm was fatal after 5 hours.[1]

The *sec*-amyl acetates are more volatile than the primary isomers and appear to be somewhat less toxic. The odor threshold for *sec*-amyl acetate has been determined as 2 ppb in air.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for *sec*-amyl acetate is 125 ppm (665 mg/m^3).

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ANILINE
CAS: 62-53-3

$C_6H_5NH_2$

Synonyms: Aminobenzene; benzenamine; phenylamine

Physical Form. Colorless to light yellow liquid that tends to darken on exposure to air and light.

Uses. Intermediate in chemical synthesis; manufacture of synthetic dyestuffs

Exposure. Inhalation; skin absorption

Toxicology. Aniline absorption causes anoxia due to the formation of methemoglobin.

In early studies, human exposure to vapor concentrations of 7–53 ppm was said to cause slight symptoms, whereas concentrations in excess of 100–160 ppm were associated with serious disturbances if inhaled for 1 hour.[1] Rapid absorption through the intact skin is frequently the main route of entry from direct contact with either the liquid or the vapor.

The formation of methemoglobinemia is often insidious; after skin absorption, the onset of symptoms may be delayed for up to 4 hours.[2] Headache is commonly the first symptom and may become quite intense as the severity of methemoglobinemia progresses. Cyanosis occurs when the methemoglobin concentration is 15% or more. Blueness develops first in the lips, the nose, and the earlobes and is usually recognized by fellow workers. The individual usually feels well, has no complaints, and is insistent that nothing is wrong until the methemoglobin concentration approaches approximately 40%. At methemoglobin concentrations of over 40%, there typically is weakness and dizziness; with up to 70% concentration, there may be ataxia, dyspnea on mild exertion, and tachycardia. Coma may ensue with methemoglobin levels of about 70%, and the lethal level is estimated to be 85–90%.[3] In general, higher ambient temperatures increase susceptibility to cyanosis from exposure to methemoglobin-forming agents.[4]

The development of intravascular hemolysis and anemia due to aniline-induced methemoglobinemia has been postulated, but neither is observed often in industrial practice, despite careful and prolonged study of numerous cases. Occasional deaths from asphyxiation caused by severe aniline intoxication are said to occur. The existence of chronic aniline poisoning is controversial, but some investigators have suggested that continuous exposure to small doses of aniline may produce anemia, loss of energy, digestive disturbance, and headache.[5]

The mean lethal dose by ingestion in humans has been estimated to be between 15 and 30 g, although death has been reported after as little as 1 g.[6] A significant elevation in methemoglobin levels was reported in adult volunteers given 25 mg orally.[6]

Peak methemoglobin levels may occur some hours after exposure, and it has been postulated that metabolic transformation of aniline to phenylhydroxylamine is necessary for the production of methemoglobin.[6] Liquid aniline is mildly irritating to the eyes and may cause corneal damage.[7]

No evidence of embryo-lethal or teratogenic effect was observed in the offspring of

rats dosed with aniline hydrochloride during gestation.[8] Signs of maternal toxicity included methemoglobinemia, increased relative spleen weight, decreased red blood cell count, and hematologic changes indicative of increased hematopoietic activity. Transient signs of toxicity were observed postnatally in the offspring through day 30. In a more recent report, subcutaneous treatment of Wistar rats with aniline hydrochloride on day 15 of gestation at doses ranging from 260 to 650 mg/kg caused a dose-dependent increase in the frequency of cleft palate in the fetuses that paralleled the increase in methemoglobin (maternal hypoxia) in dams.[9]

Aniline hydrochloride was not carcinogenic to mice when administered orally.[10] In one experiment it produced fibrosarcomas, sarcomas, and hemangiosarcomas of the spleen and body cavities in rats fed diets containing 3000 or 6000 mg/kg for 103 weeks.

The high risk of bladder cancer observed originally in workers in the aniline dye industry has been attributed to exposure to chemicals other than aniline.[10] Studies showing significant increase in bladder cancers, such as the one of 1749 rubber antioxidant workers that found 13 cases of bladder cancer vs. 3.61 expected involved significant exposure to chemicals such as *o*-toluidine or contaminants that are considered to be more potent carcinogens based on animal and human studies.[11,12] Epidemiological studies of workers exposed to aniline but to no other known bladder carcinogen have shown little evidence of increased risk; one study showed one death from bladder cancer vs. 0.83 expected in a population of 1223 men producing or using aniline.[10] Nonetheless, NIOSH has released an alert for aniline recommending that exposures be reduced to the lowest possible levels.[13]

In genotoxic assays *in vivo* treatment induced sister chromatid exchanges in the bone marrow of mice, and DNA strand breakage was induced in the liver and kidney of rats.[10] *In vitro* aniline was not mutagenic to bacteria and did not cause DNA damage.[10]

The IARC has determined that evidence for carcinogenicity is limited in animals and inadequate in humans.[10]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for aniline is 2 ppm (7.6 mg/m^3) with a notation for skin absorption and an A3 animal carcinogen with unknown relevance to humans designation.

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ANISIDINE
CAS: 29191-52-4 (o-anisidine: 90-04-0, p-Anisidine: 104-94-9)

$NH_2C_6H_4OCH_3$

Synonyms: Methoxyaniline; aminoanisole

Physical Form. *o*-Anisidine is a yellowish liquid that darkens on exposure to air; *p*-anisidine is a white solid.

Uses. In the preparation of azo dyes; corrosion inhibitor; chemical intermediate

Exposure. Inhalation; skin absorption

Toxicology. Anisidine, *o*-and *p*-isomers, causes anoxia due to the formation of methemoglobin. *o*-Anisidine was carcinogenic in experimental animals.

Workers exposed to 0.4 ppm for 3.5 hours/day for 6 months did not develop anemia, but there were some cases of headache and vertigo that may have been related to the increased levels of methemoglobin and sulfhemoglobin; erythrocytic inclusions (Heinz bodies) were observed and absorption through the skin may have been a contributing factor.[1]

Anisidine is a mild skin sensitizer, and local contact may cause dermatitis.

Mice exposed 2 hours/day at 2–6 ppm for a year developed anemia and reticulocytosis.

The oral LD_{50} of *o*-anisidine is reported to be 2000 mg/kg in rats, 1400 mg/kg in mice, and 870 mg/kg in rabbits. The oral LD_{50} of *p*-anisidine is 1400 mg/kg in rats, 1300 mg/kg in mice, and 2900 mg/kg in rabbits.[2] For both isomers subacute effects included hematologic changes, anemia, and nephrotoxicity.

A significant increase in transitional cell carcinomas of the urinary bladder was found in mice and rats fed diets containing 5000 mg/kg *o*-anisidine hydrochloride for 103 weeks.[3]

The IARC has determined that there is sufficient evidence for the carcinogenicity of *o*-anisidine in experimental animals and that it is possibly carcinogenic to humans.[2] Available data were inadequate to evaluate the carcinogenicity of *p*-anisidine.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for the *o*- and *p*-isomers of anisidine is 0.1 ppm (0.5 mg/m^3).

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ANTIMONY (and Compounds)
CAS: 7440-36-0

Sb

Compounds: Antimony trioxide; antimony trisulfide; antimony trichloride; antimony pentoxide; antimony pentasulfide; antimony pentachloride

Physical form. Silvery-white soft metal

Uses. Constituent of alloys with other metals (tin, lead, copper); sulfides used in compounding of rubber and manufacture of pyrotechnics; trioxide used as a fire retardant in plastics, rubbers, textiles, and paints; chlorides used as coloring agents and as catalysts; fluorides used in organic synthesis and pottery manufacture

Exposure. Inhalation

Toxicology. Antimony is an irritant of the mucous membranes, eyes, and skin; heavy exposure to antimony trioxide and pentoxide is associated with pulmonary injury; antimony trisulfide is considered cardiotoxic. Antimony trioxide is carcinogenic in experimental animals.

Contact of antimony compounds with the skin causes papules and pustules around sweat and sebaceous glands.[1]

Antimony poisoning was reported in 69 of 78 smelter workers during a 5-month period when antimony concentrations of breathing zone samples in the smelter building averaged 10.07–11.81 mg/m^3 of air (range 0.92–70.7 mg/m^3); dermatitis and rhinitis were reported most frequently, but other symptoms included irritation of eyes, sore throat, headache, pain or tightness in chest, shortness of breath, metallic taste, nausea, vomiting, diarrhea, weight loss, and dysosmia.[2]

Symptomless radiographic lung changes resembling the simple pneumoconiosis of coal workers were found in 44 of 262 men exposed to antimony oxide concentrations of 0.5–37 mg/m^3.[1,3] In another roentgenographic study of 51 workers exposed 9 or more years to antimony oxides, there were numerous small opacities densely distributed in the middle and lower lung fields.[4] There were no characteristic pulmonary function abnormalities, but chronic cough was a common symptom. Brief exposures to antimony trichloride, approximately 73 mg Sb/m^3, caused gastrointestinal symptoms as well as irritation of the skin and respiratory tract; urinary antimony ranged up to 5 mg/l.[5]

Six sudden deaths and two deaths due to chronic heart disease occurred among 125 abrasive wheel workers exposed to antimony trisulfide for 8–24 months.[6] At air concentrations averaging over 3.0 mg/m^3, 37 of 75 workers had electrocardiogram changes and 38 had abnormalities in blood pressure. The lack of electrocardiographic changes in the oxide exposures would seem to indicate a special effect of the sulfide.

A mortality study of 1014 men employed between 1937 and 1971 in a Texas antimony smelter found increased mortality from lung cancer (standardized mortality ratio 1.39) and a positive trend in mortality with increasing duration of exposure.[7] The data also suggested some increased mortality from nonmalignant respiratory heart disease in these workers.

Female rats exposed to 4.2 and 3.2 mg/m^3 antimony trioxide 6 hours/day, 5 days/week, for 1 year had lung tumors after an additional year of observation.[8] Similar findings were reported in another study involving heavier exposures; 27% of female rats exposed to 45 mg/m^3 antimony trioxide for 1 year and 25% of females exposed to 38 mg/m^3 antimony ore (mainly antimony trisulfide) developed lung neoplasms.[9] No lung tumors were seen in the male rats exposed to either compound or in controls. On the basis of these studies the IARC has determined that there is sufficient evidence for the carcinogenicity of antimony trioxide in animals and limited evidence for the carcinogenicity of antimony trisulfide.[10]

A subsequent chronic inhalation study in rats using lower exposure levels found no evidence of carcinogenicity.[11] A dose-related increase in cataracts and microscopic changes in the lungs were the primary effects noted from 12 months of exposure at 0.06, 0.51, or 4.5 mg/m^3 followed by a 12-month recovery period.

In a report from Russia, an increase in the number of spontaneous abortions was reported in women exposed to antimony in the workplace[12,13] Exposure levels were not available. No effects were observed in the offspring of rats given low levels of antimony trichloride in the drinking water.

Both positive and negative results have been reported in *in vitro* genotoxic assays of antimony and compounds.[13,14] Antimony triox-

ide was not genotoxic *in vivo* in the mouse bone marrow micronucleus assay or the rat liver DNA repair assay.[14]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for antimony and compounds is 0.5 mg/m^3 as Sb; antimony trioxide production is given an A2-suspected human carcinogen designation with no assigned TLV.

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ANTU (α-NAPHTHYLTHIOUREA)
CAS: 86-88-4

$C_{11}H_{10}N_2S$

Synonyms: α-Naphthylthiourea; α-naphthylthiocarbamide

Physical Form. Blue to gray powder

Uses. Rodenticide

Exposure. Inhalation; ingestion

Toxicology. ANTU dust causes pulmonary edema and pleural effusion in animals.

ANTU is probably not toxic to humans except in large amounts; the lethal dose by ingestion is estimated to be approximately 4 g/kg.[1] In a case of human intoxication by ANTU, 80 g of a rat poison containing 30% ANTU was ingested along with a considerable amount of ethanol; signs attributable to ANTU were prompt vomiting, dyspnea, cyanosis, and coarse pulmonary rales; no pleural effusion occurred, and the pulmonary signs gradually cleared.[1]

Oral administration to rats of 35 mg/kg was fatal to 60% of the animals; effects were labored respiration and muscular weakness;

autopsy revealed pleural and pericardial effusion as well as mild liver damage.[2] Tachyphylaxis or tolerance to the acute toxicity of ANTU has been observed after repeated administrations; intraperitoneal injection of 2.5 mg/kg produced moderate pulmonary edema and large pleural effusions, but two additional 2.5 mg/kg doses at 2-day intervals caused lesser degrees of edema and minimal pleural fluid.[3] Daily doses of 200 mg/kg (20% of the median lethal dose) in rabbits were cumulative, causing death in 5–6 days without pleural effusions.[2]

ANTU was not carcinogenic in rodent feeding studies.[4] Cases of bladder tumors among rat catchers exposed to ANTU have been attributed to β-naphthylamine, a manufacturing impurity of ANTU. In bacterial assays ANTU induced mutations.

Studies on the mechanism of thiourea toxicity have shown that thioureas have a high degree of specificity for pulmonary endothelial cells and that thioureas require metabolic activation before toxic effects are manifested.[5] Reduced glutathione levels have been associated with increased toxicity, but there is no evidence to suggest that the appearance of edema coincides with a decrease in glutathione. Furthermore, the induction of tolerance or resistance is not correlated with an increase in glutathione levels in rats.[5]

The 2003 threshold limit value-time-weighted average (TLV-TWA) for ANTU is 0.3 mg/m^3.

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ARSENIC (and Compounds)
CAS: 7440-38-2

As

Synonyms and Compounds: Grey arsenic; metallic arsenic; arsenic trichloride; arsenic trioxide; arsenic salts

Physical Form. Metallic arsenic is a steel gray brittle metal; arsenic trichloride is an oily liquid; arsenic trioxide is a crystalline solid

Uses/Sources. In wood preservatives; metallurgy for hardening copper, lead, alloys; pigment production; manufacture of certain types of glass; insecticides and fungicides, rodent poison; a by-product in the smelting of copper ores; dopant material in semiconductor manufacture

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Arsenic compounds are irritants of the skin, mucous membranes, and eyes; gastrointestinal effects, peripheral neuropathy, vascular lesions, skin diseases, and various cancers are reported risks of exposure to arsenic compounds.

The degree of toxicity of arsenic is dependent on the form, either inorganic or organic, and the oxidation state of the arsenical.[1] Inorganic arsenicals are generally more toxic than organic, and the trivalent forms are more toxic than the pentavalent.

Acute arsenic poisoning is rare in the occupational setting and results primarily from ingestion of contaminated food and drink.[2] Initial symptoms include burning lips, constriction of the throat, and dysphagia followed by excruciating abdominal pain, severe nausea, projectile vomiting, and profuse diarrhea.[3] Other toxic effects on the liver, blood-forming organs, the central and peripheral nervous systems, and the cardiovascular system may appear.[4] Convulsions, coma, and death follow within 24 hours in severe cases.[3] Levels of exposure associated with acute arsenic toxicity vary with the valency form of the element; trivalent arsenic compounds are the most toxic, presumably because of their avid binding to sulfhydryl groups. For arsenic trioxide the reported estimated lethal dose ranges from 70 to 300 mg.[3,4]

Acute inhalation exposures have resulted in irritation of the upper respiratory tract, even leading to nasal perforations.[4] Occupational exposure to arsenic compounds results in hyperpigmentation of the skin and hyperkeratoses of palmar and plantar surfaces, as well as dermatitis of both primary irritation and sensitization types.[1] Impairment of peripheral circulation and Raynaud phenomenon have been reported with long-term exposure.[5]

Chronic arsenic intoxication by ingestion is characterized by weakness, anorexia, gastrointestinal disturbances, impairment of cognitive function, peripheral neuropathy, and skin disorders. Noncirrhotic portal hypertension, splenomegaly, and bone marrow depression may occur.[6] Arsenic-contaminated drinking water in Taiwan has been one of the factors associated with "blackfoot disease," a progressive loss of circulation in the fingers and toes that leads to gangrene.[1]

Arsenic trichloride is a vesicant and can cause severe damage to the respiratory system on inhalation; it is rapidly absorbed through the skin, and a fatal case after a spill on the skin has been reported.[7] The vapor of arsenic trichloride is highly irritating to the eyes. Some organic arsenicals, such as arsanilates, have a selective effect on the optic nerve and can cause blindness.

Several studies have suggested an association between inorganic arsenic exposure and increased risk of developmental effects (low birth weight and congenital malformations).[8]

In a recent report, adverse pregnancy outcomes including spontaneous abortion, stillbirth, and preterm birth weights were significantly higher in a group of women chronically exposed to arsenic through drinking water.[9] Studies in animals support the view that arsenic is a developmental toxicant causing reduced birth weight, a variety of fetal malformations, and increased fetal mortality. However, in all cases, the doses required to cause these effects resulted in significant maternal toxicity.[8]

In a large number of studies, exposure to inorganic arsenic compounds in drugs, food, and water as well as in an occupational setting have been causally associated with the development of cancer, primarily of the skin and lungs.[1–4] An excess mortality in respiratory cancer has been found among smelter workers and workers engaged in the production and use of arsenical pesticides. It should be noted, however, that in a number of these studies, levels of exposure are uncertain and there is simultaneous exposure to other agents. In a follow-up of 8045 smelter workers, those with the highest estimated exposure and the longest follow-up had a ninefold increase in respiratory cancer mortality.[10]

Another large retrospective cohort study followed 3916 smelter workers and reported an overall standardized mortality ratio of 372.[11] Lung cancer mortality was related to intensity of exposure but not to duration. Histologic types of lung carcinomas were similar to those seen in smokers.

Information on the association of arsenic with skin cancer has primarily involved nonoccupational populations exposed to contaminated drinking water.[4] Ingestion of arsenic has also been associated with lung, liver, bladder, and kidney cancers. Dose-response data for these cancers are available from epidemiological studies of a Taiwanese population exposed for 45 years to high levels of arsenic in the drinking water and involving more than 7000 cases of arsenical disease. For water arsenic

concentrations of 170, 470, and 800 µg/l, the corresponding mortality rate ratios for bladder cancer were 5.1, 12.1, and 28.7 for men and 11.9, 25.1, and 65.4 for women and for kidney cancer were 4.9, 11.9, and 19.6 for men and 4.0, 13.9, and 37.0 for women.[12] An epidemiological study of lung cancer has shown a linear correlation between the standard mortality ratio of lung cancer and the concentration of arsenic found in the urine.

Chronic ingestion of trivalent arsenic in medicinal preparations was also associated with an increased incidence of hyperkeratosis and skin cancer.[4]

There is limited evidence of carcinogenicity in experimental animals. However, in one report arsenic administered for 2 years in the drinking water of female mice was associated with an increased incidence in tumors involving lung, liver, gastrointestinal tract, and skin.[1]

In genotoxic assays inorganic arsenicals are either inactive or weak mutagens but are able to produce chromosomal effects including aberrations and sister chromatid exchange in most test systems.[8] Studies of exposed human have detected higher incidences of chromosomal aberrations in peripheral lymphocytes and increases in the frequency of micronuclei in the oral mucosa cells, urothelial cells, and peripheral blood lymphocytes.[8,13]

Regarding cancer, potential mechanisms include genotoxicity, altered DNA methylation, oxidative stress, altered cell proliferation, cocarcinogenesis, and tumor promotion.[14]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for arsenic, elemental, and inorganic compounds (except arsine) as As is 0.01 mg/m^3 with an A1-confirmed human carcinogen designation.

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ARSINE
CAS: 7784-42-1

AsH_3

Synonyms: Arsenic hydride, arseniurretted hydrogen; arsenous hydride; hydrogen arsenide

Physical Form. Colorless, heavier-than-air gas

Uses/Sources. In the electronics industry to manufacture gallium arsenide and gallium arsenide phosphide for semiconductors and as a dopant; produced accidentally as a result of generation of nascent hydrogen in the presence of arsenic or by the action of water on a metallic arsenide

Exposure. Inhalation

Toxicology. Arsine is a severe hemolytic agent; abdominal pain and hematuria are cardinal features of arsine poisoning and are frequently accompanied by jaundice.

Arsine is the most acutely toxic form of arsenic.[1] It binds with oxidized hemoglobin, causing profound hemolysis of sudden onset.[2] Inhalation of 250 ppm may be fatal within 30 minutes, whereas 10–50 ppm may cause anemia and death with more prolonged exposure. Human experience has indicated that there is usually a delay of 2–24 hours after exposure before the onset of headache, malaise, weakness, dizziness, and dyspnea, with abdominal pain, nausea, and vomiting.[4–7] Dark red urine is frequently noted 4–6 hours after exposure. This often progresses to brown urine, with jaundice appearing at 24–48 hours after exposure.

An unusual bronze skin color has been noted in some patients; pigmentation of the skin and mucous membranes is more often described as ordinary jaundice and is seen in most poisoning cases. Oliguria or anuria, the most serious manifestation, may become manifest before the third day. In fatal cases, death may result from renal shutdown. Kidney failure occurs as extensive lysis by-products precipitate in the tubules and/or from hypoxic damage resulting from the reduced oxygen-carrying capacity of blood.[3] Other tissues at risk from hemolysis, anemia, and sludging of red blood cell debris within the microcirculation are the myocardium, liver, marrow, lungs, and skeletal muscles.[3] Massive hemolysis that persists for several days may produce hyperkalemia, which can result in cardiac arrest.[8] Reticulocytosis and leukocytosis are expected.[4–7] Normal red blood cell fragility and a negative Coombs test are observed. Plasma hemoglobin values of greater than 2 g/100 ml are reported. Symptoms of arsenic poisoning, in addition to those of arsine, may be present. In two reported cases, arsenic encephalopathy with extreme restlessness, memory loss, agitation, and disorientation occurred several days after an acute exposure and lasted 10 days.[6] Peripheral neuropathy appeared within a few weeks, and symptoms included numbness of the hands and feet, severe muscle weakness, and photophobia.[6]

In a report of chronic arsine poisoning in workers engaged in the cyanide extraction of gold, there was severe anemia in the absence of other signs and symptoms.[9] Hemoglobin values ranged as low as 3.2 g/100 ml; marked basophilic stippling was observed. Previous exposure to trace amounts of arsine for a period of 8 months was documented. It appears that in very small concentrations arsine exerts a cumulative effect.[4]

Inhaled arsine is oxidized to form elemental trivalent arsenic (As^{3+}) and arsenous oxide (As_2O_3), two human carcinogens.[10] Excess cancers from trivalent arsenic and arsenic trioxide have been associated with cumulative lifetime arsenic exposure. Exposure to arsine above 0.004 ppm is associated with increased urinary arsenic excretion, indicating exposure to arsenic. Current exposure limits may not prevent potential chronic toxicity.[10]

Animal studies have also shown that cumulative exposure to small amounts of arsine may cause deleterious effects. In rats repeated exposure to 0.025 ppm caused significant anemia

whereas a single exposure to 0.5 ppm caused no effects on the hematopoietic system.[11]

Arsine, at concentrations that induced maternal toxicity in rats and mice, did not affect end points of developmental toxicity.[12]

Arsine is nonirritating with a garlic-like odor. Warning properties of exposure to hazardous concentrations are inadequate.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for arsine is 0.05 ppm (0.16 mg/m^3).

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ASBESTOS
CAS: 1332-21-4

Amosite—CAS: 12173-73-5
Chrysotile—CAS: 12001-29-5
Crocidolite—CAS: 12001-28-4

Synonyms: Asbestos is a generic term applied to a number of hydrated mineral silicates including amosite, chrysotile, tremolite, actinolite, anthophyllite, and crocidolite

Physical Form. Fibers of various sizes, colors and textures

Uses. Thermal and electrical insulation; fireproofing; cement products

Exposure. Inhalation

Toxicology. Asbestos causes chronic fibrotic lung disease (asbestosis), pleural plaques and thickening, and cancers of the lungs, pleura, and peritoneum.

Asbestosis is a disorder characterized by a diffuse interstitial pulmonary fibrosis, at times including pleural changes of fibrosis and calcification.[1] Chest X ray reveals a granular change chiefly in the lower lung fields; as the condition progresses the heart outline becomes shaggy, and irregular patches of mottled shadowing may be seen. Typically, the patient exhibits restrictive pulmonary function. Accompanying clinical changes may include fine rales, finger clubbing, dyspnea, dry cough, and cyanosis.

The onset of asbestosis is dependent on intensity of dust exposure, length of exposure,

and the physical and chemical properties of the asbestos fiber.[2] In general, the grade of pulmonary fibrosis relates to the fiber burden carried by the lungs.[3] Fiber morphology is also important. Alveolar macrophages, which normally phagocytize foreign bodies deposited in the lungs, seek to engulf the asbestos fibers and remove them. The macrophages are unable to remove long fibers in this manner, which results in an ongoing focal inflammatory response. Ultimately, epithelial cells are replaced by fibrous tissue, resulting in a progressive loss of lung compliance and respiratory function. Occasionally, asbestosis may develop fully in 7–9 years and may cause death as early as 13 years after first exposure. Usually, however, pneumoconiosis becomes evident 20–40 years after the first exposure to asbestos. Once established, asbestosis progresses even after exposure has ceased.[1] Increased risk of ischemic heart disease has also been associated with asbestosis because of impaired lung function.[4]

The pleura may also be affected by asbestos. Often there is thickening of the visceral pleura from extension of the parenchymal inflammation. The parietal pleura may show patches of severe thickening, particularly over the diaphragm and the lower portions of the chest wall, resulting in the so-called pleural hyaline plaques. These may be seen by X ray, especially if calcified. The health significance of pleural abnormalities is not precisely defined, but many investigators consider the pleural plaques to be essentially benign.[5] In some cases, however, pleural thickening can lead to decreased ventilatory capacity with severe consequences. Signs of lung fibrosis and increased mortality associated with asbestosis or nonmalignant respiratory disease have been reported in occupationally exposed workers with cumulative exposures as low as 15–70 f-yr/ml for signs of lung fibrosis and 32–1271 f-yr/ml for asbestosis-associated mortality.[5]

Bronchogenic carcinoma and mesothelioma of the pleura and peritoneum are causally associated with asbestos exposure; excesses of cancer of the stomach, colon, and rectum have also been observed.[5] Among 632 asbestos workers observed from 1943 to 1967, there were 99 excess deaths (above that expected on the basis of the US white male population) for three types of malignancies—bronchogenic (63), gastrointestinal (26), and all other sites combined (10).[1]

Mesothelioma, a relatively rare and rapidly fatal neoplasm seen chiefly in crocidolite workers, may occur without radiological evidence of asbestosis at exposure levels lower than those required for prevention of radiologically evident asbestosis.[1] Mesothelioma can occur after a short intensive exposure; cases in children under 19 years of age indicate that the latent time period for development may be shorter than first estimated, although the disease may occur after a very limited exposure 20–30 years earlier.

Fiber characteristics, including durability, harshness, surface chemistry, and dimensions appear to play a role in the carcinogenic process. Width and length of fibers are important parameters in determining the carcinogenic potential of various asbestos forms, where a fiber is defined as a particle with a length-to-width ratio of at least 3:1 and a length of 5 μm or more. In animal studies, fibers longer than 8 μm and narrower than 0.25 μm were more closely linked to pleural tumors irrespective of fiber type.[6] In general, fibers with widths greater than 1 μm are not implicated in the occurrence of lung cancer or mesothelioma.[7]

Cigarette smoke is strongly implicated as a cocarcinogen among asbestos workers.[8] The incidence of lung carcinoma among nonsmoking asbestos workers is not significantly greater than that of non-asbestos workers, whereas asbestos workers who smoke have a much higher incidence. Cigarette-smoking asbestos workers have approximately 15 times the risk of developing lung cancer compared with nonsmoking asbestos workers.[9]

Asbestos has caused a variety of chromosomal aberrations both *in vivo* and *in vitro*.[5]

No obvious developmental effects were observed in animals exposed to high levels of asbestos during gestation.[4]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for all forms of asbestos is 0.1 fiber/cc (for fibers

>5 µm in length, with an aspect ratio of ≥3 : 1); there is an A1 confirmed human carcinogen designation.

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ASPHALT FUMES
CAS: 8052-42-4

Synonyms: Asphaltic bitumen; asphaltum; petroleum asphalt; bitumen

Physical Form. Brownish-black viscous liquid or solid composed essentially of hydrocarbons; residue from the evaporation of the lighter hydrocarbons from petroleum

Uses/Sources. Asphalt fumes arise from asphalt used for road construction, roofing, and coating of construction materials and in association with the production of asphalt from petroleum; in asphalt-based paints

Exposure. Inhalation; skin contact

Toxicology. Acute exposure to asphalt fumes causes irritative effects. Certain extracts of asphalt have caused a carcinogenic skin response in experimental animals.

The chemical composition of vapors and fumes from asphalt products is variable and depends on the crude petroleum source, type of asphalt, temperature, and extent of mixing.[1] Therefore, the adverse effects from asphalt may also vary considerably depending on the source of exposure.

After acute exposure, subjective symptoms including abnormal fatigue, reduced appetite, and throat and eye irritation have been reported.[2] Skin irritation, pruritus, and occasionally rashes have also been described in asphalt workers. In a study of road repair and construction workers symptoms increased with increasing concentration of asphalt fumes and with increasing asphalt temperature. In another report of female workers in a commercial lighting factory there was a causal association between exposure to asphalt fumes, irritative symptoms (nausea, headache, fatigue, skin rashes, and eye, nose and throat irritation), and macrothrombocytosis (enlarged platelets), which reversed with a reduction of exposure.[3]

Although a causal relationship cannot be established, recent studies have suggested an association between asphalt fume exposure and acute lower respiratory tract symptoms including coughing, wheezing, and shortness of breath.[1]

Epidemiological studies have reported varying results. A meta-analysis of studies involving pavers and highway workers exposed to asphalt did not find overall evidence for lung cancer among pavers.[4] In contrast, studies of roofers have generally demonstrated an excess number of lung cancer cases.[1] The conflicting evidence in epidemiological studies reflects the difficulties in establishing the exact nature of the material to which the workers are exposed and in ensuring that the exposure is to asphalt alone. Cohorts of workers such as roofers are often also exposed during their careers to asbestos and coal tar pitches, which are generally considered to be more potent carcinogens.[1,5]

A few studies have reported an association between bladder and renal cancers and occupations having the potential for exposures to asphalt.[1] In an historical cohort study of 1320 workers in the asphalt industry, there was a significant increase in brain cancer [standardized mortality ratio (SMR) 500] but not in respiratory, bladder, or gastrointestinal cancer.[6] Of 679 Danish men who were heavily exposed to asphalt, significant increases occurred in the incidences of cancer of the mouth (SMR 1111), esophagus (698), rectum (318), and lung (344).[7]

A subsequent mortality study of this same cohort found significant increases for death due to lung cancer.[8] (Mortality from noncarcinogenic respiratory diseases including bronchitis, emphysema, and asthma also occurred in excess.)

In mice skin-painting studies, skin tumors were produced by steam-refined petroleum bitumens, an air-refined bitumen in toluene, two cracking residue bitumens, and a pooled mixture of steam- and air-blown petroleum bitumens.[5] In contrast, standard roofing petroleum asphalts produced no tumors.

There was a fivefold range in mutagenicity in fumes from asphalts derived from a variety of crude oils, and the asphalts were far less mutagenic than coal tar fumes.[9]

NIOSH has determined that some workers exposed to asphalt fume are at an elevated risk for lung cancer; however, it is uncertain whether this excess is related to asphalt or other carcinogens in the workplace.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for asphalt fumes is 5 mg/m^3.

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ATRAZINE
CAS: 1912-24-9

$C_8H_{14}ClN_5$

Synonyms: 2-Chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine; 6-chloro-*N*-ethyl-*N*′-(1-methylethyl)-1,3,5-triazine-2,4-diamine

Physical Form. Colorless, crystalline solid

Uses. Herbicide

Exposure. Inhalation

Toxicology. The acute toxicity of atrazine to animals is low.

The oral LD_{50} in rats was 3080 mg/kg, and the dermal LD_{50} in rabbits was 7500 mg/kg.[1] There was minimal irritation on rabbit skin and moderate irritation when placed in the rabbit eye. No human skin or eye irritation has been reported.[2]

Cohort studies of agricultural chemical production workers found decreased mortality from all cancers among workers who had probable exposure to atrazine.[3] Findings of an increased risk of non-Hodgkin lymphoma among farmers could not be attributed to atrazine exposure when adjustment was made for other pesticide exposure.[3]

Atrazine was not carcinogenic to mice or Fischer rats after oral administration in the diet.[3] An increase incidence of mammary tumors has been found in female Sprague-Dawley females treated similarly. The IARC has determined that the mammary tumors associated with atrazine exposure involve a mechanism that is non-DNA-reactive and hormonally mediated. They further stated that this mechanism is not relevant to humans. The IARC concluded that there was sufficient evidence for the carcinogenicity of atrazine in experimental animals and inadequate evidence of carcinogenicity in humans.[3]

In a teratology study, oral doses of 0, 10, 70, or 700 mg/kg/day were given to rats on days 6 through 15 of gestation and rabbits were given oral doses of 0, 1, 5, or 75 mg/kg/day on days 7 through 19 of gestation.[4] Maternal toxicity was seen in rats at 70 mg/kg and in rabbits at 5 mg/kg. Fetal toxicity was seen in rats at 70 mg/kg and in rabbits at 75 mg/kg. Teratogenesis was not demonstrated at any of the treatment levels.

When rats were administered atrazine in drinking water at 0.1, 0.2, or 0.5 g/l for 1 or 3 weeks, they excreted as the principal metabolite 2-chloro-4-ethylamino-6-amino-s-triazine.[5] Atrazine and its metabolites have been shown to alter the activity of some testosterone-metabolizing enzymes in the rat pituitary and hypothalamus and to decrease hormone-receptor binding in the prostate.[6]

Atrazine was not mutagenic in bacteria and did not cause chromosomal aberrations in cultured rodent cells; it did induce DNA strand breaks in stomach, liver, and kidney cells of rats treated orally.[6]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for atrazine is 5 mg/m^3.

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AZINPHOS-METHYL
CAS: 86-50-0

$C_{10}H_{12}N_3O_3PS_2$

Synonyms: *O*,*O*-dimethyl-*S*-(4-oxo-1,2,3-benzotriazin-3(4H)-yl methyl phosphorothioate; Guthion; Methyl Guthion; Gusathion

Physical Form. White crystalline solid

Uses. Acaricide; insecticide

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Azinphos-methyl is an indirect inhibitor of cholinesterase.

Dosages given to volunteers for approximately 30 days ranged from 4.0 to 20 mg/person/day and did not produce clinical effects or a significant change in cholinesterase levels. In a study of eight workers engaged in the formulation of a Guthion wettable powder and exposed to concentrations up to 9.6 mg/m^3, the lowest activity of cholinesterase in blood serum was 78% of the value before exposure; there were no signs or symptoms of illness.[2]

It is expected that severe exposure would produce a broad spectrum of clinical effects indicative of massive overstimulation of the cholinergic system including headache, weakness, dizziness, blurred vision, respiratory difficulty, paralysis, convulsions, and coma.

In animals azinophos-methyl has an acute oral toxicity similar to that of parathion, although the acute dermal toxicity is less than that of parathion.[1]

Rats that inhaled azinphos-methyl at 4.72 mg/m^3, 6 hours/day, 5 days/week for 12 weeks showed significant depression of red blood cell and plasma cholinesterases; concentrations of 0.195 and 1.24 mg/m^3 were without effect.[3]

Prolonged dietary exposure of rats (13 weeks) produced biochemical and neurobehavioral evidence of cholinergic toxicity with neurobehavioral effects evident only when there was more than 20% inhibition of cholinesterase activity.[4] Rats fed azinophos-methyl for 2 years at rates of 50 ppm and later 100 ppm had normal growth rates, but plasma, red blood cell and brain cholinesterase activities were depressed in the females.[5] Dietary levels of 5 ppm were without effect, and no tumorigenic activity was noted at any dosage level. Dogs receiving 300 ppm in their feed had tremors, weakness, lethargy, and some weight loss; 5 ppm administered in the feed for 2 years was without effect on cholinesterase levels. In a chronic feed study there was suggestive evidence of carcinogenicity in male rats based on neoplasms of the thyroid and pancreatic islets; azinphos-methyl was not carcinogenic in female rats or mice of either sex.[6]

No selective developmental effects were observed in rats or mice administered up to 5 mg/kg/day during gestation.[7] In another report there was no effect on fetal cholinesterase even at doses that caused significant inhibition of maternal cholinesterase in rats administered azinphos-methyl by oral gavage on gestation days 6–15; clinical effects in dams were associated with cholinesterase inhibition greater than 20%. Despite maternal toxicity no embryotoxicity was observed.[8]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for azinphos-methyl is 0.2 mg/m^3 with a notation for skin absorption.

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BARIUM (and Compounds)
CAS: 7440-39-3

Ba

Compounds: Soluble—barium nitrate, barium sulfide, barium chloride, barium hydroxide, barium acetate; insoluble—barium sulfate

Physical Form. Elemental barium is a silver white metal; many of the compounds are white powders or crystals.

Uses. Catalyst for organic reactions; lubricating oil additive; rat poison; manufacture of paper electrodes; in fireworks; in electroplating; in medicine as a radiopaque substance for X-ray diagnosis

Exposure. Inhalation; ingestion

Toxicology. Certain compounds of barium are toxic to the cardiovascular, respiratory, gastrointestinal, hepatic, and renal systems in humans and animals.

The toxicity of barium compounds depends on their solubility, with the more soluble forms being more toxic than the relatively insoluble forms, which are inefficient sources of Ba^{2+} ions.[1]

Inhalation of insoluble barium-containing dusts may produce a benign pneumoconiosis, termed baritosis.[2] The condition is without clinical significance. Characteristic X-ray changes are those of small, extremely dense circumscribed nodules evenly distributed throughout the lung fields reflecting the radiopacity of the barium dust. Exposure of workers to concentrations ranging to 92 mg/m^3 of barium sulfate caused no abnormal signs or symptoms including no interference with lung function or liability to develop pulmonary or bronchial infection.[3] Ingestion of insoluble barium compounds also presents no problems to health, barium sulfate being widely used as a contrast agent in radiography.[4]

Barium ion is a muscle poison causing stimulation and then paralysis. Initial symptoms are gastrointestinal, including nausea, vomiting, colic, and diarrhea, followed by myocardial and general muscular stimulation with tingling in the extremities.[2] Severe cases continue to loss of tendon reflexes, general muscular paralysis, and death from respiratory arrest or ventricular fibrillation. Threshold of a toxic dose in humans is reported to be about 0.2–0.5 g Ba absorbed from the gut; the lethal dose is 3–4 g Ba.

In animal studies, rats receiving 110 mg barium/kg body weight in the drinking water as barium chloride dihydrate for 15 days had no clinical findings of toxicity. In female mice administered 85 mg/kg/day and in male mice given 70 mg/kg/day in the drinking water, for the same time period, there was no histopathologic evidence of toxicity, although relative liver weights of the dosed animals were significantly greater than those of controls.[5] In 13-week studies in mice, liver weights were lower than controls at doses above 100 mg/kg/day; at doses of 450 mg/kg/day and 495 mg/kg/day in males and females, respectively, there was multifocal to diffuse nephropathy charac-

terized by tubule dilation, regeneration, and atrophy. In 2-year studies there were no chemical-related increased incidences of neoplasms in mice or rats receiving up to 2500 ppm barium chloride dihydrate in the drinking water.[5] There were dose-related increased incidences of nephropathy in the mice.

Barium compounds have not shown mutagenic potential in *in vitro* assays.[6]

In a mating trial, no adverse anatomic effects were observed in the offspring of rats or mice receiving up to 4000 ppm in the drinking water, although rat pup weight was reduced. Reproductive indices in rats and mice were unaffected.[7]

The barium ion is a physical antagonist of potassium, and it appears that the symptoms of barium poisoning are attributable to Ba^{2+}-induced hypokalemia.[2] The effect is probably due to a transfer of potassium from extracellular to intracellular compartments rather than to urinary or gastrointestinal losses. Signs and symptoms are relieved by intravenous infusion of K^+.[2]

Barium hydroxide and barium oxide are strongly alkaline in aqueous solution, causing severe burns of the eye and irritation of the skin.[8]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for barium, and soluble barium compounds, as Ba is 0.5 mg/m^3; for barium sulfate it is 10 mg/m^3 for total dust containing no asbestos and <1% silica.

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BAUXITE
CAS: 1318-16-7

$Al_2O_3 \cdot 2H_2O$

Synonym: Beauxite

Physical Form. Dust (red, brown, or yellow)

Uses. Ore for production of alumina; adsorbent in oil refining

Exposure. Inhalation

Toxicology. Bauxite can be considered to be a nuisance particulate; long experience with mining and refining of bauxite has not revealed significant adverse health effects.

Nuisance particulates have little adverse effect on lungs and do not produce significant

organic disease or toxic effect when exposures are kept under reasonable control.[1] However, when inhaled in excessive amounts all dusts may be expected to evoke some cellular response. According to ACGIH, the lung tissue reaction caused by inhalation of nuisance particulates has the following characteristics: 1) The architecture of the air spaces remains intact. 2) Collagen (scar tissue) is not formed to a significant extent. 3) The tissue reaction is potentially reversible.

In one case report of a 70-year-old worker exclusively exposed to the dust of raw bauxite, deposits of bauxite were found in the lungs in areas of mild pulmonary fibrosis.[2] There were no clinical symptoms, and it is not clear whether the fibrosis was a response to the bauxite or whether the bauxite accumulated in preexisting fibrotic areas.

No serious adverse effects on respiratory health as determined by self-reported symptoms and spirometry were found in current employees at three bauxite mines in Australia.[3]

The nuisance dust aspect of bauxite is in sharp contrast to the limited industrial situation where lung injury was reported in Canadian workers, who in the 1940s engaged in the manufacture of alumina abrasives in the virtual absence of fume control.[4,5] Fusing of bauxite at 2000°C gave rise to a fume composed of freshly formed particles of amorphous silica and aluminum oxide. Despite the poor choice of the term—bauxite fume pneumoconiosis—sometimes used to describe the disease, scientific opinion favors the silica component as the probable toxic agent. It should be emphasized that bauxite from some sources may contain small amounts of silica.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for bauxite is 10 mg/m^3.

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BENOMYL
CAS: 17804-35-2

$C_{14}H_{18}N_4O_3$

Synonyms: Methyl 1-(butylcarbamoyl)-2-benzidimidazolecarbamate; Benlate; Benex

Physical Form. White to tan crystalline solid

Uses. Fungicide; ascaracide

Exposure. Inhalation; skin contact

Toxicology. Benomyl causes dermatitis and dermal sensitization; in experimental animals it is a reproductive toxin and teratogen.

Contact dermatitis has been reported in Japanese women who worked in a greenhouse where benomyl had been used.[1] Eruptions on the backs of the hands and on the forearms consisted of redness and edema. Cases of dermal sensitization have also been reported.[2]

In animal studies benomyl has low acute toxicity.[2] The oral LD_{50} for rats was greater than 10 g/kg, and the dermal LD_{50} in rabbits was also greater than 10 g/kg.[3] There was mild irritation when benomyl was placed on the skin of the rabbit or in the rabbit eye.

In a 90-day inhalation study, equal groups of male and female rats were exposed nose-only 6 hours/day, 5 days/week, to levels of 0, 10, 50, or 200 mg/m^3.[4] At 45 days half the animals were killed and necropsied. Degeneration of the olfactory epithelium was observed in all the males and 8 of 10 females at the highest dose level. Two of 10 males at the 50 mg/m^3 level had less severe olfactory degeneration. After 90 days of exposure, the remainder of the animals were killed and findings were essentially the same as seen at the end of 45 days. No other effects were observed. In a follow-up to this study, it was determined that the olfactory epithelial damage reported after inhalation exposure was specific to the route of exposure because the nasal cavity was not a target after dietary administration of benomyl.[5] Rats fed diets containing 0, 5000, 10,000, or 15,000 ppm benomyl for 32 days only had toxicity in the form of decreased body weight gain and food consumption at the two highest dose levels.

In another study mice were given diets containing 0, 500, 1500, 5000, or 7500 ppm benomyl for 2 years. An oncogenic response was reported in the livers of male mice dosed at 500 and 1500 ppm but not in the 5000- to 7500-ppm group; an increase in nonmalignant liver tumors was observed in all female treatment groups.[6] At this time there does not appear to be any conclusive evidence that benomyl is carcinogenic.

In a teratology study, female rats were administered 62.5 mg/kg beginning at day 6 of gestation.[7] Fetuses examined at day 16 or day 20 showed a high incidence of craniocerebral anomalies including hydrocephalus. In another study, male rats were gavaged daily with 0, 1, 5, 15, or 45 mg/kg/day.[8] After 76–79 days the animals were evaluated for reproductive endpoints. At the highest dose level minimal to moderate changes were observed including decreased testis weight and sperm production. At 62 days the males had been mated with females and reproductive performance was not affected.

Benomyl was genotoxic, causing chromosome aberrations *in vitro* and *in vivo*, but it does not directly act with DNA.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for benomyl is 0.84 ppm (10 mg/m^3).

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BENZ[*a*]ANTHRACENE
CAS: 56-55-3

$C_{18}H_{12}$

Synonyms: BA; benzanthracene; 1,2-benz(*a*)anthracene; benzo(*a*)anthracene; 2,3-benzophenanthrene; naphthanthracene; tetraphene

Physical Form. Solid; often associated with or adsorbed onto ultrafine airborne particulate matter

Sources. Benz[*a*]anthracene is a major component of the total content of polynuclear aromatic hydrocarbons, also known as polycyclic aromatic hydrocarbons; human exposure occurs primarily through smoking of tobacco, inhalation of products of incomplete organic combustion such as automobile exhaust, and ingestion of food contaminated by combustion effluents such as those that are smoked or barbecued.

Exposure. Inhalation

Toxicology. Benz[*a*]anthracene (BA) is carcinogenic to experimental animals.

The IARC considers that there is "sufficient evidence" that BA is carcinogenic to experimental animals.[1] BA has produced carcinogenic results in the mouse by gavage, intraperitoneal, subcutaneous, or intramuscular routes of administration. It caused hepatomas and lung adenomas after gavage administration of 15 doses of 1.5 mg each over a period of 5 weeks early in the lifetime of the mice.[2]

BA undergoes metabolism in animals and humans to intermediates responsible for its toxicity. These metabolic intermediates include arene oxides, dihydrodiols, and diol epoxides such as BA 3,4-dihydrodiol and BA 3,4-diol-1,2-epoxide.[3]

BA is a complete carcinogen for the mouse skin. A 0.2% solution of BA in dodecane three times weekly produced skin tumors in 11 of 21 animals with an average latent period of 61 weeks, whereas a 1% solution produced tumors in 17 of 22 animals with an average latent period of 42 weeks.[4]

BA's metabolites are genotoxic in the Ames mutation test and caused unscheduled DNA synthesis in primary rat hepatocytes.[5,6] In an *in vivo* mutagenic assay, male CD rats (6/group) were dosed three times with BA over a 24-hour interval by intratracheal instillation.[7] Lung cells were enzymatically separated and used to determine the frequency of DNA adducts, sister chromatid exchanges (SCEs), and micronuclei. BA induced DNA adducts, SCEs, and micronuclei in this rat lung cell system.

Benz(*a*)anthracene is designated an A2-suspected human carcinogen by ACGIH and has no assigned threshold limit value.

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BENZENE
CAS: 71-43-2

C_6H_6

Synonyms: Benzol; cyclohexatriene

Physical Form. Colorless liquid

Uses. Intermediate in the production of styrene, phenol, cyclohexane, and other organic chemicals; manufacture of detergents, pesticides, solvents, and paint removers; found in gasoline

Exposure. Inhalation; skin absorption

Toxicology. Acute benzene exposure causes central nervous system depression; chronic exposure causes bone marrow depression leading to aplastic anemia and is also associated with an increased incidence of leukemia.

Human exposure to very high concentrations, approximately 20,000 ppm, is fatal in 5–10 minutes.[1–3] Concentrations of 7500 ppm are dangerous to life within 30 minutes. Convulsive movements and paralysis followed by unconsciousness follow severe exposures. Brief exposure to concentrations in excess of 3000 ppm is irritating to the eyes and respiratory tract; continued exposure may cause euphoria, nausea, a staggering gait, and coma. Inhalation of lower concentrations (250–500 ppm) produces vertigo, drowsiness, headache, and nausea, whereas 25 ppm for 8 hours is without clinical effect.

The most significant toxic effect of benzene exposure is injury to the bone marrow. Chronic exposure to low concentrations may produce reversible decreases in blood cell numbers.[4] Long-term exposures to higher concentrations lead to the onset of irreversible bone marrow depression. Clinically, an initial increase followed by a decrease in erythrocytes, leukocytes, or platelets is observed, with progression to anemia, leukopenia, and/or thrombocytopenia, respectively.[3] If pancytopenia (i.e., the depression of all three cell types) occurs and is accompanied by bone marrow necrosis, the syndrome is termed aplastic anemia. The hypocellularity varies greatly from conditions in which the marrow is completely devoid of recognizable hematopoietic precursors to those in which the precusors of only one cell line are absent or arrested in their development.[5] Typical symptoms may include light-headedness, headache, loss of appetite, and abdominal discomfort. With more severe intoxication, there may be weakness, blurring of vision, and dyspnea on exertion; the mucous membranes and skin may appear pale, and a hemorrhagic tendency may result in petechiae, easy bruising, epistaxis, bleeding from the gums, or menorrhagia.[6] The most serious cases of aplastic anemia succumb within 3 months of diagnosis because of infection or hemorrhage.[7]

The mechanism of benzene-induced toxicity appears to involve the concerted action of several benzene metabolites.[1,8] Benzene is metabolized, primarily in the liver, to a variety of hydroxylated and opened-ring products that are transported to the bone marrow, where secondary metabolism occurs. Metabolites may induce toxicity both by covalent binding to cellular macromolecules and by inducing oxidative damage. Metabolites may also inhibit stromal cells, which are necessary to support growth of differentiating and maturing marrow cells.[1]

Numerous case reports and epidemiological studies suggest a leukemogenic action of benzene in humans—the leukemia tending to be acute and myeloblastic in type, often following aplastic changes in the bone marrow. Acute myelocytic leukemia may be preceded by myelodysplastic syndrome, a preleukemic state characterized by abnormal marrow architecture, inadequate hematopoiesis, and many cells with chromosome damage.[4] Benzene may also induce chronic types of leukemia.[9]

One study indicated a fivefold excess of all leukemias and a tenfold excess of myelomonocytic leukemia among benzene-exposed workers as compared with the US Caucasian male population.[10] Among shoemakers chronically exposed to benzene, the annual incidence of leukemia was 13.5 per 100,000, whereas the incidence in the general population was 6 per 100,000.[11] Four cases of acute leukemia were reported in shoemakers exposed to concentrations of benzene up to 210 ppm for 6–14 years; two of the four had aplastic anemia before leukemia; three of the four cases of leukemia were of the acute myeloblastic type; the fourth patient developed thrombocythemia in the second year after an episode of aplastic anemia, and acute monocytic leukemia developed later.[12]

A retrospective cohort study in China of 28,460 benzene-exposed workers found a leukemia mortality rate of 14 per 100,000 person-years in the benzene cohort and 2 per 100,000 person-years in the control cohort.[13] The standardized mortality ratio (SMR) was 574, and the mean latency period for induction of benzene leukemia was 11.4 years. Concentrations in the workplace where the patients had been employed were reported to range from 3 to 300 ppm but were mostly in the range of 16 to 160 ppm. The SMR in this study was similar to that in a study of two pliofilm manufacturing plants with 748 workers and exposures ranging from 16 to 100 ppm (SMR = 560).[14] In another report, a mortality update through 1982 for 956 employees exposed to benzene, there was a nonsignificant excess of total death from leukemia based on four observed cases; however, all four cases involved myelogenous leukemias, which represented a significant excess in this subcategory.[15]

Persons with aplastic anemia due to benzene exposure have been found to be at a much greater risk for developing leukemias. A follow-up of 51 benzene-exposed workers with pancytopenia revealed 13 cases of leukemia.[16] The cumulative incidence of leukemia among individuals with clinically ascertained benzene hemopathy has ranged from 10% to 17% in various studies.[17]

The IARC has concluded that epidemiological studies have established the relationship between benzene exposure and the development of acute myelogenous leukemia and that there is sufficient evidence that benzene is carcinogenic to humans.[17] Although a benzene-leukemia association has been made, the exact shape of the dose-response curve and/or the existence of a threshold for the response is unknown and has been the source of speculation and controversy.[18–22] Some risk assessments suggest exponential increases in relative risk (of leukemias) with increasing cumulative exposure to benzene. At low levels of exposure, however, a small increase in leukemia mortality cannot be distinguished from a no-risk situation.[1] In addition to cumulative dose other factors such as multiple solvent exposure, familial connection, and individual susceptibility may play a role in leukemia development.[16]

A relationship between benzene exposure and lymphoma and multiple myeloma is controversial. In one report, a statistically significant increase in deaths from multiple myeloma was found, although the numbers were small.[23]

An increased incidence of neoplasms at multiple sites has been found in chronic inhalation and gavage studies in rodents. Anemia, lymphocytopenia, bone marrow hyperplasia, and an increased incidence of lymphoid tumors occurred in male mice exposed at 300 ppm for life.[24] Gavage administration to rats in one study, and rats and mice in another, caused an increase in tumors; especially significant was an increase in zymbal gland tumors (tumors of the auditory sebaceous glands) in both reports.[25,26]

Although consistent findings of chromosomal aberrations (stable and unstable) in the nuclei of lymphocytes have been reported in exposed workers, the implications with respect to leukemia are not clear.[27] Data on exposure levels are limited but are said to range from ten to a few hundred ppm.[17] In controlled rat studies, exposure to 1, 10, 100, or 1000 ppm for 6 hours caused a dose-response relationship in the percentage of cells with abnormalities and aberrations at the two highest dose levels.[28] An increase in polychromatic erythrocytes with micronuclei (thought to be broken fragments of chromosomes that are left behind) have also been observed in benzene-treated animals.[16] Mice exposed at 10 ppm for 6 hours had a significantly increased incidence of micronuclei compared with controls.[29]

In addition to tumor induction and cytogenic damage, inhaled benzene in mice can cause immunodepressive effects at 100 ppm as manifested by reduced host resistance to a transplantable syngeneic tumor.[30]

Exposure to benzene vapor produces fetotoxicity, such as growth retardation, in mice and rats at doses that are maternally toxic. In general, benzene does not appear to adversely effect reproductive competence.[31]

Tests for phenol levels in urine have been used as an index of benzene exposure; urinary phenol concentrations of 200 mg/l are indica-

tive of exposure to approximately 25 ppm of benzene in air.[32]

Direct contact with the liquid may cause erythema and vesiculation; prolonged or repeated contact has been associated with the development of a dry, scaly dermatitis or with secondary infections.[3] Some skin absorption can occur with lengthy exposure to solvents containing benzene and may contribute more to toxicity than originally believed, but the dermal route is considered only a minor source of exposure for the general population.[33]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for benzene is 0.5 ppm (1.6 mg/m^3) with a TLV STEL of 2.5 ppm (8 mg/m^3) and an A1-confirmed human carcinogen designation and a notation for skin absorption.

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BENZIDINE

CAS: 92-87-5

$C_{12}H_{12}N_2$

Synonyms: 4,4′-Biphenyldiamine; 4,4′-diaminobiphenyl; 4,4′-bianiline

Physical Form. Colorless, crystalline compound; darkens on oxidation

Uses. Manufacture of dyestuffs; hardener for rubber; laboratory reagent

Exposure. Skin absorption; inhalation

Toxicology. Benzidine exposure is associated with a high incidence of bladder cancer in humans.

Relatively little information is available on the noncarcinogenic effects of benzidine in humans.[1] Acute dermal exposure has reportedly caused severe, recurrent eczematous dermatitis, and chronic exposure may result in sensitization dermatitis.[1]

Numerous studies have reported the occurrence of bladder cancer in workers exposed to benzidine by inhalation and through skin absorption.[1]

Of 25 workers involved in benzidine manufacture, 13 developed urinary bladder tumors and 4 renal tumors also occurred. The average duration of exposure was 13.6 years, and the average induction time from first exposure to detection of the first tumor was 16.6 years. Initial tumors made their appearance as late as 9 years after cessation of exposure. Airborne benzidine concentrations were estimated to have ranged from 0.005 to 17.6 mg/m^3 It is not known whether the cancers were influenced by concurrent exposure to other chemicals in the occupational environment.[2]

In a 30-year follow-up of a cohort of 984 workers employed at a benzidine manufacturing facility there was a significant excess of bladder tumors among men with the highest estimated level of benzidine exposure.[3] The bladder cancer risk declined in those first employed after 1950, when preventive measures were instituted.

In a plant that manufactured β-naphthylamine and benzidine, a cohort of 639 male employees with exposure from 1938 or 1939 to 1965 was studied; concentration of initial exposure, duration of exposure, and years of survival after the exposure are factors that affected the incidence of tumor formation.[4] Thirty-five percent of all malignant neoplasms were of the

bladder and kidney. The observed mortality rate for cancer of the bladder was 78 per 100,000 in the cohort, compared with 4.4 per 100,000 expected for men of the same age. Of 42 bladder and kidney neoplasms, 16 were attributed to benzidine exposure and 18 were attributed to combined exposure.

During a 17-year period, 83 workers in a benzidine department were examined cystoscopically; 34 workers had congestive lesions, 3 had pedunculated papillomas, 4 had sessile tumors, and carcinoma was found in 13 of the workers.[5]

The onset of occupational bladder tumors is insidious, and, occasionally, the disease may be in an advanced stage before any signs or symptoms appear. In general, however, benzidine exposure may produce a variety of lesions in the urinary bladder such as hyperemia, inflammation, and papillomas that precede malignancy.[6] The presence of blood in the urine or pain on urination may indicate such lesions. Detection of premalignant or malignant changes may be possible through cystoscopic examination, cytological evaluation of bladder epithelial cells shed in urine, and screening for occult blood.[6] Recurrences are frequent, and tumors may recur as papillomas or carcinomas irrespective of the nature of the original lesion.[7]

Susceptibility to bladder cancer in humans has been linked to the slow acetylator phenotype of the polymorphic NAT2 *N*-acetyltransferase gene.[1] In a study from China, a 25-fold increase in bladder cancer incidence and a 17-fold increase in bladder cancer mortality were determined in 1972 benzidine-exposed workers.[8] In the Asian population the slow acetylator phenotype occurs significantly less often than in Caucasian populations, but an association between those who contracted bladder cancer and phenotype has yet to be determined for this group. Other, more recent data have suggested that the acetylation rate may not be an important risk factor for developing bladder cancer.[1]

Benzidine exposure has been associated with chromosomal aberrations and polyploidy in the circulating peripheral lymphocytes of workers, micronucleus induction in rodents, and unscheduled DNA repair synthesis.[1] It has also tested positive in a wide variety of *in vitro* genotoxic assays.[1]

The IARC has determined that there is sufficient evidence for carcinogenicity of benzidine to humans.[9]

The ACGIH has classified benzidine as an A1-confirmed human carcinogen with no assigned threshold limit value and a notation for skin absorption.

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2,3-BENZOFURAN
CAS: 271-89-6

C_8H_6O

Synonyms: Benzofuran; benzo(*b*)furan; coumarone; cumarone; 1-oxindene

Physical Form. Liquid

Uses. As an intermediate in the polymerization of coumarone-indene resins found in various corrosion-resistant coatings such as paints and varnishes; in water-resistant coatings for paper products and fabrics; in adhesives for use in food containers

Exposure. Inhalation

Toxicology. Benzofuran is carcinogenic in experimental animals and causes kidney damage.

In 13-week studies designed to set the dose levels for a 2-year study, benzofuran in corn oil was given by gavage to both sexes of rats and mice.[1] Based on reduced mean body weights, increased severity of nephropathy, and hepatocellular necrosis, doses selected for the 2-year studies in rats were 30 and 60 mg/kg for males and 60 and 120 mg/kg for females. Based on increased mortality and nephrosis in male mice, doses selected were 60 and 120 mg/kg for males and 120 and 240 mg/kg for females. There was clear evidence of carcinogenic activity for male and female mice, based on an increased incidence of neoplasms of the liver, lung, and forestomach. There was no evidence of carcinogenic activity in male rats. There was some evidence of carcinogenic activity in female rats, based on an increased incidence of tubular cell adenocarcinomas of the kidney.

Exposure to benzofuran increased the severity of nephropathy in male rats, increased the incidence of nephropathy in female rats, and induced hepatocellular metaplasia in the pancreas of female rats. Nonneoplastic lesions observed in mice included syncytial alteration of the liver, bronchiolar epithelial hyperplasia, and epithelial hyperplasia of the forestomach.

Although no studies provide data concerning human susceptibility, it is reasonable to assume that humans with kidney or liver disease would be more susceptible to the toxic effects of 2,3-benzofuran.[2]

Benzofuran was not mutagenic in bacterial assays but did cause chromosomal aberrations and sister chromatid exchanges in cultured rodent cells.[3]

A threshold limit value-time-weighted average (TLV-TWA) for benzofuran has not been assigned.

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BENZOIC ACID
CAS: 65-85-0

C_6H_5COOH

Synonyms: Benzenecarboxylic acid; phenyl carboxylic acid; phenylformic acid

Physical Form. White crystals or powder

Exposure. Inhalation; ingestion

Toxicology. Benzoic acid is an irritant of the eyes and respiratory system.

Although specific dose levels and durations are not available, it is assumed that exposure to the dust may be irritating to the nose and eyes.[1] At elevated temperatures, fumes may cause irritation of the eyes, respiratory system, and skin.

The systemic toxicity of benzoic acid is low. Extremely large oral doses are expected to produce gastric pain, nausea, and vomiting.[2] In one case a 67-kg man ingested a single dose of 50 mg without ill effects. In other cases daily intake of 4–6 mg caused slight gastric irritation.[3] After ingestion, benzoic acid is conjugated with glycine and excreted as hippuric acid in the urine. However, no quantitative relationship exists between benzoic acid intake and the hippuric acid excreted.

The oral LD_{50} in cats and dogs is 2 mg/kg.[2] When benzoic acid is injected in rats, tremors, convulsions, and death occur.

On human skin, intermittent exposure to 22 mg for 3 days caused moderate irritation.[4] Benzoic acid does not appear to be a skin sensitizer.[5] In the eyes of rabbits, 100 mg was severely irritating.[4]

Benzoic acid was not genotoxic in bacterial assays or in *in vitro* mammalian assays.[6]

The ACGIH has not established a threshold limit value for benzoic acid.

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BENZO[*a*]PYRENE
CAS: 50-32-8

$C_{20}H_{12}$

Synonyms: B[*a*]P; BP; 3,4-benzopyrene; 3,4-benzpyrene

Physical Form. Yellow crystals

Sources. B[*a*]P is a major component of polynuclear aromatic hydrocarbons, also known as polycyclic aromatic hydrocarbons, and is usually bound to small particulate matter present in urban air, industrial and natural combustion emissions, and cigarette smoke.

Exposure. Inhalation

Toxicology. Benzo[*a*] pyrene (B[*a*]P) causes hematologic and immunologic effects; it is carcinogenic to experimental animals.

Systemic effects from B[*a*]P exposure have not been reported in humans.

Intermediate-duration oral exposure of mice has caused death due to adverse hematologic effects including aplastic anemia and pancytopenia.[1] B[*a*]P has been shown to markedly inhibit the immune system, especially T-cell-dependent antibody production by lymphocytes exposed either *in vivo* or *in vitro*. It may also induce autoimmune responses.

B[*a*]P has been carcinogenic in all animal species tested to date, including mouse, rat, hamster, rabbit, guinea pig, duck, newt, dog, monkey, and fish.[2] Intratracheal instillation and inhalation studies in a number of species have resulted in elevated incidences of respiratory tract and upper digestive tract tumors, and intraperitoneal and subcutaneous injections

have caused increases in the number of injection site tumors.[3] B[*a*]P is both an initiator and a complete carcinogen in mouse skin; increased incidences of distant site tumors have also been reported in animals as a consequence of dermal B[*a*]P exposure.

Mice fed 0, 5, 25, or 100 ppm B[*a*]P for up to 2 years had significant dose-related increases in forestomach, esophageal, and tongue papillomas or carcinomas.[4]

B[*a*]P is metabolized to approximately 20 primary and secondary oxidized metabolites and to a variety of conjugates.[5] The most potent carcinogenic metabolite is 7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene. This ultimate carcinogen binds predominantly to guanine bases in DNA to form covalent adducts.

B[*a*]P metabolites have been shown to bind to DNA in cultured human hepatocytes and in human bladder and tracheobronchial explants.[6,7] The metabolites identified were identical to those produced in other species and differed only in the relative percentages of formation.[7] Human tissues were most active in metabolizing B[*a*]P and exhibited at least a threefold higher covalent binding of metabolites to DNA than hamsters, dogs, monkeys, or rats. In addition, B[*a*]P has been tested extensively in several bacterial and mammalian cell systems and has been chosen as a positive control for the validation of some of these systems.[8]

The IARC considers that there is "sufficient evidence" that B[*a*]P is carcinogenic to experimental animals.[9]

Developmental toxicity and impaired reproductive capacity were seen in two oral studies in mice.[10,11] The lowest observed adverse effect level was 10 mg/kg/day from day 7 to day 16 of gestation.[11]

Benzo[*a*]pyrene is designated an A2-suspected human carcinogen by ACGIH and has no assigned threshold limit value.

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BENZOTRICHLORIDE

CAS: 98-07-7

$C_7H_5Cl_3$

Synonyms: Benzenyl chloride; benzoic trichloride; benzylidyne chloride; benzyl trichloride; phenylchloroform; toluene trichloride; trichlorotoluene; (trichloromethyl)-benzene

Physical Form. Clear, oily liquid

Uses. Chemical intermediate primarily in benzoyl chloride production; dye intermediate

Exposure. Inhalation; skin absorption

Toxicology. Benzotrichloride is an irritant and a suspected human carcinogen.

The liquid has been reported to be highly irritating to the skin and mucous membranes in humans.[1]

In rats benzotrichloride was lethal after a 4-hour exposure at 1000 mg/m^3 (125 ppm). The oral LD_{50} in rats was 6 g/kg. The 2-hour LC_{50} was 150 mg/m^3 (19 ppm) in rats and 60 mg/m^3 (8 ppm) in mice. Toxic effects included central nervous system excitation, irritation of the eyes and upper respiratory tract, and slowed respiration. Hyperemia of the extremities was also observed. Motor automatism and twitching of peripheral muscles were seen at 1000 mg/m^3 (125 ppm) in mice and rats, respectively. Leukopenia, mild anemia, and decreases in renal function occurred in rats after continuous inhalation exposure at 100 mg/m^3 (12.5 ppm) for 1 month.[1]

There are no data clearly relating exposure to benzotrichloride to cancer in humans. However, an excess of respiratory cancer (6 cases total) was reported in benzoyl chloride manufacturing workers who were potentially exposed to benzotrichloride.[3]

Squamous cell carcinomas of the skin were produced in three studies after skin application of benzotrichloride to mice.[1,4] Lung carcinomas, pulmonary adenomas, and lymphomas were also observed. Intraperitoneal injection of benzotrichloride produced a significant increase in the lung tumor response in strain A/J mice within 24 weeks.[5] Administration by gastric intubation of doses ranging from 2.0 to 0.0315 µl/mouse, twice a week for 25 weeks, to female ICR mice produced forestomach tumors (squamous cell carcinoma and papilloma), lung tumors (adenocarcinoma and adenoma), and tumors of the hematopoietic system (thymic lymphosarcoma and lymphatic leukemia), with dose-related response by 18 months.[6] It was concluded that the target organ of benzotrichloride carcinogenesis in mice is the local tissue that is primarily exposed and the lung and hematopoietic tissue when administered systemically.

Benzotrichloride is mutagenic in bacterial assays.[7]

The IARC has determined that combined exposures to a-chlorinated toluenes (which include benzotrichloride) are probably carcinogenic to humans.[7] There is sufficient evidence that benzotrichloride is carcinogenic in experimental animals.

The ACGIH has established a ceiling threshold limit value (TLV-C) of 0.1 ppm (0.8 mg/m^3) for occupational exposure to benzotrichloride with a skin notation and an A2 suspected human carcinogen designation.

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BENZOYL PEROXIDE
CAS: 94-36-0

$(C_6H_5CO)_2O_2$

Synonyms: Benzoyl superoxide; dibenzoyl peroxide; lucidol; oxylite

Physical Form. Granular, white solid

Uses. Bleaching flour and edible oils; additive in self-curing of plastics

Exposure. Inhalation

Toxicology. Benzoyl peroxide is an irritant of mucous membranes and causes both primary irritation and sensitization dermatitis.

Exposure of workers to levels of 12.2 mg/m^3 and higher has caused pronounced irritation of the nose and throat.[1]

Application to the face as lotion for acne treatment in two persons caused facial erythema and edema; patch tests with benzoyl peroxide were positive.[2] In contact with the eyes it may produce irritation, and if allowed to remain on the skin it may produce inflammation.[3] No systemic effects have been reported in humans. The major hazards of benzoyl peroxide are fires and explosions, which have caused serious injuries and death.[4]

Rats exposed at an atmospheric concentration of 24.3 mg/l of 78% benzoyl peroxide showed the following signs during a 4-hour exposure period: eye squint, difficulty in breathing, salivation, lacrimation, erythema, and an increase followed by a decrease in motor activity.[4] All rats appeared normal at 24 and 48 hours after exposure.

Benzoyl peroxide has been tested for carcinogenicity in mice and rats by administration in the diet and by subcutaneous injection and in mice by skin application.[5] Although no significant increases in tumor incidences were found, the IARC has determined that all of the studies were inadequate for a complete evaluation of carcinogenicity in animals. Two studies indicated that benzoyl peroxide may act as a cancer promoter on mouse skin.[6,7]

Among a small factory population, two cases of lung cancer were found in men primarily involved in the production of benzoyl peroxide, but they were also exposed to benzoyl chloride and benzotrichloride.[8] Benzoyl peroxide exposure was associated with a greater frequency of malignant melanoma in one of two case control studies; it was not associated with basal cell carcinomas of the skin in another study.[9] The IARC has determined that there is limited evidence for the carcinogenicity of benzoyl peroxide in experimental animals and that it is not classifiable as to its carcinogenicity to humans.

It was not mutagenic in bacterial assays and does not cause chromosomal damage in cultured mammalian cells.[9]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for benzoyl peroxide is 5 mg/m^3.

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BENZYL CHLORIDE

CAS: 100-44-7

$C_6H_5CH_2Cl$

Synonyms: α-Chlorotoluene; ω-chlorotoluene; (chloromethyl) benzene

Physical Form. Colorless liquid

Uses. In manufacture of benzyl compounds, cosmetics, dyes, resins

Exposure. Inhalation

Toxicology. Benzyl chloride is a severe irritant of the eyes, mucous membranes, and skin.

Benzyl chloride is a powerful lacrimator (an immediate warning sign), and at 31 ppm it is unbearably irritating to the eyes and nose.[1] At 16 ppm it is intolerable after 1 minute. Workers exposed to 2 ppm complained of weakness, irritability, and persistent headache.[2]

Lung damage and pulmonary edema are possible with severe exposure.

One author reported disturbances of liver function and mild leukopenia in some exposed workers, but this study has not been confirmed.[2]

Splashes of the liquid in the eye will produce severe irritation and will result in corneal injury. Skin contact may produce dermatitis, and skin sensitization has been reported in guinea pigs.[3]

The LC_{50} values in mice and rats for a 2-hour inhalation exposure are 80 and 150 ppm, respectively.[4] In another investigation, it was found that all mice and rats survived 400 ppm for 1 hour.[5] Cats exposed to 100 ppm 8 hours/day for 6 days exhibited eye and respiratory tract irritation that appeared sooner and with increasing severity each exposure day.[6]

Repeated high-dose subcutaneous injections produced local tumors in rats; skin application to a limited number of mice caused an increase in squamous cell carcinomas of the skin that was not statistically significant.[7,8] Administered by gavage at a dose of 50 or 100 mg/kg in mice and 15 or 30 mg/kg in rats three times per week for 2 years, benzyl chloride produced a statistically significant increase in the incidence of papillomas and carcinomas of the forestomach in mice and an increase in thyroid tumors in female rats.[9] The carcinogenic potential has not been determined in humans.[6,7] Evidence of efficient detoxification mechanisms suggests that the risk from chronic low-level exposure is small.[6] The IARC has determined that there is sufficient evidence of carcinogenicity of benzyl chloride to animals and that it is probably carcinogenic to humans.[10]

Benzyl chloride was not teratogenic in rats orally administered 100 mg/kg on days 6–15 of gestation; slight fetoxicity in the form of reduced fetal length was observed at this level.[11]

Benzyl chloride caused genetic mutations and chromosome-damaging effects in a wide variety of in vitro assays; it was not mutagenic in vivo in the mouse micronucleus assay.[10]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for benzyl chloride is 1 ppm (5.2 mg/m^3).

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BERYLLIUM (and Compounds)
CAS: 7440-41-7

Be

Synonyms/compounds: Glucinium; beryllium oxide; beryllium chloride; beryllium fluoride; beryllium hydroxide; beryllium phosphate; beryllium nitrate; beryllium sulfate; beryllium carbonate

Physical Form. Elemental beryllium is a gray metal.

Uses. Beryllium metal sheet or wire; ceramics; hardening agent in alloys used especially in the electronics field

Exposure. Inhalation

Toxicology. Exposure to compounds of beryllium may cause dermatitis, acute pneumonitis, and chronic pulmonary granulomatosis (berylliosis) in humans. The compounds are carcinogenic in experimental animals and considered to be suspected human carcinogens.

Acute lung disease, now chiefly of historical importance because of improved working conditions, has resulted from brief exposures to high concentrations of the oxide, phosphor mixtures, or the acid salts.[1] All segments of the respiratory tract may be involved, with rhinitis, pharyngitis, tracheobronchitis, and pneumonitis.[2] The pneumonitis may be fulminating after high exposure levels or less severe, with gradual onset, after lesser exposures.[3] In the majority of

cases with acute beryllium pneumonitis, recovery occurs within 1–6 months; however, fatalities due to pulmonary edema or to spontaneous pneumothorax have been reported. The human threshold of an injurious concentration by inhalation is approximately 30 mg Be/m^3 for the high-fired oxide, 1–3 mg Be/m^3 for the low-fired oxide, and 0.1–0.5 mg Be/m^3 for the sulfate.[2]

Beryllium disease is regarded as chronic if it persists for a year or more and is usually due to granulomas in the lungs.[1,4] The onset of "berylliosis" may be insidious, with only slight cough and fatigue that can occur as early as 1 year or as late as 25 years after exposure.[2] Progressive pulmonary insufficiency, anorexia, weight loss, weakness, chest pain, and constant hacking cough characterize the advanced disease. Cyanosis and clubbing of fingers may be seen in approximately one-third of cases, and cor pulmonale is another frequent sequela.[2]

Early X rays show a fine, diffuse granularity in the lungs, a diffuse reticular pattern is observed in the second stage, and finally, in the third stage, distinct nodules appear.[5]

There are many similarities between berylliosis and sarcoidosis, but in sarcoidosis the systemic effects are much more pronounced.[6]

An immunologic basis for chronic beryllium disease has been postulated and a hypersensitivity phenomenon demonstrated.[4,6] Consistent with the concept of chronic berylliosis as a hypersensitivity pulmonary reaction are the following: Persons with berylliosis also show delayed cutaneous hypersensitivity reactions to beryllium compounds; their peripheral blood lymphocytes undergo blast transformation and release of macrophage inhibition factor after exposure to beryllium in vitro; helper/suppressor T-cell ratios are depressed; and there is lack of a dose-response relationship in chronic beryllium cases.[2,4] Hypersensitization may lead to berylliosis in people with relatively low exposures, whereas nonsensitized individuals with higher exposures may have no effects.

Skin contact with soluble beryllium salts may produce either primary irritation or sensitization dermatitis characterized by pruritis with an eruption of erythematous, papular, or papulovesicular nature; the eruption usually subsides within 2 weeks after cessation of exposure.[1] Implantation of beryllium or its compounds beneath the skin may cause necrosis of adjacent tissue and formation of an ulcer; implantation of comparatively insoluble compounds may produce a localized granuloma, as has occurred from lacerations with old fluorescent tubes containing the phosphor.[3] Healing of ulcers and granulomas requires the surgical removal of the beryllium substance.[3] Conjunctivitis may accompany contact dermatitis resulting from exposure to soluble beryllium compounds; angioneurotic edema may be striking.[1,3]

Beryllium metal, beryllium-aluminum alloy, beryl ore, beryllium chloride, beryllium fluoride, beryllium hydroxide, beryllium sulfate, and beryllium oxide all produce lung tumors in rats exposed by inhalation or intratracheally.[7] The oxide and the sulfate produce lung tumors in monkeys after intrabronchial implantation or inhalation. A number of compounds produce osteosarcomas in rabbits after their intravenous or intramedullary administration.[7]

Although a number of epidemiological studies have reported an increased risk of lung cancer among occupationally exposed beryllium workers, deficiencies in the studies limit any unequivocal conclusion.[7–9] Specific criticisms concern the lack of consideration of latent effects, of smoking history, and of exposure to other potential carcinogens and the underestimation of expected lung cancer deaths in comparison populations.[10,11]

A subsequent study that accounted for smoking, included females, and extended the latency period has strengthened the evidence of carcinogenicity in humans.[12] A cohort mortality study of 689 patients with beryllium disease, as determined by a case registry, found a lung cancer standardized mortality ratio (SMR) of 2.00 based on 28 observed lung cancer deaths.[13] The lung cancer excess was more pronounced in individuals with a history of acute forms of beryllium disease than among those with chronic disease. Patients with a history of acute beryllium disease and lung cancer were found

to be employed by one plant in Lorain, Ohio, where exposures as high as 4700 µg/m^3 were reported during the 1940s.[14]

It has been noted that this exposure level is several orders of magnitude higher than those in existence today.[14] Slight excesses in lung cancer rates were found in four of five plants operating during the 1950s, when exposures were considered to be lower than the extremely high 1940s levels.[15]

Further evidence that beryllium is a human lung carcinogen was the recent finding of increased risk among workers with higher beryllium exposures when dose estimates were lagged for 10 or 20 years.[16]

The IARC has determined that there is sufficient evidence in both humans and animals for the carcinogenicity of beryllium and beryllium compounds.[7] Genotoxic assays have provided contradictory results.[12]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for beryllium, and compounds as Be, is 0.002 mg/m^3 with an A2-suspected human carcinogen designation.

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BIPHENYL
CAS: 92-52-4

$C_6H_5C_6H_5$

Synonyms: Diphenyl; phenylbenzene; bibenzene; 1,1-biphenyl; PhPh

Physical Form. Colorless to yellow solid

Uses. Heat transfer agent; fungistat for citrus fruits; in organic synthesis

Exposure. Inhalation; skin absorption

Toxicology. Biphenyl is an irritant of the eyes and mucous membranes and may exert a toxic action on the central and peripheral nervous systems.

In a study of 33 workers in one plant with prolonged exposure to concentrations ranging up to 123 mg/m^3, the most common complaints were headache, gastrointestinal symptoms (diffuse pain, nausea, indigestion), numbness and aching of limbs, and general fatigue.[1] Neurophysiologic examination of 22 of these workers showed that 19 had changes consistent with central and/or peripheral nervous system damage. In one fatal case in this plant, exposure was high for 11 years, symptoms were as just described, and, at autopsy, there was widespread liver necrosis with some cirrhotic areas, nephrotic changes, heart muscle degeneration, and edematous brain tissue.[1]

In a follow-up study, 10 of 24 workers showed electroencephalographic abnormalities that persisted 1 and 2 years after the initial investigation; 9 workers had electromyographic abnormalities that also persisted.[2]

Irritation to the eyes and mucous membranes has been reported in humans exposed at 3–4 ppm.[3]

Exposure of rats to biphenyl dust impregnated in diatomaceous earth at a concentration of 300 mg/m^3 for 7 hours/day, for 64 days caused irritation of the nasal mucosa, bronchopulmonary lesions, and slight injury to the liver and kidneys.[4]

Biphenyl in the diet of rodents caused hematologic alterations including decreased hemoglobin concentration.[5] Rats administered diets with greater than 2500 mg biphenyl/kg have shown effects on the urinary system including the formation of calculi and hyperplasia and desquamation; males typically show greater effects than females.[5] In chronic feeding studies an increase in bladder tumors was seen in male rats, and female mice have shown slight increases in the incidences of liver tumors.[5] It has been suggested that the formation of bladder tumors in male rats may be linked to the regenerative hyperplasia of the urinary epithelium caused by damage from the calculi that are only formed at high levels of exposure; the sex- and species specificity of bladder tumor development may not be relevant to humans.[5]

Biphenyl was not mutagenic in bacterial assays but was positive *in vitro* in mammalian cell systems in the presence of metabolic activation.[5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 0.2 ppm (1.3 mg/m^3).

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BISMUTH TELLURIDE
CAS: 1304-82-1

Bi_2Te_3

Synonym: Dibismuth tritelluride

Physical form. Gray solid

Uses. Semiconductors; thermoelectric cooling; power generation application; for commercial use, Bi_2Te_3 is "doped" with selenium sulfide to alter its conductivity.

Exposure. Inhalation

Toxicology. Bismuth telluride, either alone or doped with selenium sulfide, is apparently of very low toxicity.

In limited industrial experimental work with bismuth telluride under controlled conditions (vacuum hoods), no adverse health effects were encountered other than tellurium breath.[1]

In a multispecies study, dogs, rabbits, and rats were exposed to 15 mg/m^3 of bismuth telluride doped with stannous telluride for 6 hours/day, 5 days/week, for one year.[1] Small granulomatous lesions without fibrosis occurred in the lungs of dogs at 6 months. In dogs autopsied 4 months after an 8 month exposure the lesions had regressed, indicating a reversible process. Rabbits showed a similar reaction but with a decreased number of pulmonary macrophages, no fibrous tissue activity, and no cellular or fibrous tissue reaction around the dust deposits in the lymph nodes. The rats exhibited no fibrosis and no lymph node reactions. The pulmonary lesions seen in the study were present in all three exposed species but were interpreted as mild and reversible and not of serious physiologic consequence.

In a similar 11-month study in which animals were exposed to undoped bismuth telluride dust of 0.04-µm diameter at 15 mg/m^3, no adverse responses of any type were observed other than the pulmonary responses to the inhalation of an inert dust.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 10 mg/m^3 for undoped and 5 mg/m^3 for doped bismuth telluride.

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BISPHENOL A

CAS: 80-05-7

$OHC_6H_4C(CH_3)_2C_6H_4OH$

Synonyms: BPA; 4,4′-1-methylethylidene)-bisphenol; 4,4′-isopropylidenediphenol; 2,2-bis(4-hydroxyphenyl)propane; *p,p′*-dihydroxydiphenylpropane; diphenylolpropane; 4,4′-isopropylidenediphenol

Physical Form. Crystals or flakes; dust

Uses. A high-production-volume chemical used in manufacture of epoxy-phenolic resins (protective linings for food and beverage cans); monomer for polycarbonate resins (used in food contact materials such as returnable beverage bottles, infant feeding bottles, plates, and mugs); antioxidant in PVC plastics; inhibitor of end polymerization in PVC plastics

Exposure. Inhalation; skin absorption

Toxicology. Bisphenol A causes photosensitivity and slight skin and eye irritation.

Persistent photosensitivity developed in eight men after occupational exposure to hot epoxy resin fumes.[2] The condition was limited to sites contacted by the resin. Small doses of ultraviolet-A light evoked abnormal reactions consisting of erythema, edema, and papules in the clinically involved skin. Positive photopatch tests were observed to epoxy resin in four subjects and to bisphenol A in all subjects. Another study showed that bisphenol A can be released during the thermal decomposition of epoxy resin in the temperature range of 250–350°C.[3] Photosensitizing activity was explained by the formation of free radicals during exposure to ultraviolet-B radiation of bisphenol A vapor, to form a semiquinone derivative of bisphenol A.[4]

Bisphenol A causes slight skin and eye irritation.[5] It did not cause contact allergy in a guinea pig maximization test.[6] Furthermore, no cross-reactions were detected when animals sensitized to the diglycidyl ether of bisphenol A were tested with bisphenol A.

Studies of effects of bisphenol A on reproduction showed no evidence of reduction in the fertility of rats and mice.[7,8] In studies on the offspring, at doses that were maternally toxic, no fetotoxic effects occurred in rats and no teratogenic effects occurred in mice or rats. A more recent three-generation reproductive toxicity study in rats provided no evidence that low doses of bisphenol A (in the μg/kg body weight range) can adversely affect reproductive function.[9] Test doses ranged from 0.001 to 500 mg/kg/day in the diet. No-observed-adverse-effect levels were 5 mg/kg/day for adult systemic toxicity and 50 mg/kg/day for reproductive and developmental toxicity. Androgenic or antiandrogenic activity was not detected at any dose level, whereas estrogenic effects were observed only at the top dose, and then only in the presence of significant systemic maternal toxicity.

A 2-year feeding study with mice and rats yielded no evidence of carcinogenic effects.[10] Recent extensive reviews have concluded that bisphenol A is nongenotoxic *in vivo*.[11,12]

In *in vitro* studies, weak estrogenic effects of bisphenol A were found in cell line MCF7, which was established from human breast cancer cells, and in studies with cytosol preparations from isolated uteri.[13] In MCF7 cells, the estrogenic effects were seen at 1–5 ng/ml and were manifested as in increase in cell proliferation and the induction of progesterone receptors. Bisphenol A was 1000–5000 times less potent than estradiol-17.

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BORATES, TETRA, SODIUM SALTS
CAS: 1303-96-4

$Na_2B_4O_7$: anhydrous
$Na_2B_4O_7 \cdot 5H_2O$: pentahydrate
$Na_2B_4O_7 \cdot 10H_2O$: decahydrate (borax)

Synonyms/compounds: Sodium borate; sodium pyroborate; boric acid, disodium salts

Physical Form. Anhydrous—gray solid; pentahydrate—white solid; decahydrate—white solid

Uses. Cleaning compounds; fertilizers; manufacture of glazes and enamels

Exposure. Inhalation; ingestion

Toxicology. Borates are irritants of the eyes, nose, and throat; at high concentrations ingestion of the compounds can result in gastrointestinal irritation, kidney injury, and even death from central nervous system depression or cardiovascular collapse.

Under normal conditions of exposure borates are primarily irritants of the skin and respiratory system.[1] Workers exposed to anhydrous sodium tetraborate complained of nasal irritation, nose bleeds, cough, shortness of breath, and dermatitis.[2] Exposure levels were not measured, but total dust levels were described as high enough to obscure visibility in production areas. In another study of borax workers, symptoms of acute respiratory irritation including dryness of the mouth, nose, or throat, cough, nosebleeds, and shortness of breath were related to exposures of 4 mg/m^3 or more.[3]

There were more frequent symptoms of respiratory tract irritation and mucous membrane irritation among workers exposed during a 7-year period to average borax concentrations of 1.5 mg/m^3 compared with unexposed controls.[1] Occasional excursions to levels of 10 mg/m^3 produced no functional changes in respiration, and irritation was classified as mild.

Dermal effects may be noted after either direct contact with the compounds or ingestion.[1] Erythematous rash with desquamation may develop.

Systemic toxicity may occur after chronic or multiple exposures.[1] Possible effects include gastrointestinal irritation with nausea, vomiting, and diarrhea, kidney injury such as oliguria or anuria, central nervous system depression, and vascular collapse.

In rats the oral LD_{50} values for borates are essentially the same as for boric acid; they range from 3.16 to 6.08 g/kg.[4] When borax was fed to dogs and rats for 2 years, 350 ppm as boron in the diet had no effect. In a three-generation feeding study in rats, 350 ppm had no effect on fertility, litter size, weight, or appearance.

Sodium borate tested negatively in the Ames bioassay but was found to be cytotoxic to cultured human fibroblasts.[5]

The 2003 ACGIH threshold limitvalue-time-weighted average (TLV-TWA) for anhydrous and pentahydrate borates is 1 mg/m^3 and 5 mg/m^3 for the decahydrute.

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BORON OXIDE
CAS: 1303-86-2

B_2O_3

Synonyms: Boric anhydride; boron sesquioxide; boron trioxide; fused boric acid

Physical Form. Colorless crystals

Uses. In preparation of fluxes; component of enamels and glass; catalyst in organic reaction

Exposure. Inhalation

Toxicology. Boron oxide is an eye and respiratory irritant.

In 113 workers exposed to boron oxide and boric acid dusts, there were statistically significant increases in symptoms of eye irritation; dryness of the mouth, nose, and throat; sore throat; and productive cough compared with controls.[1] The mean exposure level was 4.1 mg/m^3, with a range of 1.2–8.5 mg/m^3. Exposures may occasionally have exceeded 10 mg/m^3. Because of mixed exposures, the study does not indicate whether boron oxide or boric acid dust is more important in causing symptoms, nor does it indicate the minimum duration of exposure necessary to produce symptoms.

Excessive absorption of boron oxide may lead to cardiovascular collapse, alterations in temperature regulation, and coma.[2]

Repeated exposure of rats to an aerosol at a concentration of 470 mg/m^3 for 10 weeks caused only mild nasal irritation; repeated exposure of rats to 77 mg/m^3 for 23 weeks resulted in elevated creatinine and boron content of the urine in addition to increased urinary volume.[3] Conjunctivitis resulted when the dust was applied to the eyes of rabbits, probably the result of the exothermic reaction of boron oxide with water to form boric acid; topical application of boron oxide dust to the clipped backs of rabbits produced erythema that persisted for 2–3 days.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for boron oxide is 10 mg/m^3.

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BORON TRIBROMIDE
CAS: 10294-33-4

BBr_3

Synonyms: Boron bromide; tribromoborane

Physical Form. Colorless, fuming liquid with a sharp, irritating odor

Uses. Catalyst in manufacture of diborane, ultrahigh-purity boron, and semiconductors

Exposure. Inhalation

Toxicology. Boron tribromide is expected to be an irritant of the eyes, nose, and mucous membranes.

Boron tribromide reacts violently and explosively with water to yield hydrogen bromide.[1]

Effects of short-term exposure are expected to be irritation of the eyes, nose, throat, and skin. Pulmonary edema may result from acute respiratory exposure.[2] Contact with skin or the eyes can cause burns.[2] In one case the liquid splashed in the eyes caused no immediate pain but resulted in permanent corneal injury.

The 2003 threshold limit value-time-weighted average (TLV-TWA) is 1 ppm or 10 mg/m^3 as a ceiling limit.

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BORON TRIFLUORIDE

CAS: 7637-07-2

BF_3

Synonym: Boron fluoride

Physical Form. Colorless gas; forms dense white fume in moist air

Uses. In catalysis with and without promoting agents; fumigant; flux for soldering magnesium

Exposure. Inhalation

Toxicology. Boron trifluoride gas is a severe irritant of the lungs, eyes, and skin.

Examination of 13 workers with present or past occupational exposure found 8 with abnormalities of pulmonary function; chest X rays were negative, and preshift urinary fluoride concentrations did not exceed 4 mg/l.[1] Air sampling showed concentrations ranging from 0.1 to 1.8 ppm. Dryness of the nasal mucosa and epistaxis were attributed to boron trifluoride exposure in workers exposed to high concentrations for 10–15 years.[2] Exposures of 50 ppm for 30–60 min are expected to be lethal to humans.[3]

Cotton soaked with boron trifluoride in water and placed on the skin for a day or so resulted in a typical acid burn; there was no evidence of the more severe hydrogen fluoride burn occurring because boron trifluoride has the ability to complex the fluoride ion effectively.[1]

In rats, the 4-hour LC_{50} was 436 ppm for boron trifluoride dihydrate, which is formed when boron trifluoride gas reacts with moisture. Clinical signs included gasping, excessive oral and nasal discharge, and lacrimation.[4] In a 2-week study all animals exposed at 67 ppm, 6 hours/day, died before the sixth exposure, and histopathology showed necrosis and pyknosis of the proximal tubular epithelium of the kidneys; at 24 ppm and 9 ppm signs of respiratory irritation, depression of body weight, increased lung weights, and depressed liver weights were observed. Repeated exposure for 13 weeks at 6 ppm, 6 hour/day, 5 days/week, resulted in renal toxicity in 2 of 40 rats; although clinical signs of respiratory irritation were seen, morphologic examination showed no evidence of damage. The same 13-week exposure regime at 2 ppm caused elevation of urinary, serum, and bone fluoride levels but did not result in a toxic response.[4] Guinea pigs and rats showed pneumonitis and congestion in the lungs after a 6-month exposure to a calculated concentration of 3.0 ppm (1.5 ppm by analysis), and a 4-month exposure at 1.0 ppm caused reversible tracheitis and bronchitis.[1,5]

Boron trifluoride combines with atmospheric moisture to form a white mist containing hydration and hydrolysis products.[1] The odor is detectable at 3.0 ppm, but this does not serve as an adequate warning.[1]

The 2003 ACGIH threshold limit value-ceiling limit (TLV-C) for boron trifluoride is 1 ppm (2.8 mg/m^3).

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BROMINE
CAS: 7726-95-6

Br_2

Synonyms: None

Physical Form. Dark reddish-brown, fuming, volatile liquid

Uses. In the synthesis of antiknock compounds for gasoline; in the production of fumigants, fire retardants, sanitation preparations, and chemical warfare gas

Exposure. Inhalation

Toxicology. Bromine is a severe irritant of the eyes, mucous membranes, lungs and skin.

In humans, 10 ppm is intolerable, causing severe irritation of the upper respiratory tract; lacrimation occurs at levels below 1 ppm.[1] Symptoms and signs in humans also include dizziness, headache, epistaxis, and cough, followed some hours later by abdominal pain, diarrhea, and sometimes, a measleslike eruption on the face, trunk, and extremities.[2] Exposure at 40–60 ppm is thought to cause pneumonitis and pulmonary edema within a short time, and 1000 ppm may be rapidly fatal because of choking caused by edema of the glottis and because of pulmonary edema.[3] Delayed mortality after bromine exposure has been associated with peribronchiolar abscesses and is thought to be due to deep tissue penetration and damage caused by the relatively soluble bromine.[4]

A mild degree of spermatogenic suppression and impaired reproductive performance was reported in a follow-up study of eight men accidentally exposed to bromine vapor.[5] The men were exposed between 50 and 240 minutes to unknown concentrations after a spill. Clinical manifestations including respiratory distress and chemical skin burns were noted at the time of the incident. Because of the small number in the cohort, a confident cause-result linkage cannot be established for bromine exposure and reproductive effects.

The liquid or concentrated vapor in contact with the eye will cause severe and painful burns.[6] Liquid bromine spilled on the skin causes a mild, cooling sensation on first contact, followed by a burning sensation. If bromine is not removed from the skin immediately, deep surface burns result; a brown discoloration appears, leading to the development of deep-seated ulcers, which heal slowly.

Exposure to excess bromine in pool water (8.2 µg/ml) was thought to be responsible for irritative skin rashes; eye, nose, and throat irritation; bronchospasm; reduced exercise tolerance; fatigue; headache; gastrointestinal disturbances; and myalgias in 17 adolescents.[7] Several had persistent or recurrent symptoms lasting weeks to months after exposure. Oral, inhalation, and dermal absorption may all have occurred under the exposure conditions.

Nearly 50% of mice exposed at 240 ppm for 2 hours died within 30 days; at 750 ppm, a 7-minute exposure was lethal to 40% during the same follow-up period.[8]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for bromine is 0.1 ppm (0.66 mg/m^3) with a short-term excursion limit of 0.2 ppm (1.3 mg/m^3).

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BROMINE PENTAFLUORIDE

CAS: 7789-30-2

BrF_5

Synonyms: Bromine fluoride

Physical Form. Pale yellow liquid at temperatures below 40.3°C; pungent, corrosive gas at temperatures above 40.3°C.

Uses. Oxidizer in rocket propellant systems; fluorinating agent

Exposure. Inhalation

Toxicology. Bromine pentafluoride is an extremely reactive oxidizer and is an irritant of the eyes, mucous membranes, and lungs.

Contact of the vapor or liquid with skin or eyes is expected to cause severe burns; inhalation may cause lung injury, and lower concentrations may cause watering of the eyes and difficulty in breathing.[1]

Exposure of animals to 500 ppm caused immediate gasping, swelling of eyelids, corneal opacity, lacrimation, and excessive salivation.[2] Levels of 100 ppm produced the same effects after 3 minutes; 50 ppm for 30 minutes caused deaths. Chronic exposure above 3 ppm produced severe nephrosis, marked toxic hepatosis, and severe respiratory difficulty in some of the exposed animals.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 0.1 ppm (0.72 mg/m^3).

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BROMODICHLOROMETHANE

CAS: 75-27-4

$CHBrCl_2$

Synonyms: Dichlorobromomethane; monobromodichloromethane; dichloromonobromomethane

Physical Form. Colorless liquid

Uses. As a chemical intermediate for organic synthesis and as a laboratory reagent; formerly used as a solvent and flame retardant. Currently, the major source of bromodichloromethane in the environment is

from its formation as a by-product during chlorination of water.

Exposure. Ingestion; inhalation; skin absorption

Toxicology. Bromodichloromethane is a central nervous system depressant and causes damage to the liver and kidneys; it is carcinogenic in experimental animals.

No studies are available regarding health effects of bromodichloromethane in humans.

The LD_{50} for a single gavage dose in both mice and rats has ranged from 450 to 970 mg/kg.[1–3] Clinical signs associated with these exposures include piloerection, sedation, flaccid muscle tone, ataxia, and prostration; enlargement and congestion of the liver and kidneys were observed at autopsy.[3]

Subchronic exposure to bromodichloromethane in the range of 100–300 mg/kg/day has caused hepatic injury in mice and rats characterized by increased liver weight, pale discoloration, increased levels of hepatic enzymes, and focal areas of inflammation or degeneration.[4,5] Mild effects, including slightly increased liver weights and microscopic changes, have been noted at doses as low as 40–50 mg/kg/day for 2 weeks.[4]

Damage to the kidneys has also been reported at doses similar to those that affect the liver. Increased renal weights were observed in rats receiving 200 mg/kg/day for 10 days, and increased blood urea nitrogen has been reported in mice dosed with 250 mg/kg/day for 2 weeks.[4,5]

Chronic oral studies in mice and rats show clear evidence that bromodichloromethane is carcinogenic. Male mice administered 50 mg/kg/day by gavage 5 days/week for 2 years had an increased incidence of renal carcinoma; hepatic tumors were observed in female mice similarly dosed with 75 or 150 mg/kg/day.[3] Tumors of the large intestine (intestinal carcinoma) occurred in rats at incidences of 13/50 and 45/50 in males exposed to 50 or 100 mg/kg/day, 5 days/week for 2 years, respectively; 12 of 47 females were affected at the higher dose. Kidney tumors were observed in both male and female rats exposed to 100 mg/kg/day, and in another study liver tumors occurred in females exposed to 150 mg/kg/day for 180 weeks.[3,6]

The IARC has determined that there is sufficient evidence for the carcinogenicity of bromodichloromethane in experimental animals and that it is possibly carcinogenic to humans.[7]

In genotoxic assays bromodichloromethane produced positive and negative results. It caused sister chromatid exchange in human lymphocytes but not in Chinese hamster cells; chromosomal aberrations were observed in two of three studies; it induced mutations in some bacterial assays.[7]

Bromodichloromethane was fetotoxic at doses that also caused significant maternal toxicity in a number of animal studies. However, recent studies have shown dramatic species differences in sensitivity to bromodichloromethane. After treatment on gestation day 10, F344 rats had a 62% incidence of full litter resorptions at 75 mg/kg/day, whereas Sprague-Dawley rats had 0% incidence of full litter resorptions at the same dose. Timing of the treatment with bromodichloromethane was also critical in causing resorptions in the F344 rats (75% incidence of full litter resorptions with treatment on gestation days 6–10 and 0% incidence when dosed on days 11–15).[8] Two epidemiological studies have also noted a relationship between high levels of bromodichloromethane in the drinking water and an increased risk of spontaneous abortion.[9,10]

The ACGIH has not established a threshold limit value for bromodichloromethane.

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BROMOFORM

CAS: 75-25-2

$CHBr_3$

Synonyms: Methenyl tribromide; tribromomethane

Physical Form. Colorless liquid

Uses. As a fluid for mineral ore separation; as a laboratory reagent; in the electronics industry for quality assurance programs; formerly as a sedative and antitussive

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Bromoform is a central nervous system depressant; in experimental animals it causes liver damage and is carcinogenic to rats.

Ingestion of the liquid has produced central nervous system depression with coma and loss of reflexes at doses in the range of 150 mg/kg; smaller doses have led to listlessness, headache, and vertigo; 300 mg/kg is considered to be the approximate lethal dose in humans.[1,2] Chronic effects have not been reported from industrial exposure.

In an early report, very high concentrations of 56,000 ppm and above were reported to cause death in dogs. The chief symptoms were initial excitation followed by deep sedation.[2]

The oral LD_{50} was 933 mg/kg body weight (bw) in rats and 707 and 1072 mg/kg bw in male and female mice, respectively.[3] Signs of acute toxicity were prostration, lacrimation, and lethargy. In 14-day studies, daily administration of 600 mg/kg bw induced lethargy, shallow breathing, and ataxia and was lethal to rats. In another 2-week study, 250 mg/kg/day resulted in decreases in several indices of cellular and humoral immunity in male mice; slight liver damage as indicated by altered liver enzymes was also noted.[4] Mild tubular hyperplasia and glomerular degeneration were observed in the kidneys of male mice administered 289 mg/kg bw for 14 days.[5]

Hepatocellular vacuolization was observed in male rats administered up to 200 mg/kg bw for 13 weeks and in male mice dosed at 200 and 400 mg/kg bw for the same time period.[3]

In 2-year carcinogenicity studies bromoform induced adenomatous polyps and adenocarcinomas of the large intestines of rats administered 200 mg/kg/day by gavage; no

increase in tumor incidence was observed in mice similarly treated with 100 mg/kg/day.[3]

The IARC has determined that there is limited evidence for the carcinogenicity of bromoform in experimental animals and that it is not classifiable as to its carcinogenicity to humans.[6]

Bromoform has shown positive and negative results in a variety of *in vitro* genotoxic assays. *In vivo* it did not induce micronuclei in mouse bone marrow and did not cause unscheduled DNA synthesis in rat liver.[7]

An increased incidence of minor skeletal variations occurred in the offspring of rats dosed at 100 or 200 mg/kg/day on days 6–15 of gestation.[8] No adverse effect on fertility was found in either the parental or F_1 generation of mice treated for 18 weeks at doses up to 200 mg/kg/day in a continuous breeding reproductive study; a decrease in neonatal (F_1) survival was noted in the high-dose group.[6]

The undiluted liquid was moderately irritating to rabbit eyes, but healing was complete in 1–2 days. Repeated skin contact caused moderate irritation to rabbit skin.[9]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for bromoform is 0.5 ppm (5.2 mg/m^3) with a notation for skin absorption.

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1,3-BUTADIENE
CAS: 106-99-0

C_4H_6

Synonyms: Butadiene; biethylene; divinyl; erythrene; vinylethylene

Physical Form. Colorless gas

Uses. Manufacture of synthetic rubber, especially styrene-butadiene, polybutadiene, and neoprene rubbers

Exposure. Inhalation

Toxicology. 1,3-Butadiene is an irritant of the eyes and mucous membranes; at extremely high concentration it causes narcosis in animals, and severe exposure is expected to produce the same effect in humans. It is carcinogenic in experimental animals and is considered a probable human carcinogen.

Human subjects tolerated 4000 ppm for 6 hours without apparent effect other than slight irritation of the eyes; tolerance to higher exposures appears to develop after a single exposure of 1,3-butadiene.[1] Exposure of two human volunteers to 8000 ppm for 8 hours caused eye and upper respiratory tract irritation.[1]

Dermatitis and frostbite may result from exposure to liquid and evaporating 1,3-butadiene.[2]

Deep anesthesia in rabbits was induced after 8–10 minutes at 200,000–250,000 ppm, and death occurred in 23 minutes at 250,000 ppm.[1] Recovery from brief periods of anesthesia occurred within 2 minutes of terminating exposure; no tissue changes were detectable microscopically after daily induction of anesthesia for as many as 34 times.[1] Daily exposure of rats, guinea pigs, rabbits, and dogs at 6700 ppm over 8 months resulted in no significant chronic effects.[1] In contrast, appreciable mortality occurred in mice exposed to 5000 ppm for 14 weeks.[3]

Toxicological studies have shown butadiene to be a multisite animal carcinogen with marked differences in potency across rodent species.[4]

Exposure of mice to 625 or 1250 ppm 6 hours/day, 5 days/week caused early deaths primarily due to malignant neoplasms involving multiple organs.[3] At the end of 61 weeks there were tumors in 20% of control males and 12% of control females compared with 80% and 94% of the exposed mice. The most common tumors were malignant lymphomas, heart hemangiosarcomas, and alveolar-bronchiolar neoplasms. Nonneoplastic effects associated with these exposures included testicular and ovarian atrophy and nasal cavity lesions. A second long-term inhalation study in mice over an expanded concentration range of 6.25, 20, 62.5, 200, or 625 ppm also caused increased lymphomas, hemangiosarcomas of the heart, and lung neoplasms.[5]

Chronic exposure of rats for 2 years for 6 hours/day, 5 days/week to 1000 or 8000 ppm caused a significant increase in neoplasms of the mammary gland, thyroid, uterus, and zymbal glands of exposed females and in neoplasms of the testes and pancreas (8000 ppm only) in exposed males.[6]

The greater sensitivity in mice than in rats to induction of carcinogenesis is likely related to species differences in metabolism to the active epoxide metabolites.[7]

Associations between occupational exposure to butadiene and increased risk of cancer have been examined in a number of epidemiological studies. The latest update of a cohort mortality study of 2795 male workers employed at least 6 months between 1942 and 1994 at a 1,3-butadiene facility found an increase in lymphohematopoietic cancers (42 deaths vs. 28.6 expected).[8] Subcohort analyses showed that the elevated risk of lymphohematopoietic cancers was restricted to men first employed before 1950 and that cumulative exposure was not significantly associated with risk. These results were consistent with another mortality study of a small cohort of 364 men employed in the production of the monomer; the finding of a significant excess of lymphosarcoma and reticulosarcoma was based on four deaths.[9] A retrospective follow-up of 15,649 styrene-butadiene rubber workers employed for at least 1 year at any of eight North American plants showed a consistent excess of leukemia that is likely due to exposure to butadiene or to butadiene plus other chemicals.[10,11] Deaths from non-Hodgkin lymphoma, multiple myeloma, and stomach cancer did not seem to be related to occupational exposure.[11] Taken as a whole the various epidemiological studies strongly suggest a carcinogenic hazard from 1,3-butadiene exposure, but the IARC has noted that the increased risks of cancer could be due to occupational exposures other than butadiene that have not been identified.[12]

The IARC has concluded that there is sufficient evidence for carcinogenicity to animals

and limited evidence of carcinogenicity to humans.[12]

Butadiene was mutagenic in somatic cells of both rats and mice, although potency was greater in mice.[7] Chromosomal aberrations, sister chromatid exchanges, and micronuclei were found in mice but not rats exposed at higher concentrations. There is limited evidence that 1,3-butadiene is genotoxic in humans, inducing mutagenic and clastogenic damage in somatic cells.[7]

Pregnant mice exposed to 40, 200, or 1000 ppm 1,3 butadiene 6 hours/day on gestational days 6–15 had maternal toxicity at the two highest dose groups; significant exposure-related reductions in the mean body weights of male fetuses occurred at 40 ppm and higher. There was no evidence of selective developmental toxicity in rats similarly exposed, and no increased incidence of malformations was observed in either study.[14]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for butadiene is 2 ppm (4.4 mg/m^3) with an A2-suspected human carcinogen designation.

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***n*-BUTANE**

CAS: 106-97-8

C_4H_{10}

Synonyms: Butane; butylhydride; methylethylmethane

Physical Form. Colorless gas

Uses. As a gasoline blending component to enhance volatility; as a constituent of liquid petroleum gas, which is usually a mixture of

butane and propane and is used as a home fuel; in organic synthesis; as a solvent; as a refrigerant and aerosol propellant; as a food additive

Exposure. Inhalation

Toxicology. *n*-Butane is a central nervous system depressant at high concentrations.

n-Butane may act primarily by depriving victims of oxygen.[1] Initial effects include excitation, euphoria, blurred vision, slurred speech, nausea, vomiting, and increased salivation. With increasing exposure there is confusion, perceptual distortion, hallucinations, delusions, tinnitus, and ataxia. With large doses central nervous system depression, coma, and death (resulting from anoxia, vagal inhibition of the heart, respiratory depression, or cardiac arrhythmias) may occur.[1]

In six men and women, a 10-minute exposure to butane gas at 10,000 ppm resulted in drowsiness.[2]

Voluntary inhalation of butane has led to numerous deaths. Possible mechanisms for the cause of death included the central respiratory and circulatory sequelae of the anesthetic properties of butane, laryngeal edema, chemical pneumonia, and the combined effects of cardiac toxicity and increased sympathetic activity.[3]

In animal studies, the 4-hour LC_{50} in rats was 278,000 ppm and the 2-hour LC_{50} in mice was 287,000.[4] Early studies reported similar values with 270,000 ppm for 2 hours, causing death in 40% of exposed mice, and 310,000 ppm for 2 hours, causing 60% mortality.[5] In dogs, lethality was observed at concentrations of 200,000–250,000 ppm; anesthesia and relaxation preceded death. In animal studies, there was only a small margin of safety between anesthetic and lethal concentrations.

Several studies have indicated that *n*-butane sensitizes the myocardium to epinephrine-induced cardiac arrhythmias. In anesthetized dogs, 5000 ppm caused hemodynamic changes such as decreases in cardiac output, left ventricular pressure, and stroke volume, myocardial contractility, and aortic pressure.[6] Exposure of dogs to 1–20% butane for periods of 2 minutes to 2 hours hypersensitized the heart to ventricular fibrillation induced by epinephrine.[7]

Dermal penetration of butane is not expected to any large extent, as skin contact would be transient because of volatility.[8] *n*-Butane did not cause respiratory or eye irritation in rabbits, but it was mildly to moderately irritating to the skin.[9] Liquefied butane may cause frostbite when applied directly to the skin.[8]

The high odor threshold does not provide adequate warning of overexposure.[2]

The 2003 ACGIH threshold limit value-time-weighted average for *n*-butane is 800 ppm (1900 mg/m^3), which was established because of explosivity hazards rather than toxicological concerns.

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n-BUTYL ACETATE

CAS: 123-86-4

$C_6H_{12}O_2$

Synonyms: Butyl ethanoate; acetic acid, butyl ester

Physical Form. Colorless liquid

Uses. Solvent for nitrocellulose, oils, fats, resins, waxes, and camphor; manufacture of lacquer and plastics

Exposure. Inhalation

Toxicology. *n*-Butyl acetate causes irritation of mucous membranes and the eyes; at high concentrations it causes narcosis in animals, and it is expected that severe exposure will cause the same effect in humans.

In humans, *n*-butyl acetate affected the throat at 200 ppm; severe throat irritation occurred at 300 ppm, and the majority of the subjects also complained of eye and nose irritation.[1] Only slight eye and pulmonary irritation (as determined by lung function tests) were observed in volunteers exposed to 1400 mg/m^3 for 20 minutes or 700 mg/m^3 for 4 hours.[2]

Guinea pigs exhibited signs of eye irritation at 3300 ppm; at 7000 ppm, there was narcosis within 700 minutes but no deaths after exposure for 810 minutes; 14,000 ppm was lethal after 4 hours.[3] Cats exposed to 4200 ppm for 6 hours for 6 days showed weakness, loss of weight, and minor blood changes.[4]

Impaired neurological function has been described in more recent animal studies with *n*-butyl acetate. Exposure at 8000 ppm for 20 minutes resulted in decreased locomoter activity and changes to the functional observational battery including changes in posture, decreased arousal, increased tonic/clonic movements, disturbances in gait, delayed righting reflexes, and increased sensorimotor reactivity in mice.[5] Repeated exposure of rats at 3000 ppm 6 hours/day for 65 days resulted in transient signs of sedation but no evidence of cumulative neurotoxicity based on the functional observational battery, neurohistopathology, and operant behavior end points.[6]

There are no indications of mutagenic or cytogenic effects for *n*-butyl acetate.[7]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for *n*-butyl acetate is 150 ppm (713 mg/m^3) with a TLV-STEL of 200 ppm (950 mg/m^3).

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sec-BUTYL ACETATE

CAS: 105-46-4

$C_6H_{12}O_2$

Synonyms: 2-Butanol acetate; acetic acid, secondary butyl ester

Physical Form. Colorless liquid

Uses. In solvents, especially lacquer solvents; textile sizes and paper coatings

Exposure. Inhalation

Toxicology. *sec*-Butyl acetate is considered to be an irritant of the eyes and respiratory tract. By analogy with chemically similar substances, it may be a central nervous system depressant at very high concentrations.[1]

Skin irritation may occur. *sec*-Butyl acetate has not been studied regarding its toxicity, nor are there any reports concerning harmful effects on humans.[2]

The odor of *sec*-butyl acetate is milder than that of *n*-butyl acetate, and it appears less irritative to the eyes and respiratory tract.[1]

The 2003 ACGIH threshold limit value-ceiling (TLV-C) for *sec*-butyl acetate is 200 ppm (950 mg/m^3).

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tert-BUTYL ACETATE

CAS: 540-88-5

$CH_3COOC(CH_3)_3$

Synonym: Acetic acid, *tert*-butyl ester

Physical Form. Colorless liquid

Uses. Gasoline additive; lacquer solvent

Exposure. Inhalation

Toxicology. *tert*-Butyl acetate is expected to cause irritation of the eyes and throat. It is considered a central nervous system depressant at very high concentrations.

There are no reports of adverse health effects in workers from *tert*-butyl acetate exposure.

In rats the inhalation LD_{50} is greater than 2230 mg/kg/4 hours, and the oral LD_{50} is 4100 mg/kg.[1] Signs of toxicity included dyspnea and ataxia with oral administration. Applied to rabbit skin or instilled in the eye, the liquid was mildly irritating. There are no indications of mutagenic or cytogenic effects of *tert*-butyl acetate, nor are there available carcinogenic studies.[2]

The 2003 ACGIH TLV-ceiling (TLV-C) for *tert*-butyl acetate is 200 ppm (950 mg/m^3).

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n-BUTYL ACRYLATE

CAS: 141-32-2

$C_7H_{12}O_2$

Synonyms: Acrylic acid butyl ester; 2-propenoic acid butyl ester

Physical Form. Colorless liquid with acrid odor; commercial form contains hydroquinone (1000 ppm) or hydroquinone methyl ether (15 or 200 ppm) to prevent polymerization

Uses. Manufacture of polymers and resins for textiles, paints, and leather finishes

Exposure. Inhalation; skin absorption

Toxicology. Butyl acrylate is an irritant of the eyes and skin.

In one report, a woman with dermatitis from the plastic nose pads of her spectacle frames was found on patch testing to react to 1% butyl acrylate but not to ethyl or methyl acrylate.[1] The sensitization was attributed to butyl acrylate, which might have been present in the plastic nose pads.

In an early range-finding study, exposure of rats to 1000 ppm for 4 hours was lethal to 5 of 6 animals.[2] In a more recent study, the LC_{50} for 4 hours in rats was 2730 ppm.[3] Behavior of the animals suggested irritation of the eyes, nose, and respiratory tract, with labored breathing. At necropsy, there were no discernible gross abnormalities of the major organs.

The rabbit dermal LD_{50} was on the order of 1800 mg/kg.[4] On the skin of rabbits, butyl acrylate was moderately irritating.[2] In the rabbit eye, the liquid produced corneal necrosis.

Hamsters and rats were exposed to an average concentration of 817 and 820 ppm, respectively, for 4 days.[5] In both animal species, there were distinct signs of toxicity; 4 of 10 hamsters died during the exposure. Chromosome analysis of bone marrow cells after the exposure indicated no damaging effects.

In a dermal carcinogenesis study, 25 µl of 1% butyl acrylate in acetone was applied three times weekly to mice for their lifetime.[6] No epidermal tumors were observed, indicating no evidence for local carcinogenic activity.

No neoplastic effect was observed in rats exposed to 0, 15, 45, or 135 ppm for 6 hours/day, 5 days/week for 2 years.[7] Dose-related changes, which include atrophy of the neurogenic epithelial cells and hyperplasia of the reserve cells, mainly affected the anterior part of the olfactory epithelium. In the high-dose group there was opacity of the cornea. After a 6-month postexposure period reconstructive effects were observed in both tissues.

Assays for genotoxicity have generally given negative results.[8]

The IARC has determined that there is inadequate evidence for carcinogenicity of *n*-butyl acrylate to experimental animals, and no data are available on humans.[8]

In a reproductive study, inseminated rats were exposed to butyl acrylate at 0, 25, 135, and 250 ppm 6 hours/day, from the 6th to the 15th day post coitum.[9] During the inhalation period the two high doses led to maternal toxicity, including signs of mucous membrane irritation. The same levels induced embryolethality, measured as an increased number of dead implantations. The 25-ppm level did not cause maternal toxicity or embryolethality. A teratogenic effect was not seen at any of the exposure levels. In another report in rats, butyl acrylate was not selectively toxic to the embryo or fetus, causing reduced fetal weights after gestational exposure at 200 or 300 ppm that also caused overt signs of maternal toxicity.[10]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for *n*-butyl acrylate is 10 ppm (52 mg/m^3).

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n-BUTYL ALCOHOL

CAS: 71-36-3

$C_4H_{10}O$

Synonyms: *n*-Butanol; butyric alcohol; propyl carbinol; butyl hydroxide; 1-butanol

Physical Form. Colorless liquid

Uses. Lacquer solvent; manufacture of plastics and rubber cements

Exposure. Inhalation; skin absorption

Toxicology. *n*-Butyl alcohol is an irritant of the eyes and mucous membranes and may cause central nervous system depression at very high concentrations.

Chronic exposure of humans to concentrations above 50–200 ppm causes irritation of the eyes with lacrimation, blurring of vision, and photophobia.[1,2]

In a 10-year study of workers exposed to average concentrations of 100 ppm, no systemic effects were observed.[1] Other reports have suggested that long-term exposure may cause effects on the auditory nerve resulting in hearing loss.[3]

Contact dermatitis of the hands may occur because of a defatting action of the liquid, and toxic amounts can be absorbed through the skin.[4] Direct contact of the hands with *n*-butyl alcohol for 1 hour results in an absorbed dose that is four times that of inhalation of 50 ppm for 1 hour.[4]

No effects were observed in mice exposed to 3300 ppm for 7 hours, whereas exposure to 6600 ppm produced prostration within 2 hours, narcosis after 3 hours, and some deaths.[4]

Administered to pregnant rats by inhalation 7 hours/day on days 1–19 of gestation, 8000 ppm caused reduced fetal weights, an increased incidence of skeletal malformations, and significant maternal toxicity in the form of narcosis and reduced feed consumption.[5] At 3500 ppm for the same exposure time, there were no fetal or maternal effects.

n-Butyl alcohol was not mutagenic in the Ames *Salmonella typhimurium* assay.[3] The odor threshold is approximately 15 ppm, but after adaptation the threshold can increase to 10,000 ppm.[4]

The 2003 ACGIH threshold limit ceiling value (TLV-C) for *n*-butyl alcohol is 50 ppm (152 mg/m^3) with a notation for skin absorption.

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sec-BUTYL ALCOHOL

CAS: 78-92-2

$C_4H_{10}O$

Synonyms: 2-Butanol; ethylmethyl carbinol; butylene hydrate; 2-hydroxybutane

Physical Form. Colorless liquid

Uses. Polishes, cleaning materials, paint removers, fruit essences, perfumes, and dyestuffs; synthesis of methyl ethyl ketone; lacquer solvent

Exposure. Inhalation

Toxicology. At high concentrations *sec*-Butyl alcohol causes narcosis in animals, and it is expected that severe exposure will produce the same effect in humans.

Heavy exposure reportedly causes eye, nose, and throat irritation, headache, nausea, fatigue, and dizziness.[1]

In mice, ataxia, prostration, and narcosis occurred at various times after exposure to concentrations ranging from 3,300 ppm to 19,800 ppm.[1] Exposure to 16,000 ppm for 4 hours was lethal to five of six rats.[2] Mice repeatedly exposed to a concentration of 5330 ppm for a total of 117 hours were narcotized but survived.

Administered by inhalation to pregnant rats on days 1–19 of gestation for 7 hours/day, 7000 ppm caused an increased incidence in resorptions, reduced fetal weights, significant maternal toxicity in the form of narcosis, reduced feed consumption, and reduced weight gain.[3] At 3500 ppm some maternal toxicity was observed, but there were no fetal effects.

When instilled directly into a rabbit eye the liquid caused severe corneal injury, but it was not irritating to the skin of rabbits.[2]

sec-Butyl alcohol has an odor similar to, but less pungent than, *n*-butyl alcohol. The malodorous and irritating properties probably prevent exposure to toxic levels.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for *sec*-butyl alcohol is 100 ppm (303 mg/m^3).

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tert-BUTYL ALCOHOL

CAS: 75-65-0

$(CH_3)_3COH$

Synonyms: 2-Methyl-2-propanol; trimethyl carbinol; *tert*-butanol

Physical Form. Colorless liquid or solid

Uses. Plastics, lacquers, cellulose esters, fruit essences, perfumes, and chemical intermediates; additive to unleaded gasoline

Exposure. Inhalation

Toxicology. At high concentrations *tert*-butyl alcohol causes narcosis in animals, and it is expected that severe exposure in humans will result in the same effect; with repeated exposures in rodents the urinary tract is the primary target.

In humans, heavy exposure may cause irritation of the eyes, nose, and throat; headache; nausea; fatigue; and dizziness.[1] Systemic effects have not been reported. Application of *tert*-butyl alcohol to skin causes slight erythema and hyperemia.[1]

Signs of intoxication in rats were ataxia and narcosis; the oral LD_{50} was 3.5 g/kg.[2] In a 90-day study in F344 rats and B6C3F1 mice, 0.25%, 0.5%, 1%, 2%, or 4% was administered in the drinking water.[3] The high dose was lethal to some animals, and clinical signs included ataxia in rats and ataxia, hypoactivity, and abnormal posture in mice. Gross lesions at necropsy were urinary tract calculi, renal pelvi and ureteral dilation, and thickening of the urinary bladder mucosa. In male rats the microscopic renal changes were suggestive of a 2μ-globulin nephropathy.

Increased kidney weights that correlated with increased chronic nephropathy occurred in male mice and rats exposed by inhalation to concentrations up to 2100 ppm for 13 weeks.[4]

In 2-year drinking water studies, there was some evidence of carcinogenic activity in male rats based on increased incidences of renal tubule adenomas and carcinomas; there was equivocal evidence of carcinogenicity in female mice based on increased incidences of follicular cell adenoma.[5]

Administered by inhalation for 7 hours/day on gestation days 1–19, 5000 ppm caused reduced fetal weights and maternal toxicity in the form of narcosis, reduced feed consumption, and reduced maternal weights.[6]

tert-Butyl alcohol was not genotoxic in a variety of *in vitro* and *in vivo* assays.[5]

The malodorous quality and irritant effects of *tert*-Butyl alcohol may prevent inadvertent exposure to toxic levels.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for *tert*-butyl alcohol is 100 ppm.

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BUTYLAMINE
CAS: 109-73-9

$CH_3(CH_2)_3NH_2$

Synonyms: 1-Aminobutane; *n*-butylamine

Physical Form. Colorless liquid

Uses. Intermediate for pharmaceuticals, dyestuffs, rubber chemicals, emulsifying agents, insecticides, synthetic tanning agents

Exposure. Inhalation; skin absorption

Toxicology. Butylamine is an irritant of the eyes, mucous membranes, and skin.

In humans, the liquid on the skin causes severe primary irritation and second-degree burns with vesiculation.[1] Workers exposed daily at 5–10 ppm complained of irritation of the nose, throat, and eyes and, in some instances, headache and flushing of the skin of the face.[1,2] Concentrations of 10–25 ppm are unpleasant and even intolerable to some subjects for exposure of more than a few minutes duration; daily exposures of workers to less than 5 ppm (usually 1–2 ppm) resulted in no symptoms.[1]

In rats exposed to 3000–5000 ppm there was an immediate irritant response, followed by labored breathing, pulmonary edema, and death within minutes to hours.[1]

The oral LD_{50} for *n*-butylamine in rats was 372 mg/kg versus 228, 152, and 80 mg/kg for isobutylamine, *sec*-butylamine. and *tert*-butylamine, respectively.[3] Signs of toxicity included sedation, ataxia, nasal discharge, gasping, salivation, and death. Pathologic examination showed pulmonary edema.

The concentrated liquid produced severe eye damage and skin burns in animals.[1]

The 2003 ACGIH threshold limit value-ceiling limit (TLV-C) for butylamine is 5 ppm (15 mg/m^3) with a notation for skin absorption.

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tert-BUTYL CHROMATE

CAS: 1189-85-1

$C_8H_{18}CrO_4$

Synonyms: Bis(*tert*-butyl)chromate; chromic acid, di-*tert*-butyl ester

Physical Form. Clear, colorless liquid

Uses. In specialty reactions as a source of Cr; manufacture of catalysts; polymerization of olefins; curing agent for urethane resins

Exposure. Inhalation; skin absorption

Toxicology. *tert*-Butyl chromate is expected to cause irritation of the eyes, nose, and skin.

Skin contact with *tert*-butyl chromate caused necrosis of the skin and death of rats.[1] In another report exposed rats had an increase in respiratory rate and signs of mild narcosis.[2]

tert-Butyl chromate is considered to be an inferred carcinogen because it is a hexavalent chromium compound.[2]

The 2003 ACGIH threshold limit value-ceiling limit (TLV-C) is 0.1 mg/m^3, measured as chromium trioxide, with a notation for skin absorption.

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n-BUTYL GLYCIDYL ETHER

CAS: 2426-08-6

$C_4H_9OCH_2CHOCH_2$

Synonyms: BGE; 1-*n*-butoxy-2,3-epoxypropane; 1,2-epoxy-3-butoxypropane; 2,3-epoxypropyl butyl ether

Physical Form. Colorless liquid

Uses. Viscosity-reducing agent, acid acceptor for solvents, chemical intermediate

Exposure. Inhalation

Toxicology. *n*-Butyl glycidyl ether (BGE) causes central nervous system depression and is a mild irritant of the eyes and skin in animals; it is expected that severe exposure will cause the same effects in humans.

Two workers exposed to spilled BGE for up to 4 hours in a confined space developed symptoms of coughing, vomiting, ataxia, and headache.[1] No chronic systemic effects have been reported in humans. However, sensitization dermatitis may occur with repeated skin contact.[2]

Intragastric and intraperitoneal injection of BGE in animals produced incoordination and ataxia followed by coma.[2] In rats exposed to graded vapor concentrations of BGE, effects were lacrimation, nasal irritation, and labored breathing. Testicular atrophy has also been reported in male rats after repeated exposures.[3] The LC_{50} was 1030 ppm for an 8-hour exposure in rats and greater than 3500 ppm for 4 hours in mice. At autopsy, pneumonitis was frequently observed. Three intramuscular injections of 400 mg/kg produced minimal toxic effects and a slight increase in leukocyte counts.[4] In male mice topically treated with 1.5 g/kg for 8 weeks and then mated, there was a significant increase in the number of fetal deaths compared with controls.[5]

BGE produced widely disparate degrees of skin irritation, ranging from very mild to severe, in tests by different investigators using similar methodology.[5] After a series of intracutaneous injections, 16 of 17 guinea pigs became sensitized.[6] The undiluted liquid in rabbit eyes caused mild eye irritation.[2]

BGE was mutagenic in bacterial assays, and DNA damage was induced in human cells *in vitro*.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for *n*-butyl glycidyl ether is 25 ppm (133 mg/m^3).

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n-BUTYL MERCAPTAN

CAS: 109-79-5

$CH_3(CH_2)_3SH$

Synonyms: 1-Butanethiol; thiobutyl alcohol; butyl sulfhydrate

Physical Form. Colorless liquid

Uses. Solvent; intermediate in the production of insecticides and herbicides; gas odorant

Exposure. Inhalation

Toxicology. *n*-Butyl mercaptan is a central nervous system depressant.

Accidental exposure of seven workers to concentrations estimated between 50 and 500 ppm for 1 hour caused muscular weakness and malaise; six of the workers experienced sweating, nausea, vomiting, and headache; three experienced confusion, and one of the individuals lapsed into a coma for 20 minutes.[1] On admission to the hospital, all of the workers had flushing of the face, increased rate of breathing, and obvious mydriasis. Six of the patients recovered within a day, but the most seriously affected patient experienced profound weakness, dizziness, vomiting, drowsiness, and depression.

In a proportional mortality study, exposure to butyl mercaptan, a degradation product of cotton defoliants, did not account for a higher respiratory mortality in cotton-growing areas of California.[2]

In rats, the LC_{50} for 4 hours was 4020 ppm; effects were irritation of mucous membranes, increased respiration, incoordination, staggering gait, weakness, partial skeletal muscle paralysis beginning in the hind limbs, light to severe cyanosis, and mild to heavy sedation.[3] Animals that survived single near-lethal doses by the intraperitoneal and oral routes frequently had liver and kidney damage at autopsy up to 20 days after treatment. The liquid dropped in the eyes of rabbits caused slight to moderate irritation. No dermal changes were observed when 0.2 ml of a 20% solution was applied to the clipped skin of guinea pigs for 10 days.[1]

Female mice and rats exposed 6 hours/day at concentrations of 10, 68, or 152 ppm during gestation had reduced maternal weight gain at the higher doses; embryotoxic effects and increased resorptions occurred in the mice exposed at 68 and 152 ppm.[4]

The disagreeable, skunk-like odor is detectable at about 0.0001–0.001 ppm.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for *n*-butyl mercaptan is 0.5 ppm (1.8 mg/m^3).

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***o-sec*-BUTYLPHENOL**

CAS: 89-72-5

$C_{10}H_{14}O$

Synonyms: Phenol, *o-sec*-butyl; 2-(1-methylpropyl)phenol

Physical Form. Liquid

Uses. A chemical intermediate in the production of resins, plasticizers, and other products

Exposure. Inhalation; skin absorption

Toxicology. *o-sec*-Butylphenol is a skin, eye, and respiratory irritant.

Acute occupational exposures have resulted in mild respiratory irritation as well as skin burns.[1]

Rats survived a 7-hour exposure to an atmosphere saturated with the vapor.[1] The oral LD_{50} for rats is 2700 mg/kg.[2] In guinea pigs the oral and skin absorption LD_{50} ranged between 600 and 2400 mg/kg.[1]

On the skin of rabbits 500 mg for 24 hours caused severe skin irritation, and 50 µg in the eyes of rabbits for 24 hours also produced severe irritation.[2] In another report no corneal injury was caused by direct contact of the liquid with the eyes of guinea pigs.[1]

o-sec-Butylphenol was not mutagenic in a number of bacterial assays.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for *o-sec*-butylphenol is 5 ppm (31 mg/m^3) with a notation for skin.

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p-tert-BUTYL TOLUENE

CAS: 98-51-1

$(CH_3)_3CC_6H_4CH_3$

Synonyms: *p*-Methyl-*tert*-butylbenzene; TBT; 1-methyl-4-tertiary butylbenzene

Physical Form. Clear, colorless liquid

Uses. Solvent for resins; intermediate in organic synthesis

Exposure. Inhalation

Toxicology. *p-tert*-Butyl toluene is an irritant of the mucous membranes, a central nervous system depressant and may cause cardiovascular and hematologic disturbances; chronic exposure in animals causes lung, brain, liver, and kidney damage.

Exposure of human volunteers for 5 minutes to concentrations of 5–160 ppm caused complaints of irritation of the nose and throat, nausea, and metallic taste; moderate eye irritation occurred at 80 ppm.[1] Exposed workers have complained of nasal irritation, nausea, headache, malaise, and weakness. Signs and symptoms included decreased blood pressure, increased pulse rate, tremor, anxiety, and evidence of chemical irritation from skin contact. Laboratory findings suggested slight bone marrow depression.

The LD_{50} in female rats ranged from 934 ppm for 1 hour to 165 ppm for 8 hours.[1] Principal effects were irregular gait, paralysis, narcosis, and dyspnea as well as eye irritation. At autopsy, there was pulmonary edema and severe hemorrhage in some animals. Repeated exposures of rats to 50 ppm produced liver and kidney changes and lesions in the spinal cord and brain. Male rats exposed 6 hours/day for 14 days at 20 ppm had persistent changes in the visual pathway of the central nervous system as determined by changes in visually evoked potentials.[2] The liquid on the rabbit skin was only a mild irritant.

p-tert-Butyl toluene was not mutagenic in a number of bacterial strains in the Ames assay with or without metabolic activation.[3]

The odor is recognized by most people at 5 ppm, but tolerance may be readily acquired. The irritating property may not be sufficient to protect from hazardous concentrations.

The ACGIH threshold limit value-time-weighted average (TLV-TWA) for *p-tert*-butyl toluene is 1 ppm (6.1 mg/m^3).

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CADMIUM (and Compounds)
CAS: 7440-43-9

Cd

Compounds: Cadmium oxide; cadmium carbonate; cadmium chloride; cadmium sulfate; cadmium sulfide

Physical Form. The metal is soft, ductile, silver-white, electropositive; cadmium oxide may take the form of a colorless amorphous powder or red or brown crystals.

Uses. The metal is used in electroplating, in solder for aluminum, as a constituent of easily fusible alloys, as a deoxidizer in nickel plating, in process engraving, in cadmium-nickel batteries, and in reactor control rods. Cadmium compounds are employed as TV phosphors, as pigments in glazes and enamels, in dyeing and printing, and in semiconductors and rectifiers.

Exposure. Inhalation; ingestion

Toxicology. Cadmium oxide fume is a severe pulmonary irritant; cadmium dust also is a pulmonary irritant, but it is less potent than cadmium fume because it has a larger particle size. Chronic exposure is associated with nephrotoxicity. Several inorganic cadmium compounds cause malignant tumors in animals.

Inhalation exposure to high levels of cadmium fumes or dust is intensely irritating to respiratory tissue.[1] Particle size appears to be a more important determinant of toxicity than chemical form.[1] Symptoms may include tracheobronchitis, pneumonitis, pulmonary edema, and death. However, most acute intoxications have been caused by inhalation of cadmium fume at concentrations that did not provide warning symptoms of irritation. Concentrations of fume responsible for fatalities have been 40–50 mg/m^3 for 1 hour or 9 mg/m^3 for 5 hours.[2] Nonfatal pneumonitis has been reported from concentrations of 0.5–2.5 mg/m^3, and relatively mild cases have been attributed to even lower concentrations. After an asymptomatic latent period of 4–10 hours there is characteristically nasopharyngeal irritation, a feeling of chest constriction or substernal pain, cough, and dyspnea; there also may be headache, chills, muscle aches, nausea, vomiting, and diarrhea.[3,4] Pulmonary edema may develop rapidly, with decreased vital capacity and markedly reduced carbon monoxide diffusing capacity.[4] In about 20% of cases, dyspnea is progressive, accompanied by wheezing or hemoptysis, and may result in death within 7–10 days after exposure; at autopsy the lungs are markedly congested and there is an intraalveolar fibrinous exudate, as well as alveolar cell metaplasia.[3,4] Among survivors, the subsequent course is unpredictable; most cases resolve slowly, but respiratory symptoms may linger for several weeks, and impairment of pulmonary function may persist for months.[4]

Longer-term inhalation exposure at lower levels leads to decreased lung function and emphysema.[1] Early minor changes in ventilatory functions may progress with continued exposure, to respiratory insufficiency.

Chronic exposure to cadmium results in renal damage. This damage can be identified by increased urinary levels of β_2-microglobulin, retinol-binding protein, or other low-molecular-weight proteins.[1,5] Increasing damage results in excretion of higher-molecular-weight proteins, indicating either glomerular damage or severe tubular damage.[1] The frequency of occurrence of proteinuria increases with length of exposure; in one study, persons exposed to cadmium compounds for less than 2 years had no proteinuria whereas most of those exposed for 12 years or more had

proteinuria with little other evidence of renal damage.[4] It has been estimated that overt proteinuria can occur only after 5–10 years of exposure to approximately 100 µg cadmium/m^3.[6] Renal damage may continue to progress even after exposure ceases.

The urinary excretion of cadmium itself bears no known relationship to the severity or duration of exposure and is only a confirmation of absorption.[3] Absorbed cadmium is retained by the body to a large extent, and excretion is very slow.[7]

Other consequences of cadmium exposure are anemia, eosinophilia, yellow discoloration of the teeth, rhinitis, occasional ulceration of the nasal septum, damage to the olfactory nerve, and anosmia.[8,9]

Chronic exposure to high levels of cadmium in food has caused bone disorders including osteoporosis and osteomalacia.[1] Long-term ingestion of water, beans, and rice contaminated with cadmium by a Japanese population was associated with a crippling condition, Itai-Itai disease. The affliction is characterized by pain in the back and joints, osteomalacia, bone fractures, and occasional renal failure, and it most often affected women with multiple risk factors such as multiparity and poor nutrition.[10]

Occupational exposure to cadmium has been implicated in a significant increase in lung cancer cases.[11] Occupational cohort studies from the United Kingdom and Sweden have found increased mortality rates from lung cancer, but they were not necessarily related to level and duration of cadmium exposure.[11] In an American cohort, a 2.8-fold increase in lung cancer was found in the group with the highest cadmium exposure, and the dose response trend over three exposure groups was also significant.[12] Epidemiological studies are confounded by a number of factors such as smoking, concomitant exposure to other carcinogens including nickel and arsenic, small exposure populations, and limited exposure data.[11]

A number of early studies also reported an increased risk for prostate cancer, which has not been confirmed in later studies.[11]

In long-term inhalation studies exposure to aerosols of cadmium chloride, sulfate, sulfide, and oxide has caused lung tumors in rats.[13] Subcutaneous or intramuscular injection with certain cadmium salts has caused rhabdomyosarcomas and fibrosarcomas in rats; with cadmium sulfate or cadmium sulfide there were local sarcomas, and with cadmium chloride there were local pleomorphic sarcomas and testicular interstitial cell tumors.[14–16]

The IARC has determined that there is sufficient evidence in humans for the carcinogenicity of cadmium and cadmium compounds.[11] In animals, there is sufficient evidence for the carcinogenicity of cadmium compounds and limited evidence for cadmium metal.

Both positive and negative genotoxic results have been reported.

In rat developmental studies, fetal effects including delayed ossification and decreased locomotor activity occurred at doses that also caused maternal toxicity.[17] Cadmium sulfate injected into the lingual vein of female hamsters on day 8 of pregnancy caused a high incidence of resorption and malformed offspring.[18] Acute necrosis of rat testes followed large doses orally or parenterally, but testicular effects have not been reported thus far in humans.[15]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for elemental cadmium and compounds as Cd is 0.01 mg/m^3 for total particulate dust or 0.002 mg/m^3 for the respirable fraction of dust; there is an A2-suspected human carcinogen designation.

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CALCIUM CARBONATE

CAS: 1317-65-3

$CaCO_3$

Synonyms: Limestone; chalk; dolomite; marble

Physical Form. Odorless, tasteless powder or crystal

Uses. Manufacture of quicklime, Portland cement, and paints. United States Pharmacopeia (USP) grades are used in dentifrices, cosmetics, food, and pharmaceuticals such as antacids.

Exposure. Inhalation

Toxicology. Calcium carbonate is considered to be a nuisance dust.

Although no adverse effects have been reported in the literature among workers exposed to calcium carbonate, high concentrations of the dust would be expected to act as a physical irritant to the eyes and skin.[1] Fourteen British workers exposed to heavy calcium carbonate concentrations for 12–35 years showed no trace abnormalities due to dust or any clinical sign of pneumoconiosis or chronic bronchitis on X ray.[2] Long exposure to high dust concentrations of pure calcium carbonate (quartz content less than 1.1%) did not result in lung fibrosis.

The 2003 threshold limit value-time-weighted average (TLV-TWA) is 10 mg/m^3, total dust, containing no asbestos and <1% crystalline silica.

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CALCIUM CYANAMIDE
CAS: 156-62-7

$CCaN_2$

Synonyms: Calcium saltcyanamide; calcium carbimide; cyanamide (although this synonym commonly refers to hydrogen cyanamide)

Physical Form. White or gray crystalline solid

Uses. Manufacture of calcium cyanide and dicyandiamide; formerly used as a defoliant and herbicide

Exposure. Inhalation

Toxicology. Calcium cyanamide is an irritant.

Calcium cyanamide is severely irritating to the eyes and skin and causes skin ulceration.[1] Sensitization dermatitis has been reported in 0.5–1% of exposed workers. Inhalation of the dust, presumably at high levels, has caused headache, tachypnea, hypotension, and pulmonary edema.[2] Calcium cyanamide does not liberate cyanide when acidified or in vivo. The lethal oral dose in humans is 40–50 g. In commercial form, calcium cyanamide may also contain calcium hydroxide and calcium carbonate.

Calcium cyanamide is an inhibitor of aldehyde dehydrogenase, and concurrent intake of ethanol can increase susceptibility to a transient vasomotor disturbance apparent in the face, chest, and arms known as "cyanamide blush."[3] In six male alcoholic volunteers, oral administration of 0.7 mg/kg of the chemical and ingestion of ethanol produced tachycardia and decreased diastolic blood pressure.

In a carcinogenesis feeding study at levels of 2000 ppm in both sexes of mice, and at 400 ppm in female rats and 200 ppm in male rats, calcium cyanamide did not act as a carcinogen.[4]

Calcium cyanamide was weakly mutagenic in *Salmonella typhimurium* strain TA1535 and nonmutagenic in strain TA100.[5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for calcium cyanamide is 0.5 mg/m^3.

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CALCIUM HYDROXIDE
CAS: 1305-62-0

$Ca(OH)_2$

Synonyms: Slaked lime; hydrated lime; calcium hydrate

Physical Form. White, microcrystalline powder

Uses. In the manufacture of mortar, plaster, whitewash, and paper pulp; in lubricants; in drilling fluids

Exposure. Inhalation

Toxicology. Calcium hydroxide is a relatively strong base and, therefore, a caustic irritant of all exposed surfaces of the body including the respiratory tract.

Calcium hydroxide is one of the most common causes of severe chemical eye burns.[1] In almost all cases there is a semisolid particulate paste in contact with the cornea and conjunctiva, tending to adhere and to dissolve slowly. Strongly alkaline calcium hydroxide solution is formed and causes severe injury if not removed promptly.

The 1993 Annual Survey of Occupational Injuries and Illnesses from the Bureau of Labor Statistics reported 110 cases of dermatitis attributed to calcium hydroxide (and other calcium oxides) exposure; the skin disorders resulted in a median of 9 days away from work, with 27% having more than 20 days away from work.[2]

The oral LD_{50} for rats is between 4.8 and 11.1 g/kg.[3] Rats administered tap water containing 50 or 350 mg/l had reduced food intake and were restless and aggressive at 2 months; at 3 months they showed a loss in body weight, decreased counts for erythrocytes and phagocytes, and decreased hemoglobin.[4] Autopsy showed inflammation of the small intestine and dystrophic changes in the stomach, kidneys, and liver.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for calcium hydroxide is 5 mg/m^3.

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CALCIUM OXIDE

CAS: 1305-78-8

CaO

Synonyms: Burnt lime; calx; lime; quicklime

Physical Form. Crystals, white or grayish-white lumps or granular powder

Uses. In construction materials; manufacture of steel, aluminum, and magnesium; as a scrubbing agent to remove sulfur dioxide emissions from smokestacks; manufacture of glass, paper, and industrial chemicals; in fungicides, insecticides, and lubricants

Exposure. Inhalation

Toxicology. Calcium oxide is an irritant of the eyes, mucous membranes, and skin.

The irritant effects are probably due primarily to its alkalinity, but dehydrating and thermal effects also may be contributing factors.[1] Strong nasal irritation was observed from exposure to a mixture of dusts containing calcium oxide in the range of 25 mg/m^3, but levels of 9–10 mg/m^3 produced no observable irritation.[2] Inflammation of the respiratory tract, ulceration and perforation of the nasal septum, and pneumonia have been attributed to inhalation of calcium oxide dust; severe irritation of the upper respiratory tract ordinarily causes persons to avoid serious inhalation exposure.[1,2]

Particles of calcium oxide can cause severe burns of the eyes.[3] It can produce skin burns and fissuring and brittleness of the nails.[4]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for calcium oxide is 2 mg/m^3.

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CALCIUM SILICATE

CAS: 1344-95-2

$CaSiO_3$

Synonyms: Calcium hydrosilicate; calsil; Microcel; Calflo E; Florite R; Marimet 45; tobermorite (crystalline form of synthetic calcium silicate); wollastonite is a naturally occurring fibrous form

Physical Form. White powder

Uses. Anticaking agent in table salt, foods, pharmaceuticals, and agricultural pesticides; replacement for asbestos in thermal insulation

Exposure. Inhalation

Toxicology. The toxicity of calcium silicate depends on particle size, aspect ratio, and amount of silica and respirable fiber.[1] Synthetic nonfibrous calcium silicate is considered to be a nuisance dust.

Skin irritation was reported in a worker exposed to an atmosphere permeated with calcium silicate.[1] A study of 104 wallastonite (a naturally occurring calcium silicate mineral) miners showed no relationship between the prevalence of chronic bronchitis or airflow obstruction with increasing exposure.[1] In a cohort mortality study of wollastonite quarry workers the observed numbers of deaths from all cancers combined and lung cancer were lower than expected.[2]

Effects of three commercially produced calcium silicate insulation materials were examined in rats by inhalation and intraperitoneal injection.[3] Exposure to 10 mg/m^3 of respirable dust for 7 hours/day, 5 days/week for 12 months had no effect on the survival of treated animals compared with controls. Although two pulmonary neoplasms, one malignant and one benign, were found in exposed animals, neither was the cause of death, and the incidence was not significantly different from the control group, where no tumors were found. One peritoneal mesothelioma was found in an animal from one of the inhalation groups, but this was considered to be a spontaneous tumor as none of over 100 animals injected intraperitoneally with 25 mg of calcium silicate developed these tumors.

At concentrations of 10 and 100 µg/ml, calcium silicate significantly increased the frequencies of chromosomal aberrations and sister chromatid exchanges in peripheral human blood lymphocytes.[4]

The 2003 threshold limit value-time-weighted average (TLV-TWA) for calcium silicate is 10 mg/m^3 for total dust containing no asbestos and <1% crystalline silica.

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CALCIUM SULFATE

$CaSO_4$
CAS: 7778-18-9

$CaSO_4 \cdot 2H_2O$
CAS: 10104-41-4

Synonyms: Anhydrous calcium sulfate; anhydrous sulfate of lime; gypsum ($CaSO_4 \cdot 2H_2O$; plaster of paris ($CaSO_4 \cdot 1/2H_2O$)

Physical Form. Crystal or powder

Uses. The insoluble anhydrite is used in cement formulations and as a paper filler; the soluble anhydrite is used as a drying agent; the hemihydrate is used for wall plaster and wallboard; gypsum is used in manufacture of plaster of paris and portland cement.

Exposure. Inhalation

Toxicology. Calcium sulfate is considered to be a nuisance dust.

There have been no reports of adverse effects in humans exposed to calcium sulfate. Excessive concentrations would be expected to cause reduced visibility and skin and upper respiratory tract irritation.[1] One report on gypsum miners attributed adverse effects to respirable quartz rather than calcium sulfate.[2]

The 2003 threshold limit value-time-weighted average (TLV-TWA) is 10 mg/m^3, total dust, containing no asbestos and <1% crystalline silica.

CAMPHOR

CAS: 76-22-2

$C_{10}H_{16}O$

Synonyms: 2-Bornanone; 2-camphanone; 2-keto-1,7,7-trimethylnorcamphane

Physical Form. Translucent crystals with characteristic odor

Uses. Plasticizer for cellulose esters and ethers; manufacture of plastics; in lacquers and varnishes; in explosives; in pyrotechnics; as moth repellant; as preservative in pharmaceuticals and cosmetics

Exposure. Inhalation; skin absorption

Toxicology. Camphor is an irritant of the eyes and the nose; at high concentrations it is a convulsant.

Camphor is readily absorbed from all sites of administration, producing a feeling of coolness on the skin, whereas oral doses cause a sensation of warmth in the stomach.[1]

Symptoms of vapor exposure in humans are irritation of the eyes and nose and anosmia; these symptoms occur at concentrations above 2 ppm.[2] Heavy exposures cause nausea, anxiety, confusion, headache, dizziness, twitching of facial muscles, spasticity, convulsions, and coma.[1,3,4]

Most camphor poisonings in humans are

due to accidental ingestion.[5] With mild poisoning, gastrointestinal tract symptoms are more common than neurological symptoms and include irritation of the mouth, throat, and stomach. Severe poisoning is characterized by convulsions.

Ingestion of 6–10 g of camphor by two men resulted in psychomotor agitation and hallucinations.[6] The probable lethal dose for humans is in the 50–500 mg/kg range.[5] Camphor may be expected to be somewhat irritating on contact with the eye, but no serious eye injuries have been reported.[7]

Animal bioassays showed that camphor was not carcinogenic in rats injected subcutaneously; however, when the cancer promoter croton oil was concurrently applied to the skin of mice, 2 of 110 treated mice developed carcinomas.[8]

Camphor was not teratogenic to rats or rabbits when administered orally during the fetal period of organogenesis at doses up to 1000 mg/kg body weight (bw)/day or 681 mg/kg bw/day, respectively.[9] Signs of maternal toxicity included clonic convulsions, reduced motility, and reduced body weight gain in rats and reduced food consumption and body weight gain in rabbits.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for camphor is 2 ppm (12 mg/m^3) with a short-term excursion limit of 3 ppm (19 mg/m^3).

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CAPROLACTAM
CAS: 105-60-2

$C_6H_{11}NO$

Synonyms: ε-Caprolactam; 2-oxohexamethyleneimine; aminocaproic lactam

Physical Form. White crystalline solid

Uses. Monomer for manufacture of polycaprolactam (Nylon 6) used in carpets, textiles, clothing, and tires

Exposure. Inhalation

Toxicology. Caprolactam (dust or vapor) is an irritant of the eyes, mucous membranes, respiratory tract, and skin and, rarely, a convulsant.

Human test panel exposures to vapor levels ranging from 53 to 521 mg/m^3 resulted in eye and throat irritation in all those exposed.[1] In a study of workers exposed to vapor over a period of 18 years at levels up to 100 ppm, there were complaints of severe discomfort from burning of the eyes, nose, and throat.[2] Eye irritation did not occur at 25 ppm, but nose and throat irritation occurred in some at 10 ppm.

An earlier study of German workers

exposed to the dust at various levels (mean 61 mg/m^3) reported eye, nose, and throat irritation, epistaxis, and a bitter taste in the mouth.[3] Seizures, fever, and dermatitis occurred in a worker after 3 days of occupational exposure to caprolactam at unmeasured levels.[4] An absence of organic central nervous system abnormalities on physical examination strongly implicated caprolactam as the cause of the seizures.

In eight workers chronically exposed to approximately 70 times the threshold limit value (TLV), the only effects noted were peeling and/or fissuring of the skin.[5]

Doses of 350–600 mg/kg intraperitoneally to rats produced tremor, convulsions, and bloody eye discharge.[6]

Whole body exposure of rats 6 hours/day, 5 days/week for 13 weeks at levels of 24, 70, and 243 mg/m^3 resulted in respiratory effects (keratinization of the metaplastic epithelium in the larynx) at the highest exposure level with complete recovery within 4 weeks after exposure.[7] Treatment-related responses such as labored breathing and nasal discharge were observed during many of the exposures, but these also abated during the recovery period.

In a three-generation reproduction study, rats were given caprolactam in the diet at 0, 1000, 5000, and 10,000 ppm.[8] No teratogenic effects were observed. Caprolactam was tested for carcinogenicity in the diet of mice and rats, and no carcinogenic effect was observed.[9] The IARC evaluation concluded that there is evidence suggesting a lack of carcinogenicity of caprolactam in experimental animals and that it is probably not carcinogenic to humans.[10]

Caprolactam was not mutagenic in bacterial assays or in *in vivo* rodent assays; it did induce chromosomal aberrations and aneuploidy in human lymphocytes *in vitro*.[10]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for caprolactam dust is 1 mg/m^3 with a short-term excursion limit of 3 mg/m^3; the TLV-TWA for caprolactam vapor is 5 ppm (23 mg/m^3) with a short-term excursion limit of 10 ppm (46 mg/m^3).

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CARBARYL
CAS: 63-25-2

$C_{12}H_{11}NO_2$

Synonyms: 1-Naphthyl methylcarbamate; Sevin

Physical Form. Crystals of a white or grayish, odorless solid

Uses. Insecticide

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Carbaryl is a short-acting anticholinesterase agent with the important characteristic of rapid reversibility of inhibition of the enzyme.

The clinical picture of carbaryl intoxication results from inactivation of cholinesterase, resulting in the accumulation of acetylcholine at synapses in the nervous system, skeletal and smooth muscle, and secretory glands.[1–4] Signs and symptoms of overexposure may include: (1) muscarinic manifestations such as miosis, blurred vision, lacrimation, excessive nasal discharge or salivation, sweating, abdominal cramps, nausea, vomiting, and diarrhea; (2) nicotinic manifestations including fasiculation of fine muscles and tachycardia; and (3) central nervous system manifestations characterized by headache, dizziness, mental confusion, convulsions, coma, and depression of the respiratory center.

A single dose of 250 mg (approximately 2.8 mg/kg) ingested by an adult resulted in moderate poisoning; after 20 minutes, there was sudden onset of abdominal pain followed by profuse sweating, lassitude, and vomiting; 1 hour after ingestion, and after administration of a total of 3 mg of atropine sulfate, the person felt better and was completely recovered after another hour.[1] In one reported case of long-term exposure, a 75-year-old man was exposed for 8 months after repeated excessive applications of a 10% dust formulation inside his home. Signs and symptoms were compatible with cholinesterase inhibition in addition to a significant weight loss.

Workers exposed to carbaryl dust at levels that occasionally reached 40 mg/m^3 had slight depression in blood cholinesterase activity but no clinical symptoms.[3] In general, cases of occupational poisoning by carbaryl are rare because mild symptoms appear long before a dangerous dose is absorbed, furthermore, rapid spontaneous recovery of inhibited cholinesterase occurs.

In a study of 59 workers exposed to concentrations ranging from 0.23 to 31 mg/m^3 over a 19-month period, there were no signs or symptoms of anticholinesterase activity.[5] In the most heavily exposed workers, relatively large amounts of 1-naphthol (a metabolite of carbaryl) were excreted in the urine and the blood cholinesterase activity was slightly depressed. It was concluded that an excretion level of total (free plus conjugated) 1-naphthol significantly above 400 µg/100 ml of urine indicates absorption and metabolism of carbaryl.

On the skin, concentrated solutions may cause irritation and systemic intoxication.[1] Allergic skin reactions are rare but have been reported.[3] Men accidently exposed to 85% water-wettable powder as a dust complained of burning and irritation of the skin but recovered in a few hours without any treatment except bathing. Their blood cholinesterase levels were only slightly depressed.[2]

In a 2-year study with carbaryl in the diet of CD-1 mice an increase in vascular tumors was found in males at all doses tested (lowest dose 100 ppm, equal to 15 mg/kg body weight per day).[8] Tumors of the thyroid, liver, and urinary bladder were observed in Sprague-Dawley rats at doses of 7500 ppm in the diet.[8]

A cohort study of 765 men who had been employed between 1960 and 1994 in a carbaryl unit did not identify any significant cancer risk.[8]

The possible effect of carbaryl on reproduction and/or teratogenesis has been explored in rats, mice, guinea pigs, rabbits, dogs, and other species. In general, developmental toxicity including reduced fetal weight, fetal resorptions, and the occurrence of malformation has occurred only at doses that cause significant maternal toxicity.[3,6] No significant changes in sperm count or fertility have been found in cohort studies of exposed workers.[3]

Carbaryl is not considered to be genotoxic.[8]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for carbaryl is 5 mg/m^3.

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CARBON BLACK

CAS: 1333-86-4

Synonyms: Carbon; activated carbon; acetylene carbon; decolorizing carbon; actibon; channel black; furnace black; thermal black; gas black; lamp black; ultracarbon

Physical Form. Black crystal; powder that varies in particle size and degree of aggregation

Uses. In the rubber, plastic, printing, and paint industries as a reinforcing agent and a pigment

Exposure. Inhalation

Toxicology. There are no well demonstrated health hazards to humans from acute exposure to carbon black.

Commercial carbon black is a spherical colloidal form of nearly pure carbon particles and aggregates with trace amounts of organic impurities adsorbed on the surface. Potential health effects usually are attributed to these impurities rather than to the carbon itself. Soots, by contrast, contain mixtures of particulate carbon, resins, tars, and so on, in a nonadsorbed state.[1]

Carbon black particles are deposited in the lungs on inhalation exposure of humans. The exposure may cause slight radiological changes that vary because of different exposure circumstances, concomitant exposures to other compounds, and varying radiological techniques.[1] Reduction in lung function and bronchitis have been reported in some studies.

A significant loss in pulmonary function was reported in a group of 125 Nigerian carbon black workers exposed to levels of up to 34 mg/m^3.[2] The most common respiratory symptom was cough with phlegm, but radiograms were normal. Significant annual declines in FEV_1 and FVC and radiological lung changes were reported in another group of 35 workers exposed to concentrations less than 10 mg/m^3.[1] In contrast, a survey of over 500 carbon black workers in the United States and in the United Kingdom found no statistical difference in spirometry, chest radiograph, physical examination, or reported symptoms.[3] A 1988 report on 913 men employed in the production and handling of carbon black in the United States also found no evidence of pulmonary function effects from dust exposure, as determined by spirometry.[4]

A study of over 3000 carbon black workers employed primarily in Western Europe determined that smoking was the principal factor affecting lung function in the workers and exposure to carbon black had no more effect than that expected from a nuisance dust. There was no evidence of any increased incidence of radiological abnormality in the workers surveyed.[5] A follow-up on much of this same

cohort found a correlation between small opacities of the lungs (category 0/1 or greater) and cumulative dust exposure.[6] Exposure to carbon black was also associated with some increased prevalence of respiratory effects including cough, sputum, and symptoms of chronic bronchitis, as well as small decrements in lung function tests. These results are considered to be consistent with a nonirritant effect of carbon black dust on the airways combined with dust retention in the lungs.

A number of studies have examined the carcinogenic potential of chronic carbon black exposure. A retrospective cohort study of 1200 men employed at four carbon black plants from 1935 to 1974 found no significant increase in total mortality, mortality from heart disease, or mortality due to malignant neoplasms.[7] An update of this cohort through 1994 found no increase in overall or cause-specific mortality.[8] Elevated lung cancer standardized mortality ratios (SMRs) were found at two of five United Kingdom factories manufacturing carbon black.[9] However, lung cancer risk did not increase with cumulative exposure to carbon black or with duration of employment. A cohort of Italian longshoremen exposed to high concentrations of carbon black had a significantly increased frequency of bladder cancer.[10] Limitations in the studies include confounding concomitant exposures, lack of exposure data, and lack of consistent results across studies.

In animal studies significant increases in the incidences of lung tumors have been observed in female rats after inhalation exposure.[1] Repeated inhalation by monkeys caused deposition of the dust in the lungs with minimal or no fibrous tissue proliferation.[11]

The major concern with carbon black exposure is the simultaneous exposure to polycyclic aromatic hydrocarbons that are strongly adsorbed to the respirable carbon black particles and from which PAHs may be elutriated *in vivo* under conditions of human exposure.[12] However, in a number of studies, attempts to elutriate PAH with biological fluids have been largely unsuccessful, and prolonged extraction with boiling aromatic solvents is required for quantitative desorption. Carbon black has been implicated as a cocarcinogen in animal studies in the presence of high-fat diets and other carcinogens.[13]

The IARC has determined that there is inadequate evidence in humans and sufficient evidence in experimental animals for the carcinogenicity of carbon black; there is also sufficient evidence in experimental animals for the carcinogenicity of carbon black extracts.[1]

Most assays for mutagenicity are negative.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for carbon black is 3.5 mg/m^3.

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CARBON DIOXIDE

CAS: 124-38-9

CO_2

Synonym: Carbonic acid gas

Physical Form. Colorless gas (solid is "dry ice")

Uses/Source. By-product of ammonia production, lime kiln operations, and fermentation; used in carbonation of beverages, as propellant in aerosols, and as dry ice for refrigeration. Exposures may occur in a variety of work settings, including farm silos, fermentation tanks, wells, shipping, mining, and fire fighting, and in frozen food industries utilizing dry ice.

Exposure. Inhalation

Toxicology. Carbon dioxide usually is considered a simple asphyxiant, although it also is a potent stimulus to respiration and both a depressant and an excitant of the central nervous system.

Numerous human fatalities have occurred after people entered fermentation vats, wells, and silos where the air had been replaced largely by carbon dioxide.[1,2] In other cases, death or injuries may be caused by the toxicity of carbon dioxide alone and are not due to oxygen deprivation. At levels that are considered immediately dangerous to life and health, oxygen displacement by carbon dioxide may be as little as 1%.[3] The most immediate and significant effects of acute exposure at high concentrations are those on the central nervous system.[1] Concentrations of 20–30% (200,000–300,000 ppm) result in unconsciousness and convulsions within 1 minute of exposure. At concentrations of approximately 120,000 ppm, unconsciousness may be produced with longer exposures of 8–23 minutes. Neurological symptoms, including psychomotor agitation, myoclonic twitches, and eye flickering, have appeared after 1.5 minutes at 100,000–150,000 ppm.[1] Inhalation of concentrations from 60,000 to 100,000 ppm may produce dyspnea, headache, dizziness, sweating, restlessness, paresthesias, and a general feeling of discomfort; at 50,000 ppm there may be a sensation of increased respiration, but subjects rarely experience dyspnea.[4] After several hours of exposure to 2% carbon dioxide (20,000 ppm), subjects develop headache and dyspnea on mild exertion.[5] Circulatory effects in humans exposed to carbon dioxide include increases in heart rate and cardiac output.[6]

Adaptation to low levels, 1.5–3.0% carbon dioxide, has occurred with chronic exposure.[1] Carbon dioxide at room temperature will not injure the skin, but frostbite may result from contact with dry ice or from the gas at low temperatures.

It is important to note that because carbon dioxide is heavier than air, pockets of the gas may persist for some time in areas such as pits unless ventilation is provided.

Limited experimental studies in test animals have raised some concerns about the ability of carbon dioxide to harm reproductive parameters. Acute exposures to 25,000–

100,000 ppm were reported to cause mild and reversible testicular injury in rats at all test levels. Twenty-four-hour exposures of rats to 60,000 ppm on days 5–21 of pregnancy (1 day per cohort) caused an increase in cardiac malformations; the incidence of cardiac malformations was 23.4% in the test group versus 6.8% in the control group, with the highest incidence occurring when exposure occurred on day 10.[8]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for carbon dioxide is 5000 ppm (9000 mg/m^3) with a short-term excursion limit of 30,000 ppm (54,000 mg/m^3).

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CARBON DISULFIDE
CAS: 75-15-0

CS_2

Synonyms: Carbon bisulfide; carbon disulphide

Physical Form. Colorless liquid

Uses. Manufacture of rayon viscose fibers and cellophane film; solvent for lipids, sulfur, rubber, phosphorus, oils, resins, and waxes; insecticide

Exposure. Inhalation; skin absorption

Toxicology. Carbon disulfide causes damage to the central and peripheral nervous systems and may accelerate the development of, or worsen, coronary heart disease.

Exposure of humans to 4800 ppm for 30 minutes causes coma and may be fatal.[1] Carbon disulfide intoxication can involve all parts of the central and peripheral nervous systems, including damage to the cranial nerves and development of peripheral neuropathy with paresthesias and muscle weakness in the extremities, unsteady gait, and dysphagia.[2] A follow-up of workers with clinical and electromyographic evidence of neuropathy attributed to carbon disulfide exposure showed no significant improvement 10 years after exposure was discontinued, suggesting a permanent axonal neuropathy.[3]

In extreme cases of intoxication, a Parkinsonism-like syndrome may result, characterized by speech disturbances, muscle spasticity, tremor, memory loss, mental depression, and marked psychic symptoms; permanent disability is likely.[2] Psychosis and suicide are established risks of overexposure to carbon disulfide.[4]

Other reported effects of exposure to carbon disulfide are ocular changes (blind spot enlargement, contraction of peripheral field, corneal anesthesia, diminished pupillary reflexes, nystagmus, and microscopic

aneurysms in the retina), gastrointestinal disturbances (chronic gastritis and achlorhydria), renal impairment (albuminuria, microhematuria, elevated blood urea nitrogen, and diastolic hypertension), and liver damage.[2,5] Hearing loss to high-frequency tones has also been reported.[6]

Effects commonly caused by repeated exposure to carbon disulfide vapor are exemplified by a group of workers with a time-weighted average (TWA) exposure of 11.2 ppm (range 0.9–127 ppm) who complained of headaches and dizziness; in other workers with a TWA of 186 ppm (range 23–389 ppm) complaints also included sleep disturbances, fatigue, nervousness, anorexia, and weight loss. The end-of-the-day exposure coefficient of the iodine azide test on urine was a good indicator of workers who were, or had been, symptomatic.[7]

Overexposure to carbon disulfide has been associated with an increase in coronary heart disease. In a mortality study of viscose rayon workers, 42% of deaths were certified to coronary heart disease vs. 17% in unexposed workers.[8] A follow-up of this cohort showed a similar pattern with a standardized mortality ratio (SMR) for ischemic heart disease of 172 in spinning operatives.[9] This study also found that the risk declined after exposure ceased, suggesting a direct cardiotoxic or thrombotoxic effect of carbon disulfide rather than an atherogenic effect. A retrospective cohort mortality study of 10,418 men employed in the US rayon industry between 1957 and 1979 found excess deaths from arteriosclerotic heart disease among those potentially most heavily exposed (242 vs. 195.6 expected).[10] There also were excess deaths from suicide (29 vs. 18.8 expected) in one of the four plants investigated. In a Finnish cohort, removal from exposure of workers with coronary risk factors and reduction of levels to 10 ppm caused a dramatic decrease in cardiovascular mortality.[11] Recent cohort studies found that the prevalence of coronary heart disease (electrocardiogram abnormalities and chest pain) was higher in carbon disulfide-exposed workers; abnormalities were significant in workers with long exposures (20 years), suggesting that coronary risk was associated with the high carbon disulfide levels that previously existed in these workplaces.[12,13] Additional cardiovascular effects observed in workers repeatedly exposed to carbon disulfide are bradycardia, tachycardia, and other arrhythmias.[5]

Conflicting studies have appeared regarding the ability of carbon disulfide to affect reproductive function.[6] Hypospermia, abnormal sperm morphology, menstrual cycle irregularities, increased menstrual flow and pain, and a slight increase in miscarriages have been reported in some studies, whereas other studies have not found adverse effects. A retrospective cohort study of 265 female workers exposed 15 years before the study to concentrations averaging 1.7 to 14.8 mg/m^3 showed no significant differences in rates of toxemia, spontaneous abortion, stillbirth, premature or overdue delivery, or congenital malformation.[14] However, exposed females had a higher incidence of menstrual disturbances (primarily irregularity) than the nonexposed group. Pregnant rats and rabbits exposed at 20 and 40 ppm, 7 hours/day, showed no evidence of embryotoxicity or teratogenicity. In another report, hydrocephalia was observed in rats exposed to 32 and 64 ppm, 8 hours/day, throughout gestation.[6]

Chronic exposure of animals for periods less than 1 year has not shown a carcinogenic potential for carbon disulfide.[6] Furthermore, epidemiological studies do not support a carcinogenic risk under moderate exposure conditions.[15]

Splashes of the liquid in the eye cause immediate and severe irritation; dermatitis and vesiculation may result from skin contact with the vapor or the liquid.[1,2] Although ingestion is unlikely to occur, it may cause coma and convulsions.[1,2]

Both positive and negative results have been found in genotoxic assays.[16]

Carbon disulfide is foul-smelling, but the odor is not sufficient to give adequate warning of hazardous concentrations.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for carbon disulfide is 10 ppm (31 mg/m^3) with a notation for skin absorption.

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CARBON MONOXIDE
CAS: 630-08-0

CO

Synonyms: Carbonic oxide; exhaust gas; flue gas

Physical Form. Odorless, colorless, tasteless gas

Sources. Incomplete combustion of organic fuels; vehicle exhaust; space heaters; gas and kerosene lanterns

Exposure. Inhalation

Toxicology. Carbon monoxide (CO) causes tissue hypoxia by preventing the blood from carrying sufficient oxygen.

Carbon monoxide combines reversibly with the oxygen-carrying sites on the hemoglobin molecule with an affinity ranging from 210 to 240 times greater than that of oxygen; the carboxyhemoglobin thus formed is unavailable to carry oxygen.[1] In addition, partial saturation of each hemoglobin molecule with carbon monoxide results in tighter binding of oxygen to hemoglobin; this shifts the oxygen-hemoglobin dissociation curve, further reducing oxygen delivery to the tissues.[2] Carbon monoxide also may exert a direct toxic effect by binding to myoglobin and cellular cytochromes, such as those contained in respiratory enzymes.

Although carbon monoxide poisoning represents a multisystem insult, the cardiac and

central nervous systems are particularly sensitive to the effects of hypoxia.[1,2] Most clinical manifestations are referable to the central nervous system, but it is likely that myocardial ischemia is responsible for many carbon monoxide-induced deaths.[3]

With exposure to high concentrations (4000 ppm and above), transient weakness and dizziness may be the only premonitory warnings before coma supervenes; the most common early aftermath of severe intoxication is cerebral edema.[4,5] Severe visual disturbances also occur as a consequence of acute poisoning in which there has been a period of unconsciousness.[6] After recovery from coma, in cases with residual loss of vision, the pupils are reactive to light despite subject blindness, indicating that the damage is cortical in origin. Typically, complete recovery takes place in a few hours to a few days. Exposure to concentrations of 500–1000 ppm causes the development of headache, tachypnea, nausea, weakness, dizziness, mental confusion, and in some instances, hallucinations; the person is commonly cyanotic.[1–4] Because carboxyhemoglobin has a bright red color, occasionally someone will exhibit the unusual combination of hypoxia together with a bright red color of the fingernails, mucous membranes, and skin; however, this "cherry-red cyanosis" usually is seen only at autopsy.[4]

Exposure to 50 ppm for 90 minutes may cause aggravation of angina pectoris; exposed anginal patients may show a negative inotropic effect (weakened force of myocardial contraction); 50 ppm for 120 minutes may cause aggravation of intermittent claudication.[7]

The clinical effects of CO exposure are aggravated by heavy labor, high ambient temperature, and altitudes above 2000 feet; pregnant women are particularly susceptible to the effects of CO.[1]

The reaction to a given blood level of carboxyhemoglobin is extremely variable; some persons may be in a coma with a carboxyhemoglobin level of 38%, whereas others may maintain an apparently clear sensorium with levels as high as 55%. Levels of carboxyhemoglobin over 60% usually are fatal; 40% is associated with collapse and syncope; above 25% there may be electrocardiographic evidence of a depression of the S-T segment; between 15% and 25% there may be headache and nausea; levels below 15% rarely produce symptoms. The blood of cigarette smokers usually contains 2–10% and sometimes as high as 18% carboxyhemoglobin, and nonexposed persons have an average level of 1%; heme metabolism is an endogenous source of CO.[1]

Exposure of nonsmokers to 50 ppm for 6–8 hours results in carboxyhemoglobin levels of 8–10%.[1–3] Several investigators have suggested that the results of behavioral tests such as time discrimination, visual vigilance, choice response tests, visual evoked responses, and visual discrimination threshold may be altered at levels of carboxyhemoglobin below 5%.[1]

Transient central nervous system symptoms or rapid death are not the only results of CO poisoning.[3] The occurrence of late, fatal demyelination is a rare but dreaded complication. Furthermore, it is inappropriate to assume that because a patient with CO poisoning shows improvement, residual mental damage may not occur.[3] A report of 63 patients studied 3 years after CO poisoning indicated that 13% showed gross neuropsychiatric damage directly attributable to their CO intoxication, 33% showed a "deterioration of personality" after poisoning, and 43% reported memory impairment.[8] A syndrome of headache, fatigue, dizziness, paresthesias, chest pains, palpitations, and visual disturbances has been associated with chronic carbon monoxide poisoning.[9]

Chronic carbon monoxide poisoning may be difficult to diagnose because carboxyhemoglobin levels correlate poorly with symptoms and symptoms may be misdiagnosed as a viral syndrome or psychological depression. Distinguishing features of chronic carbon monoxide poisoning include the absence of myalgias, fever, sore throat, and adenopathy; simultaneous illness in homebound family members and pets; and improvement with exposure to fresh air. The diagnosis can be confirmed by finding a source of carbon monoxide in the home (e.g., defective furnaces), workplace, or vehicle; negative screenings for other illnesses; abnormal carboxyhemoglobin levels; and abatement of

symptoms when the CO source has been eliminated.

Occupational exposure of New York City tunnel officers to excess levels of CO was associated with a 35% excess risk of arteriosclerotic heart disease mortality.[10] The excess risk was thought to be due to repeated, short-term peak exposures on the order of 400 ppm and appeared to be reversible on cessation of exposure.

A review of 60 case reports of carbon monoxide exposure during pregnancy found fetal outcome related to maternal blood carboxyhemoglobin and maternal toxicity.[11] In cases in which the mother did not become unconscious, fetal outcome was generally good. However, where the mother experienced unconsciousness or coma, fetal outcome tended to be poor (death or survival with anatomic or functional abnormalities). Anatomical malformations, including mongoloid-type features, missing and deformed limbs, and oral cavity anomalies, also showed a marked correlation to exposure during the first trimester.

Animal experiments support the developmental findings found in humans and suggest that prenatal exposure at maternally nontoxic levels may also damage the fetal central nervous system.[12,13] Exposure of pregnant rats to 150 ppm produced only minor reductions in pup birthweights, but evaluation of learning and memory processes suggested a functional deficit in the central nervous system that persisted into adulthood of exposed offspring.[12,13] Congenital spinal deformities have been reported in the offspring of mice exposed for 7 hours during gestation at doses of 200, 400, or 600 ppm.[14]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for carbon monoxide is 25 ppm (29 mg/m^3).

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CARBON TETRABROMIDE

CAS: 558-13-4

CBr_4

Synonyms: Tetrabromomethane; methane tetrabromide

Physical Form. Colorless solid

Uses. Used to a limited extent as an intermediate in organic synthesis

Exposure. Inhalation

Toxicology. Carbon tetrabromide is a lacrimator; high concentrations may cause upper respiratory irritation and injury to the lungs, liver, and kidneys. Chronic exposure is expected to cause liver injury.

Exposure of rats 7 hours/day, 5 days/week for 6 months at 0.1 ppm caused no effects.[1] Exposure at higher but unstated levels caused poor growth and fatty changes in the liver. In the eyes of rabbits the material caused severe irritation and irreversible corneal damage. The vapor is a lacrimator. On the skin of rabbits it caused slight irritation.

An early report in the Russian literature indicated that chronic exposure of rats to 0.07–74 ppm for 4 months caused irritation of the eyes and respiratory tract and damage to the liver.[1] A more recent study exposed rats to a single intraperitoneal injection of 25–125 µl/kg. Renal dysfunction, rather than hepatic effects, was seen in the form of oliguria, aciduria, and hypoosmolality.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for carbon tetrabromide is 0.1 ppm (1.4 mg/m^3) with a short-term excursion limit of 0.3 ppm (4.1 mg/m^3).

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CARBON TETRACHLORIDE

CAS: 56-23-5

CCl_4

Synonyms: Carbon tet; tetrachloromethane

Physical Form. Colorless liquid

Uses. In the manufacture of chlorofluorocarbons, which in turn are primarily used as refrigerants; formerly used widely as a solvent, also as a grain fumigant and in fire extinguishers. Because of toxicity consumer uses have been discontinued and only industrial use remains.

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Carbon tetrachloride causes central nervous system depression and severe damage to the liver and kidneys; it is carcinogenic in experimental animals and has been classified as a potential human carcinogen.

In animals the primary damage from intoxication is to the liver, but in humans the majority of fatalities have been due to renal injury with secondary cardiac failure.[1,2] Human autopsy reports have confirmed renal tubular necrosis. In humans, liver damage occurs more often after ingestion of the liquid than after inhalation of the vapor.

Human fatalities from acute renal damage have occurred after exposure for 0.5-1 hour to concentrations of 1000–2000 ppm; occasional sudden deaths have been due to ventricular fib-

rillation.[1] Exposure to high concentrations results in symptoms of central nervous system depression including dizziness, vertigo, incoordination, and mental confusion; abdominal pain, nausea, vomiting, and diarrhea are frequent.[1–4] Cardiac arrhythmias and convulsions have also been reported. Polycythemia followed by anemia and hemodilution may occur. Within a few days, jaundice may appear and liver injury can progress to toxic necrosis. At the same time, acute nephritis may occur with albumin, red and white blood cells, and casts in the urine; there may be oliguria, anuria, and increased nitrogen retention resulting in the development of uremia. The no observed adverse effect level for acute human exposure is 10 ppm for a 3-hour exposure.[5]

There are several reports of adverse effects in workers who were repeatedly exposed to concentrations between 25 and 30 ppm; nausea, vomiting, dizziness, drowsiness, and headache were frequently noted.[1] Chronic exposure has caused cases of various abnormalities of the eyes such as reduced visual field.

Carbon tetrachloride is absorbed through the skin of humans, although much less readily than from the lung.[6] After use as a shampoo or as a solvent for removal of adhesives from skin, a number of fatal or near-fatal cases have been reported. It has been noted that these exposures must have also involved high levels of inhalation exposure as well as dermal exposure. It has been estimated that immersion of both hands in the liquid for 30 minutes would yield an exposure equivalent to breathing 100–500 ppm for 30 minutes.

The liquid splashed in the eye causes pain and minimal injury to the conjunctiva. Prolonged or repeated skin contact with the liquid may result in skin irritation and blistering.[1,4]

A number of substances including ethanol, isopropyl alcohol, polybrominated biphenyls, phenobarbital, and benzo(*a*)pyrene have been shown to synergistically affect carbon tetrachloride toxicity.[4] Alcohol has been a concomitant factor in many of the human cases of poisoning, especially in cases in which severe liver and kidney damage have occurred.[2] Some substances such as chlordecone greatly potentiate the toxicity of carbon tetrachloride at doses at which both substances are not considered toxic; effects include extensive hepatoxicity characterized by total hepatic failure and greatly potentiated lethality.[7]

The mechanism of carbon tetrachloride hepatotoxicity generally is viewed as an example of lethal cleavage, where the CCl_3—Cl bond is split in the mixed-function oxidase system of the hepatocytes. After this cleavage damage may occur directly from the free radicals (·CCl and ·Cl) and/or from the formation of toxic metabolites such as phosgene.[4]

Animal studies demonstrate that carbon tetrachloride produces hepatocellular carcinomas in the mouse, rat, and hamster.[4] Mice administered 1250 or 2500 mg/kg approached nearly a 100% incidence of hepatocellular carcinomas vs. 6% or less in various controls. Hamsters receiving 190 and 380 mg/kg by gavage had a 100% liver cell carcinoma incidence for those animals surviving past week 43.[8]

Sensitivity to carbon tetrachloride-induced neoplasms varied widely among five strains of rats receiving twice-weekly subcutaneous injections of 2080 mg/kg as a 50% solution in corn oil.[9]

A number of animal studies suggest that hepatomas occur only after liver necrosis and fibrosis have occurred and, therefore, that carbon tetrachloride is not a direct liver carcinogen.[4] One early study, however, found that liver necrosis and its associated chronic regenerative state probably were not necessary for tumor induction, although a correlation was found between the degree of liver necrosis and the incidence of hepatomas.[10]

In humans, cases of hepatomas have appeared years after acute exposure to carbon tetrachloride, however, none of the cases could establish a causal link between the exposure and development of neoplasms.[4] Epidemiological studies have also given inconclusive results. A cancer mortality study of a population of rubber workers reported a significantly elevated odds ratio relating carbon tetrachloride with lymphatic leukemia, and lymphosarcoma and reticulum cell carcinoma.[11,12] A recent retrospective cohort mortality study of aircraft maintenance workers found an increased risk of

non-Hodgkin lymphoma and multiple myeloma among women, but not men, with carbon tetrachloride exposure.[13] To date all the studies have been characterized by mixed exposures and a lack of carbon tetrachloride data, which limits the evaluation of effects.

The IARC has determined that there is sufficient evidence for carcinogenicity in animals, inadequate evidence for carcinogenicity in humans, and an overall evaluation that carbon tetrachloride is possibly carcinogenic to humans.[14]

Carbon tetrachloride was fetotoxic to rats when administered on days 6–15 of gestation at 300 or 1000 ppm, 7 hours/day; an increase in skeletal anomalies due to delayed development was observed in the offspring. Signs of maternal toxicity included weight loss and hepatic damage.[15]

The sweetish odor of carbon tetrachloride does not provide satisfactory warning of exposure.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for carbon tetrachloride is 5 ppm (31 mg/m^3) with a short-term excursion limit of 10 ppm (63 mg/m^3), an A3-animal carcinogen designation, and a notation for skin absorption.

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CATECHOL
CAS: 120-80-9

$C_6H_4(OH)_2$

Synonyms: 1,2-dihydroxybenzene; pyrocatechol; 1,2-benzenediol

Physical Form. Colorless crystals

Uses. In the manufacture of rubber antioxidants and monomer inhibitors to stop radical polymerization; in dyes, as a photographic developer; in formulations for pharmaceuticals, perfumes, inks, and insecticides

Exposure. Inhalation; skin absorption

Toxicology. Catechol is a skin, eye, and respiratory tract irritant and at high concentrations may cause convulsions; it acts as a cocarcinogen in animal skin-painting studies and produces stomach tumors after oral administration in rodents.

Skin contact with catechol causes dermatitis. Absorption through the skin may give rise to symptoms similar to those seen in phenol poisoning: an increase in blood pressure and the occurrence of convulsions.[1]

A report on the health effects of Japanese factory workers exposed to catechol and phenol for 2 years found that most of the workers complained of cough and sputum, occasional sore throat, and eye irritation.[2] The respiratory disorders were not noted in the control group of workers. The incidence of skin eruptions (7/13) was also higher in the exposed workers compared with the controls (2/13). Concentrations of catechol in workroom air ranged from 8 mg/m^3 up to 322 mg/m^3 of air.

Contact of 0.5 g of catechol with the intact and abraded skin of rabbits for up to 24 hours produced slight to moderate erythema and slight edema of the intact areas and necrosis of the abraded areas.[3] The single-dose skin penetration LD_{50} was estimated to be 0.8 g/kg. Subdermal hyperemia and edema were noted at autopsy, but there were no internal gross lesions.[3]

Application of 0.1 g into the eyes of rabbits caused moderate conjunctivitis, with exudate and corneal opacity; at 72 hours after exposure, they showed severe conjunctivitis, iritis, and diffuse corneal opacities; 14 days after exposure, all of the treated eyes had pannus formation and keratoconus.[3]

In rats, the single-dose oral LD_{50} was estimated to be 0.3 g/kg, based on mortality during a 14-day postexposure period. At autopsy, the rats that died during the observation period had hyperemia of the stomach and intestines.[3]

No deaths resulted when rats inhaled 1500, 2000, or 2800 mg/m^3 catechol for 8 hours; in the two higher-exposure groups, tremors appeared in 6–7 hours and persisted through the first postexposure day.[3] After a 14-day holding period, the six rats exposed at 2800 mg/m^3 had blackened toes and tails; some of the toes were missing, as well as the tips of the tails of all exposed animals. Similar tail loss occurred in two of six animals exposed at 2000 mg/m^3. No toxic signs were seen in the 1500 mg/m^3 group. Injected intraperitoneally into female mice, a dose of 0.37 mmol/kg produced convulsions in 50% of the animals.[4]

Administered by gavage at dose levels of 150 and 300 mg/kg, 5 days/week for 13 weeks, catechol induced lesions of the forestomach in mice and rats.[5] The higher dose was lethal to most of the animals, and histopathologic examination showed acanthosis and squamous papillomas of the forestomach. Male mice also had carcinoma in situ of the forestomach, which was considered to be treatment related. In a recent study dietary levels of 0.1% and 0.2% caused benign proliferative lesions in the pyloric gland of male F344 rats treated up to 104 weeks, and levels of 0.4% and 0.8% induced adenocarcinomas.[6]

In skin-painting studies in mice, catechol increased the carcinogenic effects of benzo[*a*]pyrene (B(*a*)P).[7] A group of 50 mice were treated with 2 mg of catechol plus 5 µg of B(*a*)P in 0.1 ml of acetone, three times/week for 52 weeks. The incidence of skin tumors was compared with that obtained from groups treated with B(*a*)P only, catechol only, or vehicle only or untreated controls. The catechol plus B(*a*)P group had incidences of 35/50

papillomas and 31/50 squamous carcinomas, as compared with incidences of 13/50 and 10/50 for the B(*a*)P-only group, respectively. No tumors occurred in the catechol-only, vehicle-only, or untreated control groups. In a later study, four dose levels of catechol in B(*a*)P were evaluated for carcinogenicity.[8] The catechol-only B(*a*)P-treated groups had the following incidences of skin tumors: 0.25 mg catechol + B(*a*)P, 72%; 0.1 mg catechol + B(*a*)P, 66%; 0.01 mg catechol + B(*a*)P, 18%; and 0.001 mg catechol + B(*a*)P, 24%. No skin tumors were observed in the vehicle-only control group, whereas 11% of the B(*a*)P-treated group and 21% of the catechol-only treated groups had skin tumors. It was determined that doses of 0.1 mg and above were cocarcinogenic but the lower doses were not.[8]

The IARC has determined that there is sufficient evidence for the carcinogenicity of catechol in animals and that it is possibly carcinogenic to humans.[9]

Catechol was genotoxic in mammalian cells *in vitro*, causing chromosomal aberrations and sister chromatid exchanges.[9]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 5 ppm (20 mg/m^3) with a notation for skin absorption.

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CELLULOSE (and Compounds)
CAS: 9004-34-6

$(C_6H_{10}O_5)_n$

Synonyms: None

Physical Form. Natural cellulose is a highly crystalline, white solid with a molecular weight varying from 300,000 to greater than 1,000,000.

Uses/Sources. Wood contains 50–70% cellulose; cotton and other textile fibers of plant origin contain 65–95%; rayon is prepared by dissolving natural cellulose and then precipitating it from solution, with some loss of crystallinity. Cellulose is made into cellophane film and is used to form fibers, resins, coatings and gums.

Exposure. Inhalation

Toxicology. Cellulose is inert and is classified as a nuisance dust.

It has little, if any, adverse effect on the lung, and there are no reports of organic disease or toxic effect.[1] The health effects attributed to wood, cotton, flax, jute, and hemp are not attributable to their cellulose content but rather to the presence of other substances.

Cellulose fibers were found in the blood and urine of human volunteers fed dyed cellulose; there were no ill effects.[2]

In animal studies of cellulose derivatives, the only consistent effect of very high doses in the feed appears to be a reduction in the nutritional value of the feed, which manifests itself as a decrease in body weight gain or an increase in food consumption.[3] Doses up to 5000 mg/kg/body weight/day, or 10% in the diet, have been found to be nontoxic.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for cellulose is 10 mg/m^3.

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CESIUM HYDROXIDE
CAS: 21351-79-1

CsOH

Synonym: Cesium hydrate

Physical Form. Colorless or yellow solid

Uses. As a catalyst in the polymerization of cyclic siloxanes; for electrolytes in batteries

Exposure. Inhalation; skin contact

Toxicology. Cesium hydroxide is an irritant of the eyes.

The oral LD_{50} in rats was 1026 mg/kg.[1] In rabbits a 5% solution was irritating to abraded skin and extremely irritating in the eyes. No evidence of skin sensitization was found in treated guinea pigs.

There are no reports of adverse effects in humans. By analogy to NaOH, the effects from dust or mist could be expected to vary from mild irritation of the upper respiratory tract to pneumonitis, depending on the severity of the exposure. The greatest industrial hazard is rapid tissue destruction of the eyes on contact with the solid or a concentrated solution. If cesium hydroxide is not removed from the skin, it is anticipated that burns will occur after a period of time. Ingestion would be expected to cause corrosion of the lips, mouth, tongue, and pharynx, as well as abdominal pain.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for cesium hydroxide is 2 mg/m^3.

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CHLORDANE
CAS: 57-74-9

$C_{10}H_6C1_8$

Synonyms: Chlordan; Velsicol 1068; CD-68; Toxichlor; Octa-Klor; 1,2,4,5,6,7,8-octachloro-2,3,3*a*,4,7,7*a*-hexahydro-4,7-methanoindene

Physical Form. Viscous amber liquid; technical-grade chlordane contains about 45 constituents, including 7–10% heptachlor

Uses. Insecticide; currently approved for underground termite control only

Exposure. Skin absorption, ingestion, inhalation

Toxicology. Chlordane is a convulsant; it is carcinogenic in experimental animals.

Established cases of chlordane poisoning have been associated with gross exposure either by ingestion or skin contact.[1] Typically, the poisoning is characterized by onset of violent convulsions within 1/2–3 hours and either death or recovery within a few hours to a day. After ingestion, nausea and vomiting may precede signs of central nervous system overactivity. Convulsions may be accompanied by confusion, incoordination, excitability, or coma. In one instance, accidental ingestion of approximately 300 ml of a 75% chlordane solution (215 g chlordane) was survived despite rapid onset of respiratory, gastrointestinal, and neurological effects.[2] In this case, the chlordane level in whole blood was 5 mg/l at 3.5 hours after ingestion. Kinetic analysis of blood chlordane levels with time suggested a half-life of 7 hours for distribution in the body and 34 days for elimination.[2]

Although limited by dose-response information, impairment of both neurophysiological and psychological functions (including slowing of reaction time, balance dysfunction, reductions in cognitive function, and deficits of recall) has been associated with chronic chlordane exposure.[3]

Skin absorption of chlordane is rapid; a worker who spilled a 25% suspension of chlordane on the clothing, which was not removed, began having convulsions within 40 minutes and died shortly thereafter.[4]

Technical-grade chlordane is stated to be irritating to the skin and mucous membranes, but this may be more true of earlier chlordane formulations with significant hexachlorocyclopentadiene contamination.[1,4]

Mice kept in saturated vapor of technical chlordane without hexachlorocyclopentadiene for 25 days showed no symptomatic effects.[1] The oral LD_{50} values for rats range from 200 to 590 mg/kg.[4]

In experimental animals, prolonged exposure to dietary levels exceeding 3–5 mg/kg resulted in the induction of hepatic microsomal enzymes and, at a later stage, liver hypertrophy with histologic changes.

At dosages above 30 mg/kg in the diet, chlordane interfered with reproduction in rats and mice, but this effect was reversible after exposure ceased.[4] Pre- and postnatal exposures to chlordane altered the development of the immune system in rodents.[5] A dose-related increase in the incidence of hepatocellular carcinomas was found in male and female mice fed approximately 60 mg/kg chlordane for 80 weeks.[6] In rats, increases in the incidences of thyroid follicular cell neoplasms were observed.[5]

In human case reports, chlordane exposure has been linked to neuroblastoma, aplastic anemia, and acute leukemia, but only circumstantially.[1] In a 1987 report, 25 new cases of blood dyscrasia, including leukemias, production defects, and thrombocytopenic purpura (generally after home termite treatment with chlordane/heptachlor), were reported.[7] The authors noted the rarity of many of the conditions and, hence, the difficulty of finding statistically significant results.

Epidemiological studies have not shown a clear association between chlordane exposure and cancer mortality. No excess deaths from lung cancer were observed in termite control workers (with particular exposure to chlordane and heptachlor), in comparison with other pesticide applicators.[8] Follow-up of 1400 men employed in the manufacture of chlordane, heptachlor, and/or endrin also showed a deficit of deaths from all cancers and a small excess of lung cancers, although smoking histories were not documented.[9] A study of 800 workers employed at a chlordane production plant for 3 months or more during the period 1946–1985 showed a slightly less than expected overall death rate, and no trend with duration of employment was seen for respiratory cancer.[10] Four case control studies showed a modest increase in non-Hodgkin lymphoma with exposure to chlordane.[5]

IARC has concluded that there is inadequate evidence for carcinogenicity of chlordane

to humans and sufficient evidence for its carcinogenicity to animals.[5]

Chlordane was not mutagenic to bacteria.[5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for chlordane is 0.5 mg/m^3 with a notation for skin absorption and an A3-confirmed animal carcinogen with unknown relevance to humans designation.

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CHLORDECONE
CAS: 143-50-0

$C_{10}Cl_{10}O$

Synonym: Kepone

Physical Form. Tan to white crystalline solid

Uses. Pesticide (leaf-eating insects and fly larvae); products containing chlordecone were cancelled in 1978

Exposure. Inhalation

Toxicology. Chlordecone is toxic to the nervous system, liver, and reproductive system.

The first reports of effects in humans concerned the cases of intoxication workers of the Life Science Products Company in Hopewell, Virginia.[1,2] This was a small improvised unit lacking in dust control which was generated by a process operated over a period of 16 months. On initial assessment, at least 9 of the 33 employees of the company were severely affected and showed memory impairment, slurred speech, tremor, opsoclonus (eye twitching), and liver damage; blood levels of the compound up to 25 ppm were found.[2]

Subsequent examination of 117 of 149 current or previous employees of this plant showed that 57 had present or past symptoms of intoxication, including weight loss, tremor of the upper extremities, ataxia, incoordination, arthralgia, skin rash, and abnormal liver function tests. The incidence of illness was 67% in production workers and 16% for other employees of the plant. The wives of two workers had objective tremor; each had washed her husband's work clothes.[3] Sural nerve biopsies from affected workers showed significant histologic damage to nonmyelinated and smaller myelinated fibers, with relative sparing of larger myelinated fibers.[4]

In early animal studies, the compound reportedly caused tremor, the severity of which depended on the dosage level and duration of exposure; tremors persisted for a week or more

after single exposures and cumulatively developed from daily repeated, individually ineffective doses. In male rats, the oral LD_{50} was 132 mg/kg.[5]

Reproductive studies showed that 14 pairs of mice that received 40 ppm chlordecone in the diet for 2 months before mating and during the test produced no litters, whereas 14 control pairs produced 14 first litters and 14 second litters. Further studies in mice found that infertility in chlordecone-exposed females was due to an absence or reduction in the number of ovulated oocytes. Prenatal exposure of rats has also been shown to persistently alter neurobehaviors in adults.[7]

Chlordecone is thought to produce some of its reproductive outcomes by mimicking the effects of excessive estrogens. The ability to cause constant estrus and other estrogen-like effects has been repeatedly confirmed in rodents.[3]

Gestational exposure of rats and mice caused embryo-/fetotoxicity and teratogenicity at doses that were severely toxic to dams.[8] Dermal exposure of male rabbits has been reported to cause testicular atrophy.[8]

Chronic exposure of mice and rats caused an increase in liver tumors.[8] Chlordecone is not considered to be genotoxic but may act as a tumor promoter.[8]

Chlordecone in blood is a good biomarker of exposure because of chlordecone's association with plasma proteins and its long half-life.[7]

The ACGIH has not established a threshold limit value for chlordecone.

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CHLORINATED DIBENZO-*p*-DIOXINS

CAS: 1746-01-6 (2,3,7,8-TCDD)

$C_{12}H_4Cl_4O_2$

Synonyms: Chlorinated dibenzo-*p*-dioxins (CDDs) are a family of 75 different compounds commonly referred to as polychlorinated dioxins. The CDD family is divided into eight groups of chemicals based on the number of chlorine atoms in the compound. The groups with two through eight chlorine atoms are called dichlorinated dioxin (DCDD), trichlorinated dioxin (TrCDD), tetrachlorinated dioxin (TCDD), pentachlorinated dioxin (PeCDD), hexachlorinated (HxCDD), heptachlorinated dioxin (HpCDD), and octachlorinated dioxin (OCDD). The chlorine atoms can be attached at any of eight positions. The name of each CDD indicates both the number and positions of the chlorine atoms. For example, the CDD with four atoms at positions 2,3,7, and 8 on the dioxin molecule is 2,3,7,8-TCDD, which is one of the most toxic of the CDDs to mammals and the one that has received the most attention.

Physical Form. Colorless solids or crystals

Sources. CDDs occur naturally and are also produced by human activities.[1] They are naturally produced by the incomplete combustion of organic material by forest fires and volcanic action. CDDs may be formed during the chlorine gas bleaching process formerly used by pulp and paper mills. They occur as contaminants in the manufacturing process of certain chlorinated organic compounds, such as chlorinated phenols. 2,3,7,8-TCDD is a by-product of the production of 2,4,5-trichlorophenol (2,4,5-TCP), which was used to produce hexachlorophene, and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T, a component of the herbicide Agent Orange). Other chlorinated chemicals such as pentachlorophenol (PCP), used to preserve wood, do contain some of the more highly chlorinated CDDs, but not usually 2,3,7,8-TCDD. Currently, CDDs are primarily released to the environment during combustion of fossil fuels (coal, oil, and natural gas) and wood and during incineration processes (municipal and medical solid waste and hazardous waste).

Exposure. Ingestion; inhalation; skin contact

Toxicology. Chlorinated dibenzo-*p*-dioxins (CDDs) cause chloracne, may cause hepatotoxicity, immunotoxicity, reproductive toxicity, developmental toxicity, and central nervous system toxicity, and are considered to be a human carcinogen.

The most obvious health effect in humans for exposure to CDDs is chloracne, a severe skin disease characterized by follicular hyperkeratosis (comedones) occurring with or without cysts and pustules.[2–4] Unlike adolescent acne, chloracne may affect almost every follicle in an involved area, and it may be more disfiguring than adolescent acne.[5]

Chloracne generally appears on the face and upper body but may extend to the upper arms, back, chest, abdomen, outer thighs, and genitalia. In milder cases, the lesions heal several months after exposure ends. In more severe cases, the lesions may last for many years after exposure and have been observed up to 30 years after initial onset.[4,6] In some cases lesions have resolved temporarily and then returned. Scarring may result from the healing process. Other skin effects have also been noted to accompany chloracne, such as hyperpigmentation and hirsuitism (also known as hypertrichosis or abnormal distribution of hair).[7]

Peripheral and central nervous system effects have been reported in case reports and epidemiological studies from exposure to CDDs and are associated with signs and symptoms of both central and peripheral nervous system effects shortly after exposure. In some cases, the effects lasted several years. However, evaluation of individuals 5–37 years after the last exposure has not indicated any long-lasting abnormalities.[8]

The IARC has classified 2,3,7,8-TCDD as a Group I carcinogen, that is, an agent carcinogenic to humans.[9] Statistically significant increases for all cancers were found in highly exposed workers with longer latency periods. Although the standard mortality ratio (SMR) values are low, they are consistent across studies with the highest exposures, with a SMR of 1.4. The evidence for site-specific cancers is weaker, with suggestion of a possible relationship between soft tissue sarcoma, non-Hodgkin lymphoma, or respiratory tract cancer.. The most important studies for the evaluation of carcinogenicity were four cohort studies of herbicide producers (one each in the United States and Netherlands, two in Germany) and one cohort of residents in a contaminated area in Seveso, Italy. The carcinogenicity of CDDs has been demonstrated in several animal studies.

There is suggestive but inconclusive evidence of adverse cardiovascular effects in humans exposed to relatively high concentrations of CDDs.[10] Increased deaths from chronic heart disease were observed in the Seveso cohort, but psychosocial factors could not be ruled out. No clear dose-response relationships were seen among the Ranch Hand cohort. Increased deaths from heart and circulatory disease were reported among German workers exposed to CDDs. No evidence of adverse cardiovascular effects was observed in US workers.

Hepatotoxic effects, such as elevated GGT levels and small alterations in lipid profile, have sometimes been observed in humans after exposure to high 2,3,7,8-TCDD levels. In general, the effects have been mild and in some cases appear to have been transient.[11]

A median half-life of 7.1 years for excretion in humans was estimated for 2,3,7,8-TCDD in a group of 36 Vietnam veterans.[12] Further studies have indicated that the half-life may be closer to 8.7 years.[13] CDDs are lipophilic compounds that can concentrate in maternal milk.[14] An analysis of 526 individual milk samples from a German population indicated a mean 2,3,7,8-TCDD level of 3.2 ng/kg milk fat.[15]

In LD_{50} studies in animals, 2,3,7,8-TCDD was the most potent CDD congener studied. Guinea pigs are the most sensitive species (0.6 µg/kg), with hamsters being the most resistant—with up to 5000 times greater lethal doses (1157 µg/kg).[16,17] In all studies cited, the animals died after a latent period of several days (mean values ranged from 9 to 42 days). In almost all of the laboratory animals, a pronounced wasting syndrome appeared to be a major contributor to lethality. It was characterized by body weight loss and adipose tissue depletion.

Reproductive toxicity to 2,3,7,8-TCDD has been demonstrated in animals.[18–20] The effects include pre- and postimplantation losses in females, morphologic and functional changes in male and female reproductive organs, and hormonal imbalance in both sexes. A number of developmental effects have been observed in animals acutely exposed to 2,3,7,8-TCDD by the oral route. Effects observed in offspring of animals include cleft palate, kidney anomalies, immune system damage (thymic atrophy and immunosuppression), impaired development of the reproductive system, decreased growth, and fetal/newborn mortality.

Clearly, humans are exposed to a complex mixture of CDDs and other halogenated aromatic hydrocarbons such as chlorinated dibenzofurans (CDF) and polychlorinated biphenyls (PCBs). The toxicological concerns resulting from exposure to mixtures, as well as the gaps in available information for evaluation of potential risks of these materials, led an EPA Technical Panel to recommend an interim method for risk estimation. Thus was born the Toxicity Equivalent Factor (TEF) method, which was developed and validated in animals.[21–25] The TEF approach compares the relative potency of individual CDD congeners to that of 2,3,7,8-TCDD, which is the most potent and extensively studied congener. The TEF for 2,3,7,8-TCDD is expressed as 1.0, and TEF for all other CDD congeners, CDFs, and dioxin-like PCBs are less than 1.0, thus reflecting their lower potency.

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CHLORINATED DIPHENYL OXIDE

CAS: 55720-99-5

$C_6H_2Cl_3OC_6H_2Cl$ *(approximate)*

Synonyms: Chlorinated phenyl ethers; monochlorodiphenyl oxide, dichlorodiphenyl oxide, etc., through hexachlorodiphenyl oxide

Physical Form. Varies from colorless, oily liquids to yellowish, waxy semisolids as the equivalents of chlorine increase from 1 to 6

Uses. Chemical intermediates; in the electrical industry

Exposure. Inhalation, skin absorption

Toxicology. Chlorinated diphenyl oxide causes an acneform dermatitis (chloracne).

Limited experience with humans has shown that exposure to even small amounts of the higher chlorinated derivatives, particularly hexachlorodiphenyl oxide, may result in appreciable acneform dermatitis.[1] Chloracne is usually persistent and affects the face, ears, neck, shoulders, arms, chest, and abdomen (especially around the umbilicus and on the scrotum). The most sensitive areas are below and to the outer side of the eye (malar crescent) and behind the ear.[2] The skin is frequently dry with noninflammatory comedones and pale yellow cysts containing sebaceous matter and keratin.

No cases of systemic toxicity have been reported in humans.

In laboratory animals, cumulative liver damage has resulted from repeated intake, and, in general, the toxicity increases with the degree of chlorination. Liver injury is characterized by congestion and varying degrees of fatty degeneration. In animals, these compounds cause severe skin irritation with topical application.[3] Animal experiments suggest that absorption from dermal application can result in systemic toxicity, including liver injury and weight loss. In guinea pigs, a single oral dose of 0.05–0.1 g/kg of material containing four or more equivalents of chlorine resulted in death 30 days after administration.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for chlorinated diphenyl oxide is 0.5 mg/m^3.

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CHLORINE

CAS: 7782-50-5

Cl_2

Synonyms: None

Physical Form. Greenish-yellow gas with an irritating odor

Uses. Metal fluxing; sterilization of water supplies and swimming pools; bleaching agent; synthesis of chlorinated organic chemicals and plastics; pulp and paper manufacturing; detinning and dezincing iron

Exposure. Inhalation

Toxicology. Chlorine is a potent irritant of the eyes, mucous membranes, and skin; pulmonary effects range from respiratory irritation to edema. Chlorine reacts with tissue water to form hydrochloric and hypochlorous acids.

Mild mucous membrane irritation may occur at 0.2–16 ppm; eye irritation occurs at 7–8 ppm, throat irritation at 15 ppm, and cough at 30 ppm.[1] Toxic pneumonitis and pulmonary edema can be expected at 40–60 ppm. A level of 430 ppm is lethal after 30 minutes, and 1000 ppm is fatal after a few deep breaths.[1,2] Other studies have shown that at least some subjects develop eye irritation, headache, and cough at concentrations as low as 1–2 ppm.

The location and the severity of respiratory tract involvement are functions of both the concentration and the duration of exposure. With significant exposures, laryngeal edema with stridor, acute tracheobronchitis, and chemical pneumonitis have been described.[3] Death at high exposure is mainly from respiratory failure or cardiac arrest due to toxic pulmonary edema.[4] Bronchopneumonia may be a potentially lethal complication. In one accident, exposure of humans to unmeasured but high concentrations for a brief period of time caused burning of the eyes with lacrimation, burning of the nose and mouth with rhinorrhea, cough, choking sensation, and substernal pain.[5] These symptoms were frequently accompanied by nausea, vomiting, headache, dizziness, and sometimes syncope. Of 33 victims who were hospitalized, all suffered tracheobronchitis, 23 progressed to pulmonary edema, and, of those, 14 progressed to pneumonitis.[3] Respiratory distress and substernal pain generally subsided within the first 72 hours; cough increased in frequency and severity after 2–3 days and became productive of

thick mucopurulent sputum; cough disappeared by the end of 14 days.

In another accidental exposure of five chlorine plant workers and 13 nonworkers, rales, dyspnea, and cyanosis were observed in the most heavily exposed and cough was present in nearly all the patients. Pulmonary function tests 24–48 hours after exposure showed airway obstruction and hypoxemia; these conditions cleared within 3 months except in four of the chlorine workers, who still showed reduced airway flow and mild hypoxemia after 12–14 months.[6]

After acute exposures to chlorine gas, both obstructive and restrictive abnormalities on pulmonary function tests have been observed. Eighteen healthy subjects exposed after a leak from a liquid storage tank had diminished FEV_1, FEF 25–75%, and other flow rates within 18 hours of exposure. Follow-up studies at 1 and 2 weeks demonstrated resolution of these abnormalities in the 12 subjects with an initial chief complaint of cough, whereas the 6 subjects with a chief complaint of dyspnea had persistently reduced flow rates. Repeat studies in 5 months were normal in all patients studied except for mildly reduced flow rates in two patients who were smokers.[7]

Of 19 healthy persons exposed in an accident at a pulp mill and tested within 24 hours, 10 (53%) had a reduced FEV_1 (less than 75%), and 13 (68%) had increased residual volumes (greater than 120%), suggesting obstruction with air trapping. Periodic follow-up testing over the next 700 days demonstrated gradual resolution of these abnormalities in all but three subjects tested, who had persistently reduced FEV_1. Two of these three patients were smokers.[8] In contrast, a study of four healthy patients exposed to a leak at a swimming pool showed acute mild reductions in forced vital capacity, total lung capacity, and diffusing capacity, presumably related to mild interstitial edema. All lung function impairment was temporary and cleared entirely within one month. There was no residual lung damage.[9]

In all of these studies, some subjects acutely exhibited mild arterial hypoxemia, increases in alveolar-arterial oxygen tension difference, and respiratory alkalosis. Mild transient hyperchloremic metabolic acidosis, with a normal anion gap, has been described in a patient after chlorine inhalation, presumably related to systemic absorption of hydrochloric acid.[10]

Some studies of survivors of massive chlorine exposures have shown either persistent obstructive or restrictive deficits, but preexposure data on these patients were not available. Persistent respiratory symptoms, bronchial obstruction, and bronchial hyperresponsiveness were observed in 82%, 23%, and 41 % of chronically exposed pulp mill workers, respectively, 18–24 months after cessation of exposure.[11] In most cases it is not known whether prolonged symptoms after chlorine exposure are due to aggravation of preexisting conditions such as tuberculosis, asthma, chronic obstructive pulmonary disease, or heart disease.[12,13]

In high concentrations, chlorine irritates the skin and causes sensations of burning and pricking, inflammation, and vesicle formation.[12] Liquid chlorine causes eye and skin burns on contact.[14]

Administered in the drinking water for 2 years, 0.05–0.3 mmol/kg/day did not cause a clear carcinogenic response in rats or mice.[15]

In general, animal studies have demonstrated no selective reproductive or teratogenic effects of chlorine.[2]

The range of reported odor thresholds for chlorine is 0.03–3.5 ppm; however, because of olfactory fatigue, odor does not always serve as an adequate warning of exposure.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 0.5 ppm (1.5 mg/m^3) with a short-term excursion limit of 1 ppm (2.9 mg/m^3).

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CHLORINE DIOXIDE

CAS: 10049-04-4

ClO_2

Synonyms: Chlorine oxide; chlorine peroxide

Physical Form. Yellow to reddish-yellow gas

Uses. Bleaching cellulose, paper pulp, flour; purification, taste and odor control of water; oxidizing agent; bactericide and antiseptic

Exposure. Inhalation

Toxicology. Chlorine dioxide gas is a severe respiratory and eye irritant.

Exposure of a worker to 19 ppm for an unspecified time period was fatal.[1] Repeated acute exposure of workers to undetermined concentrations caused eye and throat irritation, nasal discharge, cough, wheezing, bronchitis, and delayed-onset pulmonary edema.[2] Repeated exposure may also cause chronic bronchitis.[2]

Examination of 13 individuals 5 years after they were occupationally exposed to a chlorine dioxide leak revealed sensitivity to respiratory irritants and nasal abnormalities.[3] Delayed deaths occurred in animals after exposure to 150–200 ppm for less than 1 hour.[4] Rats exposed daily to 10 ppm died after 10–13 days of exposure; effects were nasal and ocular discharge and dyspnea; autopsy revealed purulent bronchitis. Another study reported that two to four 15-minute exposures to 5 ppm for 1 month did not alter the blood composition or lung histology of rats; similar exposures to 10–15 ppm caused bronchitis, bronchiolitis, catarrhal alveolar lesions, and peribronchial infiltration.[5] Lesions healed within 15 days after treatment. Rats and rabbits exposed for 30 days to 5 or 10 ppm (2 hours/day) had localized bronchopneumonia with elevated leukocyte counts; slight reversible pulmonary lesions were found after exposures of 2.5 ppm for 4–7 hours/day. No adverse reactions were

observed in rats exposed to about 0.1 ppm for 5 hours/day for 10 weeks.[4]

Administered in the drinking water of rats daily for 9 months, 1, 10, 100, or 1000 mg/l chlorine dioxide caused a depression in red blood cell counts, hemoglobin concentration, and packed cell volumes and a decrease in erythocytic fragility. Rat body weight was decreased in all groups after 10 and 11 months of treatment.[6]

Oral gavage of rat pups with 14 mg/kg/day from postnatal day 5 through 20 caused reductions in serum thyroxine levels that correlated with depressed behavioral parameters.[7] Further studies using the same protocol reported decreased cell proliferation in the cerebellum and forebrain on postnatal days 11 and 21, respectively.[8] In yet another study, 14 mg/day of chlorine dioxide on postnatal days 1–20 was associated with some neurotoxicity (decreased forebrain weight and reduced synapse formation on day 35), but the neurotoxicity was not correlated with any antithyroid activity of this chemical.[9]

In a multigenerational study, doses up to 10 ml/kg administered for 2.5 months before breeding and through the breeding and gestational periods did not cause any adverse effects in the parental generation.[10] All parameters examined in the F_1 generation except vaginal weight in female weanlings were unaffected by gestational and lactational chlorine dioxide exposure. There were no changes in thyroid hormone parameters that appeared to be attributable to chlorine dioxide treatment.

Both positive and negative results have been reported in *in vitro* genotoxicity studies of chlorine dioxide.[11] *In vivo* assays did not find increases in micronucleus induction, chromosomal aberrations, or sperm head morphology after oral exposure, but they did find increases in micronucleus induction after intraperitoneal injection.[11]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for chlorine dioxide is 0.1 ppm (0.28 mg/m^3) with a short-term excursion limit of 0.3 ppm (0.83 mg/m^3).

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CHLORINE TRIFLUORIDE

CAS: 7790-91-2

ClF_3

Synonym: Chlorine fluoride

Physical Form. Colorless gas, pale green liquid, or white solid

Uses. Fluorinating agent; incendiary; igniter and propellant for rockets; in nuclear reactor fuel processing; pyrolysis inhibitor for fluorocarbon polymers

Exposure. Inhalation

Toxicology. Chlorine trifluoride gas is an extremely severe irritant of the eyes, respiratory tract, and skin in animals.

The injury caused by chlorine trifluoride is in part attributed to its hydrolysis products, including chlorine, hydrogen fluoride, and chlorine dioxide. Effects in humans have not been reported but may be expected to be very severe; inhalation may cause pulmonary edema, and contact with eyes or skin may cause severe burns.[1–4]

Exposure of rats to 800 ppm for 15 minutes was fatal, but nearly all survived when exposed for 13 minutes. There was severe inflammation of all exposed mucosal surfaces, resulting in lacrimation, corneal ulceration, and burning of exposed areas of skin.[4] In another study, exposure of rats to 480 ppm for 40 minutes or to 96 ppm for 3.7 hours was fatal; in the latter group, effects were pulmonary edema and marked irritation of the bronchial mucosa. Chronic exposure of dogs and rats to about 1 ppm, 6 hours/day for up to 6 months caused severe pulmonary irritation and some deaths.[2]

The 2003 ACGIH ceiling-threshold limit value (C-TLV) for chlorine trifluoride is 0.1 ppm (0.38 mg/m^3).

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CHLOROACETALDEHYDE

CAS: 107-20-0

$ClCH_2CHO$

Synonyms: Monochloroacetaldehyde; 2-chloroacetaldehyde

Physical Form. Colorless liquid

Uses/Sources. In the manufacture of 2-aminothiazole; to facilitate bark removal from tree trunks; formed during the chlorination of drinking water; a metabolite of vinyl chloride

Exposure. Inhalation; skin absorption

Toxicology. Chloroacetaldehyde is a severe irritant of the eyes, mucous membranes, and skin; it is toxic and carcinogenic to the liver of male mice.

Inhalation of 5 ppm by rats caused eye and nasal irritation.[1] In rabbits, the LD_{50} for skin absorption was 0.022 ml/kg for 30% chloroacetaldehyde in water solution.[2] This solution on the skin or in the eyes of rabbits produced severe damage.

Male B6C3F1 mice exposed to 0.1 g/l chloroacetaldehyde via the drinking water for 104 weeks (mean ingested dose 17/mg/kg/day) had a significant increase in the prevalence of liver carcinomas (31% vs. 10% in controls). No

significant changes were noted in the spleen, kidneys, or testes of treated animals compared with controls.[3]

Chloroacetaldehyde has been reported to be an inhibitor of DNA synthesis and to form DNA adducts; it is mutagenic in *Salmonella typhimurium* and in Chinese hamster cells.[4–6]

Limited in vivo genotoxicity studies with chloroacetaldehyde were negative.[7]

The 2003 ACGIH threshold limit value-ceiling (TLV-C) for chloroacetaldehyde is 1 ppm (3.2 mg/m^3).

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CHLOROACETONE

CAS: 78-95-5

$ClCH_2COCH_3$

Synonyms: Monochloroacetone; chloropropanone; 1-chloro-2-propanone; acetonyl chloride

Physical form. Colorless to amber liquid, often with 5% $CaCl_2$ as a stabilizer

Uses. Manufacture of couplers for color photography; intermediate in manufacture of perfumes, antioxidants, drugs, plant growth regulators, defoliants, and herbicides

Exposure. Inhalation; skin absorption

Toxicology. Chloroacetone is a lacrimator and a severe irritant of the eyes, mucous membranes, and skin.

Chloroacetone was introduced as a war gas in 1914.[1] An airborne level of 605 ppm was found to be lethal for humans after 10 minutes, and 26 ppm was intolerable after 1 minute of exposure. Effects of exposure are immediate lacrimation followed by irritation of the upper respiratory tract and a burning sensation on the skin. The odor is pungent and suffocating but is not considered adequate for warning.

An employee who was directly exposed to hot chloroacetone was hospitalized with irritation of the eyes and upper respiratory tract plus skin irritation. Eight hours after exposure there was development of blisters on the skin. All signs and symptoms disappeared after 7 days.

The 1-hour LC_{50} in rats was 262 ppm, and the oral LD_{50} was 100 mg/kg. In animal experiments lung edema and hydrothorax have occurred after inhalation exposure.[2] Repeated oral administration causes necrosis of the liver, spleen, adrenal gland, and testis, as well as ulceration and perforation in the gastric area in rats.[2] The dermal LD_{50} in rabbits was 141 mg/kg, indicating significant skin absorption.[1]

The 2003 ACGIH ceiling-threshold limit

value (C-TLV) for chloroacetone is 1 ppm (3.8 mg/m^3) with a notation for skin absorption.

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α-CHLOROACETOPHENONE

CAS: 532-27-4

$C_6H_5COCH_2Cl$

Synonyms: 2-Chloro-1-phenylethanone; phenacyl chloride; phenyl chloromethyl ketone; tear gas; chemical Mace

Physical Form. Crystals

Uses. Chemical warfare agent (CN); principal constituent in riot control agent Mace; in tear gas formulations for personal protection devices

Exposure. Inhalation

Toxicology. α-Chloroacetophenone is a potent lacrimating agent and an irritant of mucous membranes; it causes dermatitis of both primary irritation and sensitization type.

In one fatal case of exposure, death occurred as a result of pulmonary edema; exposure occurred under unusual circumstances that caused inhalation of high concentrations.[1] Human volunteers exposed to levels of 200–340 mg/m^3 could not tolerate exposure for longer than 30 seconds.[2] Effects were lacrimation, burning of the eyes, blurred vision, tingling of the nose, rhinorrhea, and burning of the throat.[1] Less frequent symptoms included burning in the chest, dyspnea, and nausea.

Sporadic cases of dermatitis due to primary irritation by α-chloroacetophenone have been reported.[3,4] Allergic contact dermatitis to this substance in chemical Mace has been documented by patch test evaluation, and it is said to be a potent skin sensitizer.[3,4]

Eye splashes cause marked conjunctivitis and may result in permanent corneal damage.[5] The lacrimation threshold ranges from 0.3 to 0.4 mg/m^3, and the odor threshold is 0.1 mg/m^3.[5]

In 14-day studies rats exposed to 4.8 mg/m^3 showed excessive lacrimation, partial closure of the eyelids, dyspnea, erythema, and weight loss.[6] During the first week of exposure, a concentration of 19 mg/m^3 was lethal to all rats whereas 10 mg/m^3 was lethal to mice. In 2-year inhalation studies there was no evidence of carcinogenicity to mice exposed to 2 or 4 mg/m^3 or in male rats exposed to 1 or 2 mg/m^3; equivocal evidence of carcinogenicity was present in exposed female rats based on a marginal increase in fibroadenomas of the mammary gland.[6] 2-Chloroacetophenone was not mutagenic in bacterial assays, nor did it induce sister chromatid exchanges in Chinese hamster ovary (CHO) cells. A slight increase in chromosomal aberrations was observed.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for α-chloroacetophenone is 0.05 ppm (0.32 mg/m^3).

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CHLOROACETYL CHLORIDE

CAS: 79-04-9

$ClCH_2COCl$

Synonyms: Monochloroacetyl chloride; chloroacetic acid chloride; CAC

Physical Form. Colorless liquid

Uses. Intermediate in manufacture of chloroacetophenone and various other chemicals

Exposure. Inhalation; skin absorption

Toxicology. In humans, chloroacetyl chloride (CAC) is a lacrimator; it also causes respiratory effects including dyspnea, cyanosis, and cough and skin effects including erythema and burns.

A 44-year-old male worker experienced a large skin area exposure to a mixture of CAC, benzene, and xylidine.[1] The worker was put under a shower within 5 minutes of the accident, but shortly thereafter he began to have respiratory difficulties and experienced an apparent grand mal seizure. The patient was still comatose 2 years after the accident. Burns caused by the chloroacetyl chloride were believed to have enhanced skin absorption of the other two chemicals, although the relative contribution of the three chemicals to the patient's condition is unknown. The authors stated that the CAC manufacturer had provided information on two fatalities from CAC exposure, one after massive skin contact followed by death within a few minutes. According to that manufacturer, other data indicated that CAC may promote ventricular arrhythmias.

In a similar incident, a worker was drenched by a mixture of the same three materials and sodium carbonate.[2] He suffered extensive first- and second-degree burns and pulmonary edema despite immediately being placed under a shower. The outcome was not reported. Other workers involved in the rescue suffered blisters on their hands and complained of chest tightness and nausea up to 2 days later.

Chloroacetyl chloride is rapidly broken down to hydrochloric acid and chloroacetic acid in the presence of water, and these decomposition products may be responsible for the severe irritant effects.

An industrial hygienist was not able to detect odor at 0.011 ppm, found 0.023 ppm barely detectable, and 0.140 ppm "strong."[3] He experienced no eye irritation at 0.140 ppm but reported painful eye irritation and lacrimation around 1.0 ppm.

The oral LD_{50} in rats was between 187 and 229 mg/kg.[3] The 1-hour LC_{50} was 660 ppm for male rats and 750 ppm for females; lacrimation and labored breathing occurred during exposures, and autopsy confirmed lung and nasal tissue congestion. In a 30-day inhalation study with rats, mice, and hamsters, concentrations of 5 or 2.5 ppm 6 hrs/day, 5 days/week caused deaths in rats and mice but not hamsters; respiratory tract lesions were visible at necropsy, with the most severe response observed in the nasal region. Slight respiratory tract and eye irritation were observed in all species at 0.5 ppm. Applied to the skin of rabbits the lethal dose was between 300 and 500 mg/kg.

Chloroacetyl chloride was not genotoxic in a number of assays.[4]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for chloroacetyl chloride is 0.05 ppm (0.23 mg/m^3) with a notation for skin absorption.

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CHLOROBENZENE
CAS: 108-90-7

C_6H_5Cl

Synonyms: Phenylchloride; monochlorobenzene; chlorobenzol; benzene chloride

Physical Form. Colorless liquid

Uses. Manufacture of phenol, aniline, DDT; solvent for paint; color printing; dry cleaning industry

Exposure. Inhalation

Toxicology. Chlorobenzene is irritating to the skin and mucous membranes; it can cause central nervous system depression and liver and kidney damage.

In humans, eye and nasal irritation occur at 200 ppm, and at that level the odor is pronounced and unpleasant; industrial experience indicates that occasional short exposures are not likely to produce more than minor skin irritation, but prolonged or frequently repeated contact may result in skin burns.[1] In one case of accidental poisoning from ingestion of the liquid by a child, there was pallor, cyanosis, and coma, followed by complete recovery.[2]

Cats exposed to 8000 ppm showed severe narcosis after 1/2 hour and died 2 hours after removal from exposure, not; but they tolerated 660 ppm for 1 hour.[3] Exposed animals showed eye and nose irritation, drowsiness, incoordination, and coma, followed by death from the most severe exposures. Several species of animals exposed daily to 1000 ppm for 44 days showed injury to the lungs, liver, and kidneys, but at 475 ppm there was only slight liver damage in guinea pigs.

Leukopenia and depressed bone marrow activity were found in mice exposed at 544 ppm, 7 hours/day for 3 weeks or at 22 ppm, 7 hours/day for 3 months.[4] Only slight transient hematologic effects were found in rats and rabbits exposed at 250 ppm, 7 hours/day for 24 weeks.[5] Administered to dogs in capsule form, 272.5 mg/kg/day for up to 92 days caused an increase in immature leukocytes and some deaths.[6] Postmortem findings included gross and/or microscopic pathology in liver, kidneys, gastrointestinal mucosa, and hematopoietic tissue. No consistent effects were observed at 54.5 mg/kg/day.

In 91-day gavage studies, dose-dependent necrosis of the liver, degeneration or focal necrosis of the renal proximal tubules, and lymphoid or myeloid depletion of the spleen, bone marrow, and thymus were produced by doses of 250 mg/kg/day or greater in both sexes of rats and mice, although the incidences of the lesions varied considerably by sex and species.[7,8] No toxic effects were observed at doses of 125 mg/kg/day or less. Gastric intubation of 120 mg/kg/day for 2 years produced a slight but statistically significant increase in neoplastic nodules of the liver in male rats. Increased tumor frequencies were not observed in female rats or in male or female mice receiving monochlorobenzene.

Concentrations up to 450 ppm, 7 days/week, 6 hours/day did not adversely affect reproductive performance or fertility in a two-generation rat study.[9] In rats and rabbits, inhalation of 590 ppm 6 hours/day during

periods of major organogenesis did not produce structural malformations.[10]

Chlorobenzene was not mutagenic in a variety of bacterial and yeast assays. Existing data suggest that genotoxicity may not be an area of concern for chlorobenzene exposure in humans.[11]

Although the odor of chlorobenzene is pronounced and unpleasant, it is not sufficient to give warning of hazardous concentrations.[1]

The 2003 threshold limit value-time-weighted average (TLV-TWA) for chlorobenzene is 10 ppm (46 mg/m^3) with an A3-confirmed animal carcinogen with unknown relevance to humans designation.

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o-CHLOROBENZYLIDENE MALONONITRILE

CAS: 2698-41-1

$ClC_6H_4CH{=}C(CN)_2$

Synonyms: CS; OCBM; chlorobenzylidene malononitrile; 2-chloro-benzylidene malononitrile

Physical Form. White, crystalline solid

Uses. Active ingredient in tear gas

Exposure. Inhalation; skin absorption

Toxicology. *o*-Chlorobenzylidene malononitrile (CS) aerosol is a potent lacrimator and upper respiratory irritant.

Characteristic effects of CS exposure are instantaneous conjunctivitis, blepharospasm, burning, and pain.[1] Prolonged exposure to high concentrations in enclosed spaces may cause pulmonary edema and severe bronchospasm.[1]

In human experiments, concentrations ranging from 4.3 to 6.7 mg/m^3 were barely tolerated when reached gradually over a period of 30 minutes.[2] After cessation of exposure, a

burning sensation and deep pain in the eyes persisted for 2–5 minutes. Severe conjunctivitis lasted for 25–30 minutes, and erythema of the eyelids with some blepharospasm was present for 1 hour. There was a burning sensation in the throat with cough, followed by a constricting sensation in the chest; no therapy other than removal from exposure was necessary.

At a concentration of 1.5 mg/m^3, three of four men developed headache during a 90-minute exposure; one subject developed slight eye and nose irritation.[2] On the skin, the powder caused a burning sensation, which was greatly aggravated by moisture; erythema and vesiculation resembling second-degree burns were produced. Both sensitization and subsequent allergic contact dermatitis can result from a single exposure.[3]

In animals, the manifestation of lethal toxicity is different after intravenous, intraperitoneal, oral, and inhalation routes. After intravenous administration, there is rapid onset of signs characteristic of effects on the nervous system due to the alkylating properties of CS.[4] High doses of intraperitoneal CS result in expression of the cyanogenic potential of the malononitrile radical. By the oral route, local inflammation in the gastrointestinal tract contributes to toxicity. Lethal toxicity from inhalation is due to lung damage leading to asphyxia or, in the case of delayed deaths, bronchopneumonia secondary to respiratory tract damage. Rats survived a 10-minute exposure at 1800 mg/m^3, but 20 of 20 succumbed after 60 minutes at 2700 mg/m^3.

o-Chlorobenzylidene malononitrile did not cause a mutagenic response when tested in a variety of assays that examined point mutations, germinal gene mutations, chromosomal breaks, and mitotic chromosome misdistribution.[5] Although limited, a study of the repeated inhalation toxicity of CS in mice, rats, and guinea pigs did not find a relationship between tumors in a particular site and total dose of CS.[6] F344N rats exposed at 0.075, 0.25, or 0.75 mg/m^3 and B6C3F1 mice exposed at 0.75 or 1.5 mg/m^3 6 hours/day, 5 days/week for 2 years had no compound-related incidences of neoplasm.[7] Nonneoplastic lesions occurred primarily in the nasal passages and included hyperplasia and squamous metaplasia of the respiratory epithelium.

The 2003 ACGIH ceiling-threshold limit value (C-TLV) for *o*-chlorobenzylidene malononitrile is 0.05 ppm (0.39 mg/m^3) with a notation for skin absorption.

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CHLOROBROMOMETHANE
CAS: 74-97-5

CH_2BrCl

Synonyms: Monochloromonobromomethane; bromochloromethane; methylene chlorobromide; monobromochloromethane; chloromethyl bromide

Physical Form. Colorless liquid

Uses. Fire fighting agent

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Chlorobromomethane is a mild irritant of the eyes and mucous membranes; at high concentrations it causes central nervous system depression.

Exposure of three firefighters to unknown but very high vapor concentrations was characterized by disorientation, headache, nausea, and irritation of the eyes and throat. Two of the three became comatose; one had convulsive seizures, and the other had respiratory arrest from which he was resuscitated.[1] Recovery was slow but complete. Some effects may have been due to the inhalation of thermal decomposition products.

Prolonged skin contact may cause dermatitis.[1] The liquid in the eye causes an immediate burning sensation, followed by corneal epithelial injury and conjunctival edema.[2]

Concentrations near 30,000 ppm were lethal to rats within 15 minutes; toxic signs included loss of coordination and narcosis. This level of exposure produced pulmonary edema, and in cases of delayed deaths, there was interstitial pneumonitis.[3] Concentrations as low as 3000 ppm for 15 minutes produced light narcosis in rats. No toxic effects were observed in rats, rabbits, and dogs exposed 7 hours/day, 5 days/week for 14 weeks to 1000 ppm.[4]

Early studies in animals indicate that the target organs are the liver and the kidney after repeated inhalation or oral exposure at high concentrations.[5]

Metabolic studies of inhaled chlorobromomethane in rats have shown production of carbon monoxide, halide ions, and other reactive intermediates.[6] It has been noted that some central nervous system effects may be a consequence of elevated carbon monoxide in the blood, which can result from chlorobromomethane metabolism.[5]

Chlorobromomethane is a bacterial cell mutagen both with and without activation and can also induce chromosomal aberrations in in vitro assays.[5]

Chlorobromoethane has a distinctive odor at 400 ppm; however, the odor is not disagreeable and does not provide sufficient warning properties.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for chlorobromomethane is 200 ppm (1060 mg/m^3).

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p-CHLORO-*m*-CRESOL

CAS: 59–50–7

$CH_3C_6H_3ClOH$

Synonyms: PCMC; 4-chloro-*m*-cresol; 3-methyl-4-chlorophenol; Candaseptic; Preventol CMK

Physical Form. Crystals, usually with a phenolic odor

Uses. Antiseptic; as a preservative in cosmetics

Exposure. Inhalation

Toxicology. *p*-Chloro-m-cresol (PCMC) causes kidney damage in male rats after chronic exposure.

PCMC was evaluated for chronic toxicity and carcinogenicity in Wistar rats (50/sex/dose level) when administered in the feed for 24 months at doses of 0, 400, 2000, and 10,000 ppm.[1] Over 104 weeks, rats ingested 21, 103.1, and 558.9 mg (males) and 27.7, 134.3, and 743.5 mg (females). All the effects observed were associated with the highest exposure level. These included decreased body weight gain for both sexes, increased incidence of female rats found in poor condition of health, increased relative kidney weights for both sexes, and gross and micropathologic evidence of kidney damage (i.e., papillary necrosis, cortical dilation, and fibroses) in males only. There was no indication of carcinogenic potential of the substance up to and including the 10,000-ppm exposure level.

In a developmental toxicity study, PCMC was administered to pregnant Wistar rats by oral gavage at doses of 0, 30, 100, and 300 mg/kg body weight/day on days 6–15 of gestation.[2] The 100 mg/kg body weight/day dose was reported as maternally toxic because of reduction of body weight gain and food consumption in dams. At 300 mg/kg body weight/day a 25% mortality of the dams was reported. Clinical signs (unspecified) of toxicity were observed on several days during the administration period. A statistically significant increase of early resorptions and a decrease in mean fetal weights were observed only in the 300 mg/kg body weight/day dose group.

No evidence of mutagenicity was seen in bacterial assays.[3]

Occular irritation has been reported in rabbits at concentrations as low as 0.05%.[3] Some evidence of dermal irritation and sensitization has been reported in animal and human studies.[3]

A threshold limit value has not been assigned to PCMC.

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CHLORODIBROMOMETHANE

CAS: 124-48-1

$CHBr_2Cl$

Synonyms: Dibromochloromethane; monochlorodibromomethane

Physical Form. Colorless liquid

Uses. One of four common trihalomethanes formed after chlorination of water supplies; in the past used to make fire extinguisher fluids,

spray can propellants, refrigerator fluids, and pesticides; only small amounts currently produced for laboratory use

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Chlorodibromomethane is a central nervous system (CNS) depressant at extremely high concentrations; it is toxic to the liver and kidneys of rodents and induces hepatocellular tumors in mice after long-term exposure.

In animal studies, the oral LD_{50} typically ranges between 800 and 1200 mg/kg.[1,2] Acute signs of intoxication include sedation, flaccid muscle tone, ataxia, and prostration; death is due to CNS depression. In cases in which death does not occur until several days after acute exposure, hepatic and renal injury may be the cause of death.

It should be noted that in humans opportunities for exposure to acutely lethal doses of chlorodibromomethane are remote. In animals, no direct effects of oral exposure to chlorodibromomethane have been noted for the respiratory, cardiovascular, hematologic, or musculoskeletal systems or on the skin or eyes. One study indicated that short-term oral exposure of mice to doses of 125 mg/kg/day could produce significant changes in both the humoral and the cell-mediated immune systems.[3]

In the drinking water of rats, 137 and 165 mg/kg/day of chlorodibromomethane for 90 days produced mild toxicity in the liver; the observed vacuolar changes due to fatty infiltration were reversible after a 90-day recovery period.[4]

Administered by gavage to rats and mice for 13 weeks, 250 mg/kg/day of chlorodibromomethane caused hepatic and renal toxicity in male and female rats and in male mice.[5] Results of 2-year gavage studies showed fatty metamorphosis and cytoplasmic changes in the livers of rats receiving up to 80 mg/kg/day; in mice receiving up to 100 mg/kg/day of the chemical, hepatic lesions included necrosis and hepatocytomegaly in males and calcification and fatty change in females.[5,6] Evidence of nephrosis was seen in male mice and female rats.

In the same 2-year gavage study, chlorodibromomethane significantly increased the incidence of hepatocellular adenomas, as well as the combined incidence of hepatocellular adenomas or carcinomas, in the high-dose female mice. The incidence of hepatocellular carcinomas was significantly increased in the high-dose male mice although the combined incidence of hepatocellular adenomas or carcinomas was only marginally significant. Under the conditions of the gavage studies, there was no evidence of carcinogenicity in rats receiving doses of 40 or 80 mg/kg/day for 2 years; there was equivocal evidence of carcinogenicity in male mice receiving 100 mg/kg/day for 2 years and some evidence of carcinogenicity in female mice receiving 50 or 100 mg/kg/day for 2 years.

There was no increase in tumor incidence in mice given chlorodibromomethane in drinking water for life.[7]

There is no clear epidemiological evidence for the carcinogenicity of chlorodibromomethane in humans. However, a number of studies suggest an association between chronic ingestion of trihalomethanes in chlorinated drinking water and increased risk of bladder or colon cancer.[6] These studies cannot provide information on whether any observed effects are due to chlorodibromomethane or to one or more of the hundreds of other by-products that also are present in chlorinated drinking water.

The IARC has determined that there is limited evidence for the carcinogenicity of chlorodibromomethane in experimental animals and that it is not classifiable as to its carcinogenicity to humans.[7]

Chlorodibromomethane was not genotoxic *in vivo* but gave positive results in a number of *in vitro* assays.[7,8]

No teratogenic effects were observed in rats given 200 mg/kg/day during gestation.[9] At doses of 685 mg/kg/day, which caused marked maternal toxicity, there were significant decreases in litter size, gestational survival, and postnatal body weight and survival.[10]

A 2003 ACGIH threshold limit value (TLV) has not been established.

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CHLORODIFLUOROMETHANE

CAS: 75-45-6

$CHClF_2$

Synonyms: Freon 22; monochlorodifluoromethane; difluoromonochloromethane

Physical Form. Colorless, nearly odorless, nonflammable gas

Uses. Aerosol propellant; refrigerant; low-temperature solvent

Exposure. Inhalation

Toxicology. Chlorodifluoromethane gas causes central nervous system depression and cardiac effects; extremely high concentrations may cause a deficiency of oxygen with the risk of unconsciousness or death.

There have been few reports of adverse health effects in workers despite nearly 50 years of commercial use of chlorodifluoromethane.[1] Fatalities have been reported however, in connection with intentional inhalation with death due to acute respiratory arrest.[2]

The incidence of cardiac palpitations was compared in two employee groups.[3] One group of 118 employees was exposed to an average concentration of 300 ppm chlorodifluoromethane during its use as a tissue preservative. The control group of 85 employees came from a different department and had no chemical exposure. The number of employees exhibiting palpitations was significantly higher in the exposed group than in the control group. An epidemiological study involving workers exposed to chlorofluorocarbons, including chlorodifluoromethane, showed no increased mortality due to heart, circulatory, or malignant disorders.[1]

Animal studies found an LC_{50} of 277,000 ppm for a 30-minute exposure in mice and a threshold concentration of 300,000 ppm for death in rabbits.[4] Chlorodifluoromethane was thought to have an irritative effect on the respiratory system or a stimulative effect on the parasympathetic system, which caused a great amount of mucous fluid, rattling in the chest, and high cyanosis.[4] The cause of death was thought to be respiratory insufficiency from aspiration of mucous fluid into the lungs. Exposure of rats and guinea pigs for 2 hours to levels of 75,000–100,000 ppm caused excitation and/or dysfunction in equilibrium.[5] Narcosis occurred at 200,000 ppm, and animals died at 300,000–400,000 ppm.

Studies in the dog and other species show that high concentrations (above 50,000 ppm) in association with injected epinephrine are required to produce cardiac arrythmias.[1] This is a relatively low order of potency in comparison with other chlorofluorocarbons.[1]

Pregnant rats exposed to 50,000 ppm 6 hours/day on days 6–15 of gestation had decreased body weight gain, and their offspring had an increased incidence of anophthalmia (absent eyes).[1] At this dose chlorodifluoromethane did not affect the pregnant rabbit or her offspring, nor was there any effect on male fertility in the rat or the mouse.

Evaluation of tumor data from lifetime studies showed an increased incidence of fibrosarcomas, some involving the salivary gland, in male rats chronically exposed to 50,000 ppm.[1] Negative results were obtained for females. Other studies in mice or in rats receiving oral doses were negative or inconclusive.[6] The IARC has determined that there is limited evidence for carcinogenicity to animals and inadequate evidence for carcinogenicity to humans.[6]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 1000 ppm (3540 mg/m^3).

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CHLORODIPHENYL, 42% CHLORINE
CAS: 53469-21-9

$C_{12}H_7Cl_3$

Synonyms: Aroclor 1242; polychlorinated biphenyl; PCB

Physical Form. Straw-colored liquid

Uses. Dielectric in capacitors and transformers; investment casting processes; heat exchange fluid; hydraulic fluid; no longer produced in the US

Exposure. Skin absorption; ingestion; inhalation

Toxicology. Chlorodiphenyl, 42% chlorine (one of over 200 possible chlorinated compounds that comprise polychlorinated biphenyls or PCBs) is an irritant of the eyes and

mucous membranes, is toxic to the liver, and causes an acneform dermatitis (chloracne). It is a liver carcinogen in animals.

In humans, systemic effects are anorexia, nausea, edema of the face and hands, and abdominal pain.[1] In a survey of 34 workers exposed to concentrations of up to 2.2 mg/m^3, complaints were a burning sensation of the face and hands, nausea, and a persistent (uncharacterized) body odor.[1] One had chloracne, and five had an eczematous rash on the legs and the hands.[1] Although hepatic function tests were normal, the mean blood level of chlorodiphenyl in the exposed group was approximately 400 ppb, whereas none was detected in the control group.[1]

Cases of mild to moderate skin irritation and chloracne have been reported in workers exposed to 0.1 mg/m^3 for several months. Levels of 10 mg/m^3 were unbearably irritating, presumably to mucous membranes and skin.[2] Chloracne does not appear to occur at concentrations below 0.1 mg/m^3.

Chloracne usually is persistent and affects the face, ears, neck, shoulders, arms, chest, and abdomen (especially around the umbilicus and on the scrotum). The most sensitive areas are below and to the outer side of the eye (malar crescent) and behind the ear. The skin frequently is dry with noninflammatory comedones and pale yellow cysts containing sebaceous matter and keratin. Evidence of liver disease often is seen in association with PCB-induced chloracne.[3]

Some studies of occupationally exposed groups have revealed evidence of liver injury by serum enzyme studies or other liver function tests. Adverse effect and dose-effect relationships have not been consistent within and between studies, raising the possibility that other factors (e.g., alcohol intake, other exposures) could be responsible.[2] Review of these studies indicates that some liver effects may have occurred with repeated exposures at concentrations below 0.1 mg/m^3, assuming PCBs were responsible. Several deaths due to toxic hepatitis have been reported among workers exposed to mixtures of PCBs with chlorinated naphthalenes; such effects have not been observed with PCB exposure alone.[2]

A cross-sectional survey of 205 capacitor manufacturing workers with a geometric mean serum PCB level of 18.2 ppb, standard deviation (SD) 2.88, found no statistically significant correlations between PCB levels and clinical chemistry results, including SGOT, GGTP, and LDH levels.[4] The primary dielectric used in the plant was Aroclor 1242. However, another cross-sectional survey of 120 railroad transformer workers with mean plasma PCB levels of 33.4 ppb did reveal statistically significant correlations of PCB level with serum triglyceride and SGOT (but not SGPT or GGTP) levels.[5] There was a significant correlation between self-reported direct dermal contact with PCBs and the plasma PCB level. In a survey of 80 heavily exposed capacitor or transformer manufacturing workers in Italy with mean blood PCB levels of about 340 ppb, there was a correlation between blood PCB levels and abnormal liver findings (including hepatomegaly and increased GGTP, SGOT, and SGPT levels).[6] Even in this latter group, except for a few cases of chloracne, no other symptoms or findings referable to PCB exposure were present. The biological significance of these generally mild elevations in serum enzymes is also unclear.

Industrial hygiene studies support the notion that the dermal and dermal/oral, rather than the respiratory, routes of exposure are the predominant contributors to body burden among workers occupationally exposed to PCBs.[7]

Serious adverse health effects were attributed to PCBs after accidental ingestion in 1968 by over 1000 Japanese people who ingested PCB-contaminated rice bran oil for a period of several months.[8,9] The contamination of the oil (estimated 1500–2000 ppm) occurred when heat transfer pipes immersed in the oil during processing developed pin-sized holes. The clinical aspects of the poisoning included chloracne, brown pigmentation of the skin and nails, distinctive hair follicles, increased eye discharge, swelling of eyelids, transient visual disturbance, and systemic gastrointestinal symptoms with jaundice. In some patients, symptoms persisted 3 years after PCB exposure was discontinued. Infants born to poisoned

mothers had decreased birth weights and showed skin discoloration. Chemical analysis of the contaminated rice bran oil revealed significant amounts of polychlorinated dibenzofurans (PCDFs) as well as PCBs.[10] High concentrations of PCDFs were found in blood and adipose tissue of Yusho victims. In contrast, in a group of workers occupationally exposed to PCBs, PCB levels were higher than in the Yusho victims but PCDFs were not generally detected.[10,11] Animal experiments have reproduced some findings seen in Yusho victims with administration of PCDFs but not PCBs. Thus it appears that PCDFs were the main causative agents in the induction of Yusho disease.[10,11]

Epidemiological studies have suggested an association between occupational exposures to PCBs and cancer at several sites, particularly the liver, biliary tract, intestines, and skin (melanoma).[12] A cohort study of 544 male and 1557 female workers employed between 1946 and 1978 in an Italian capacitor manufacturing plant using PCB mixtures (with 54%, then 42% chlorine) found statistically significant excesses of total cancer deaths in males (14 obs. vs. 7.6 exp.) and females (12 obs. vs. 5.3 exp.), cancer of the gastrointestinal tract in males (6 obs. vs. 2.2 exp.) and hematologic neoplasms in females (4 obs. vs. 1.1 exp.)[13] Of the six gastrointestinal tract malignancies in males, the primary sites were stomach (2), pancreas (2), liver (1), and biliary tract (1). There was an excess of hematologic neoplasms in males (3 obs. vs. 1.1 exp.), but this excess was not statistically significant. The authors qualified their conclusions regarding excess malignancies because of the small number of deaths in the cohort, the occurrence of some tumors in workers with minimal exposure or short latency intervals, and the disparate sites and types of tumors.

An update of a retrospective cohort mortality study of 2588 US workers exposed to PCBs in two capacitor manufacturing plants found a statistically significant excess for cancer of the liver and biliary passages [5 observed vs. 1.9 expected, standardized mortality ratio (SMR) 263]. Both Aroclor 1254 (54% chlorine) and 1242 (42% chlorine) had been used at different times in both plants. Although the workers studied had positions involving greater exposure to PCBs than other workers in the plants, historical levels of exposure were unknown. Four of the five cases of liver and biliary tract cancer occurred in women in plant two. All five workers were first employed in the 1940s and early 1950s, when exposures were presumed to be the highest, however, analysis did not reveal that risk was associated with time since first employment or length of employment in "PCB-exposed" jobs. The small number of cases was also noted.[14]

A significant excess risk of death from malignant melanoma (8 observed, 2.0 expected) was observed in a cohort study of 3588 capacitor manufacturing workers exposed to Aroclor 1242 and then 1016.[15]

All PCB mixtures adequately tested in mice and rats have shown carcinogenic activity.[2] For example, of 20 rats fed Aroclor 1242 at 100 ppm in the diet for 24 months, 11 developed liver tumors, of which 3 were hepatomas. A significant incidence of hepatocellular neoplasms was found in female rats but not males in another study of Arochlor 1242 in the diet.[16] Evidence from bioassays suggests that the less highly chlorinated PCBs (e.g., Aroclor 1242) have less carcinogenic potential than the more highly chlorinated mixtures (e.g., Aroclor 1254).[2]

A number of agencies have determined that there is sufficient evidence of carcinogenicity in experimental animals for PCBs and that they are a probable human carcinogen.[12]

The genotoxicity of PCBs has been tested in *in vivo* and *in vitro* studies with generally negative results.[12]

Reproductive effects in animals have included reduced implantation rate and prolonged estrus in rats and prolonged menstruation and decreased fertility in monkeys.[12] In male rats and mice gestational or lactational exposure can adversely affect sperm morphology and production. Comparison of the reproductive histories of 200 women exposed to PCBs during the production of capacitors with the histories of controls showed only a slight relationship between estimated PCB levels in serum and decreased birth weight.[17]

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CHLORODIPHENYL, 54% CHLORINE
CAS: 11097-69-1

$C_6H_2Cl_3C_6H_3Cl_2$

Synonyms: Arochlor 1254; Aroclor 1254; polychlorinated biphenyl; PCB

Physical Form. Viscous liquid

Uses. Dielectric in capacitors and transformers; investment casting processes; heat exchange fluid; hydraulic fluid; no longer produced in the US

Exposure. Skin absorption; ingestion; inhalation

Toxicology. Chlorodiphenyl, 54% chlorine (Arochlor 1254) , a polychlorinated biphenyl or PCB, is an irritant of the eyes and mucous

membranes. It is toxic to the liver of animals, and severe exposure may produce a similar effect in humans. It also causes an acneform dermatitis (chloracne). It is a liver carcinogen in animals.

Note. For a full description of the toxicology of this compound, see the entry for chlorodiphenyl, 42% chlorine immediately preceding this entry. Special characteristics of the 54% chlorine compound are given below.

Rats exposed to 5.4 mg/m^3 of the 54% chlorine compound for 7 hours daily for 4 months showed increased liver weight and injury to liver cells; 1.5 mg/m^3 for 7 months also produced histopathologic evidence of liver damage, which was considered to be of a reversible character.[1] The minimal lethal dose when the liquid was applied to the skin of rabbits was 1.5 g/kg.[2] The vapor and the liquid are moderately irritating to the eye; contact of the chemical with skin leads to removal of natural fats and oils, with subsequent drying and cracking of the skin.[2]

After application of radiolabeled PCB, 54% chlorine, to the skin of guinea pigs, 56% of the applied dose was absorbed.[3]

Administration of a PCB mixture (mean chlorine content 54%) twice a week for 6 weeks via a stomach tube to rats at relatively low dose levels led to histopathologic changes in the liver, increases in cholesterol and triglyceride levels, and serum enzyme increases. At the 2 mg/kg dose, centrilobular hepatic necrosis and elevated cholesterol levels were observed. Increases in bilirubin and triglyceride levels occurred only at 50 mg/kg and increases in SGOT (AST) and SGPT (ALT) only at doses above 50 mg/kg.[4]

All PCB mixtures adequately tested in mice and rats have shown carcinogenic activity.[1] For example, hepatomas developed in 9 of 22 BALB/cj male mice fed Arochlor 1254 at 300 ppm for 11 months.[5] Of 27 rats fed Arochlor 1254 at 100 ppm in the diet for 24 months, 19 developed liver tumors, 6 of which were hepatomas, compared with 1 neoplastic nodule in 23 controls. A dose-dependent increase in liver tumors and a decrease in mammary gland tumors was observed in female rats exposed at concentrations ranging from 25 to 200 ppm for 24 months; a small increase was noted in the incidence of thyroid gland follicular cell adenomas in males.[6] The tumors that were produced were mostly benign and did not curtail the natural life span of the animals. Evidence from bioassays suggests that the more highly chlorinated PCBs (e.g., Arochlor 1254) have more carcinogenic potential than the less highly chlorinated mixtures (e.g., Arochlor 1242).[5]

Mortality studies provide suggestive evidence that occupational exposure to PCB's containing 54% chorine are associated with cancer at several sites, particularly liver, biliary tract, intestines, and skin.[7]

Arochlor 54 was not mutagenic in *Salmonella* assays; it was not genotoxic in rodent assays in vivo.[7]

Adverse reproductive effects have been observed in animals fed PCB in the diet.[1] Fetal resorptions were common, and dose-related incidences of terata were found in pups and piglets when females were fed Arochlor 1254 at 1 mg/kg/day or more. Long-term low-level maternal exposure of rats before breeding and throughout gestation and lactation caused permanent hearing deficits, decreased serum thyroid hormones, and reproductive effects.[8] PCBs have been observed in human cord blood and in tissues of newborn humans and animals.[1]

The 2003 threshold limit value-time-weighted average (TLV-TWA) is 0.5 mg/m^3 with a notation for skin and an A3-confirmed animal carcinogen with unknown relevance to humans designation.

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CHLOROFORM

CAS: 67-66-3

$CHCl_3$

Synonyms: Trichloromethane; methenyl chloride; methane trichloride

Physical Form. Colorless liquid

Uses. Manufacture of fluorocarbons for refrigerants, aerosol propellants, plastics; purifying antibiotics; solvent; photographic processing; dry cleaning

Exposure. Inhalation

Toxicology. Chloroform is a central nervous system depressant and hepatotoxin; renal and cardiac damage may also occur. It is carcinogenic in experimental animals.

Chloroform was abandoned as an anesthetic agent because of the frequency of cardiac arrest during surgery and of delayed death due to hepatic injury.[1] Concentrations used for the induction of anesthesia were in the range of 20,000–40,000 ppm, followed by lower maintenance levels.[2] Continued exposure to 20,000 ppm results in respiratory failure, cardiac arrhythmia, and death.[1] Effects of damage to the liver typically are not observed for 24–48 hours after exposure.[1] Symptoms include progressive weakness, prolonged vomiting, delirium, coma, and death. Increased serum bilirubin, ketosis, and lowered blood prothrombin and fibrinogen are reported. Death usually occurs on the 4th or 5th day, and autopsy shows massive hepatic necrosis.

In experimental human exposures, 14,000–16,000 ppm caused rapid loss of consciousness; 4100 ppm or less caused serious disorientation, whereas single exposures of 1000 ppm caused dizziness, nausea, and aftereffects of fatigue and headache.[2] Prolonged exposure to concentrations ranging from 77 to 237 ppm caused lassitude; digestive disturbances; frequent, burning urination; and mental dullness; whereas 20–70 ppm produced milder symptoms.[3] Of 68 chemical workers exposed regularly to concentrations of 10–200 ppm for 1–4 years, nearly 25% had hepatomegaly.[1] However, another group exposed repeatedly to about 50 ppm experienced no signs or symptoms.[1]

High concentrations of vapor cause conjunctival irritation and blepharospasm.[4] Liquid chloroform splashed in the eye causes immediate burning pain and conjunctival irritation; the corneal epithelium may be injured, but regeneration is prompt, and the eye returns to normal in 1–3 days.[4] Applied to the skin, chloroform causes burning pain, erythema, and vesiculation.[1]

In acute animal studies, target organs identical to those observed in humans (central nervous system, liver, and kidney) have been identified.[5] Studies in mice and rats have also shown that exposure to concentrations ranging up to 300 ppm, 6 hours/day for 7 days can produce concentration-dependent lesions in the nasal passages.[6]

Evidence for the carcinogenicity of chloroform in experimental animals after chronic oral administration includes statistically significant increases in renal epithelial tumors in male rats, hepatocellular carcinomas in mice, and renal tumors in male mice.[7–9] In these studies, the carcinogenicity of chloroform is organ specific to primarily the liver and kidneys; these organs also are the target of acute chloroform toxicity and covalent binding by reactive intermediates (phosgene, carbene, chlorine ion) of chloroform metabolism.[1] Typically, doses of chloroform that do not produce necrosis are not carcinogenic. This suggests that the increased proliferation of liver and kidney cells during regeneration after necrosis may be involved in the development of tumors.[5,10] Furthermore, most studies suggest that chloroform is not genotoxic, supporting the case for an epigenetic mechanism of carcinogenicity. Chloroform also possesses antitumorigenic properties when administered in the drinking water of animals previously treated with the hepatocarcinogens ethylnitrosourea and ethylnitrosamine or 1,2-dimethylhydrazine, a gastrointestinal tract carcinogen.[11]

Small increases in rectal, bladder, and colon cancer have been observed in several studies of human populations with chlorinated drinking water. Because other possible carcinogens were present along with chloroform, it is impossible to identify chloroform as the sole carcinogenic agent. On the basis of sufficient animal evidence and limited epidemiological evidence, the IARC regards chloroform as a probable human carcinogen.[12]

In animals, chloroform causes some fetal loss and delays in fetal development when administered during gestation at levels of 100 ppm or more.[13] Teratogenic effects such as cleft palate were observed in the mouse only at doses associated with maternal toxicity.[14]

Several substances alter the toxicity of chloroform in animals—most probably by modifying the metabolism to a reactive intermediate.[1] Factors that potentiate chloroform's toxic effects include ethanol, polybrominated biphenyls, steroids, and ketones. Disulfiram, its metabolites, and a high-carbohydrate diet appear to protect somewhat against chloroform toxicity.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for chloroform is 10 ppm (49 mg/m^3) with an A2-suspected human carcinogen designation.

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bis(CHLOROMETHYL)ETHER

CAS: 542-88-1

$ClCH_2OCH_2Cl$

Synonyms: BCME; chloromethyl ether; chloro(chloromethoxy)methane; dichloromethyl ether; symmetrical dichloro-dimethyl ether; dimethyl-1–1′-dichloroether

Physical Form. Colorless liquid

Uses. Chemical intermediate

Exposure. Inhalation; skin absorption

Toxicology. bis(Chloromethyl)ether (BCME) is a mucous membrane and respiratory irritant; it is a recognized human carcinogen.

In humans, concentrations of 3 ppm are reported to be distinctly irritating. A fatal case of accidental acute poisoning of a research chemist by BCME has been reported.[1] Increased frequency of chronic cough and low end-expiratory flow rates has been described to occur in a dose-related fashion with exposure to BCME and chloromethyl methyl ether (CMME).[2]

A retrospective study of 136 BCME workers employed at least 5 years revealed 5 cases of lung cancer, which represented a ninefold increase in lung cancer risks; 0.54 cases would have been expected to occur in the plant population.[3] The predominant histologic type of carcinoma was small cell undifferentiated. Exposure ranged from 7.5 to 14 years, and the mean induction period was 15 years. In addition, abnormal sputum cytology was observed in 34% of 115 current workers with exposure to BCME for 5 or more years, as contrasted with 11% in a control group.

In another study, 6 cases of lung cancer occurred among 18 technical department workers, a group known to experience very high BCME exposure; other cases of lung cancer were reported among 50 production workers.[4] Oat cell carcinomas occurred in five of eight cases.

BCME is also found as an impurity (1–7%) in the related CMME. Fourteen cases of lung cancer, mainly of oat cell type, were reported in a chemical plant where exposure to CMME occurred.[5] In the reported epidemiological studies, insufficient evidence is available to separate the carcinogenic effects of the two compounds.[6]

A follow-up of CMME (BCME) workers found no increased risk of respiratory cancer among those exposed less than 1 year to a 12-fold increase among those exposed 10 years or more.[7] Latency did not appear to be inversely related to dose but, instead, peaked at approximately 20 years from initial exposure. After 30 years of observation 25 of 67 deaths in CMME (BCME)-exposed chemical workers were due to lung cancer (80% small cell carcinoma). Standardized mortality ratios were elevated among the moderately and heavily exposed workers and peaked at 23.1 the first decade and then declined to 7.4 and 7.9 in later decades.[8]

A cohort study of 1203 workers at an ion-

exchange resin manufacturing plant in France found a rate ratio of 5.5 for lung cancer for CMME (containing BCME)-exposed workers compared with unexposed workers. There were 11 cases of lung cancer (10 small cell carcinoma) among the 258 exposed workers vs. 8 cases of lung cancer(1 small cell carcinoma) in the unexposed.[9]

Features implicating BCME as the primary causative carcinogenic agent in human studies include: a) early age at death, b) development of lung cancer among nonsmokers as well as cigarette smokers, and c) unusual histologic type-small cell or oat cell carcinoma, rather than the squamous cell carcinoma common among male smokers.

Exposure to 1 ppm for 6 hours/day, 5 days/week for 82 days caused lung tumors in 26 of 47 animals, with an average of 5.2 tumors per tumor-bearing animal; 20 of 49 controls developed lung tumors, with 2.2 tumors per tumor-bearing animal.[10] In 19 rats exposed to 0.1 ppm BCME 6 hours/day for 101 exposures, five squamous cell carcinomas of the lung and five esthesioneuroepitheliomas arising from the olfactory epithelium were observed.[11] Cutaneous application of 2 mg of BCME to mice three times/week for 325 days caused papillomas in 13 of 20 animals; 12 of these papillomas progressed to squamous cell carcinomas.[12]

In general, positive results were obtained when BCME was tested for mutagenicity *in vitro*. It has also been reported to increase unscheduled DNA synthesis and the level of transformed cells in in vitro assays.[13]

The IARC has concluded that there is sufficient evidence of carcinogenicity of BCME to both humans and animals.[14]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for bis(chloromethyl)ether is 0.001 ppm (0.0047 mg/m^3) with an A1-confirmed human carcinogen designation.

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CHLOROMETHYL METHYL ETHER

CAS: 107-30-2

C_2H_5ClO

Synonyms: CMME; dimethylchloroether; methyl chloromethyl ether

Physical Form. Colorless liquid

Uses. Chemical intermediate; preparation of ion-exchange resins

Exposure. Inhalation

Toxicology. Chloromethyl methyl ether (CMME) exposure has been associated with an increased incidence of human lung cancer.

Among 111 CMME workers observed during a 5-year period, there were four cases of lung cancer; this was eight times the incidence of a control group of plant workers with similar smoking histories.[1] Evidence of a lung cancer risk was further supported by the retrospective identification of a total of 14 cases among chemical operators in a plant engaged in synthesis of CMME. Except for one case of doubtful exposure, the duration of exposure was 3–14 years, and the age at diagnosis ranged from 33 to 55 years. During the synthetic process, fumes were often visible. The employees considered it a good day if the entire building had to be evacuated only three or four times per 8-hour shift because of noxious fumes. Three of the men had never smoked, and one had smoked a pipe only; the other ten had smoked one or more packs of cigarettes per day. Oat cell carcinoma was histologically confirmed in 12 cases, whereas the doubtful exposure case was squamous cell carcinoma; the cell type in one case was not determined.[1]

In another study of 669 workers exposed during 1948–1972, 19 died of lung cancer although only 5.6 cases were expected.[2] There were higher relative risks for workers exposed to intermediate to high levels of CMME for 1 or more years.[2]

In a study of 276 men exposed to CMME and followed through 1980 at a plant in the United Kingdom in operation since 1948, there were 10 deaths from lung cancer, with a relative risk of 10.97 compared with an unexposed group.[3] The occurrence of lung cancer appeared to be related to both the estimated exposure level and the duration of exposure. Among a subgroup of 51 workers who began work after the process was enclosed in 1972, no deaths from lung cancer had been observed through 1980. In another factory where 394 men had been exposed to CMME at lower estimated exposure levels, no excess of lung cancer was observed.[3]

Lung cancer occurred at a higher rate among potentially exposed CMME workers at a factory in France (rate ratio 5.0 compared with nonexposed workers and 7.6 compared with an external referent population).[4] The average age at diagnosis was 10.5 years lower than nonexposed cases, and the predominantly small cell cancers of the exposed were mostly oat cell type.

The most recent report of a cohort of CMME chemical workers followed for 30 years found 67 deaths with 25 attributable to lung cancer and a dose-response relationship.[5] Standardized mortality ratios were elevated among the moderately and heavily exposed workers, peaking at 23.1 in the first decade and then declining to 7.4 and 7.9 in later decades. Small cell carcinoma accounted for 80% of the moderately and heavily exposed cases, and 3 of 12 heavily exposed cases occurred in nonsmokers.

It should be noted that commercial CMME contains 1–7% of highly carcinogenic bis(chloromethyl)ether (BCME). In the reported epidemiological studies, insufficient evidence is available to differentiate the carcinogenic effects of the two compounds.[6]

Furthermore, when CMME is hydrolyzed, HCl and formaldehyde are produced, which may recombine to form BCME. Therefore, although findings may reflect the carcinogenicity of BCME, commercial-grade CMME also must be considered to be a carcinogen, but perhaps of a lower potency than that of BCME.

CMME is a mucous membrane and respiratory irritant in both humans and animals.[7,8] Acute exposure of rats and hamsters resulted in pulmonary edema and hemorrhage and necrotizing bronchitis.[8] Human exposure to CMME has been reported to cause breathing difficulties, sore throat, fever, and chills.[7] An increased frequency of chronic cough and low-end expiratory flow rates has been observed in a dose-related fashion with exposure to CMME and BCME.[9]

Technical-grade CMME (contaminated with BCME), on subcutaneous injection in mice, has produced local sarcomas.[6] Dermal application of mice, followed by a phorbol ester promoter, resulted in an apparent excess of skin papillomas and carcinomas. Inhalation studies in mice showed an equivocally increased occurrence of lung tumors compared with unexposed controls.[6]

The IARC has concluded that there is sufficient evidence for carcinogenicity of technical-grade CMME to both humans and animals.[10]

ACGIH has designated chloromethyl methyl ether as an A2-suspected human carcinogen; a numerical threshold limit value is not recommended.

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1-CHLORO-1-NITROPROPANE
CAS: 600-25-9

$CH_3CH_2CHClNO_2$

Synonyms: None

Physical Form. Colorless liquid

Uses. Fungicide

Exposure. Inhalation

Toxicology. 1-Chloro-1-nitropropane is an irritant of the eyes and mucous membranes. It is a pulmonary irritant in animals, and severe exposure is expected to cause the same effect in humans.

Systemic effects in humans have not been reported.

The lethal oral dose in rabbits is 0.05–0.10 g/kg, which is approximately five times more toxic than the nonchlorinated mononitroparaffin.[1] Rabbits exposed to 2600 ppm for 2 hours died, but 2200 ppm for 1 hour was nonlethal. Effects included irritation of the eyes and mucous membranes, and autopsy revealed pulmonary edema and cellular necrosis of the heart, liver, and kidneys.[2,3]

1-Chloro-1-nitropropane was mutagenic in *Salmonella* assays both with and without activation.[4]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 1-chloro-1-nitropropane is 2 ppm (10 mg/m^3).

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CHLOROPENTAFLUOROETHANE

CAS: 76-15-3

C_2ClF_5

Synonyms: F-115; FC 115; Refrigerant 115; Propellant 115; Freon 115

Physical Form. Colorless gas

Uses. Refrigerant, aerosol propellant

Exposure. Inhalation

Toxicology. Chloropentafluoroethane has low inhalation toxicity and little potential for cardiac sensitization.

Inhalation studies with chloropentafluoroethane in anesthetized dogs, rats, and monkeys showed that exposure to 100,000–250,000 ppm, under certain conditions, caused an increase in blood pressure, accelerated heart rate, depression of myocardial contractility and sensitized the heart to epinephrine.[1–3] Compared with other chlorofluorocarbons, it is ranked among the least potent for cardiac sensitization.[4]

In a NIOSH Health Hazard Evaluation of refrigeration workers exposed far below the threshold limit values (TLVs) for chloropentafluoroethane and chlorodifluoromethane, 27 workers were medically evaluated.[5,6] Seventy-one percent complained of dizziness and lightheadedness compared with twenty-one percent of controls. Palpitations were reported in 36% of exposed and none of the non-exposed workers. No clinical neurological or electroneurophysiological abnormalities were detected in eight of the refrigeration repair workers followed for 3 years during continuous employment.[6]

Death from acute respiratory arrest has occurred after intentional inhalation of an azeotrophic mixture of chlorodifluoromethane and chloropentafluoroethane.[7]

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CHLOROPICRIN

CAS: 76-06-2

CCl_3NO_2

Synonyms: Trichloronitromethane; nitrochloroform

Physical Form. Colorless, slightly oily liquid

Uses. Fumigant for cereals and grains; a soil insecticide; war gas

Exposure. Inhalation

Toxicology. Chloropicrin is a severe irritant of the eyes, mucous membranes, skin, and lungs.

A lethal exposure for humans is stated to be 119 ppm for 30 minutes, with death resulting from pulmonary edema. Particular injury occurs in the medium and small bronchi.[1] In addition to pulmonary irritation, human exposure results in lacrimation, cough, nausea, vomiting, and skin irritation; persons injured by inhalation of chloropicrin vapor are said to be more susceptible to subsequent exposures.[1]

A concentration of 15 ppm could not be tolerated longer than 1 minute even by persons acclimated to chloropicrin; exposure to 4 ppm for a few seconds is temporarily disabling because of irritant effects. Concentrations of 0.3–0.37 ppm have resulted in painful eye irritation in 3–30 seconds.[1]

A man accidentally exposed to residual spray of undetermined concentration had dry cough, and his nasal and pharyngeal mucosa were red and edematous.[2]

In mice exposure to 9 ppm caused a 50% decrease in respiratory rate. Lesions included ulceration and necrosis of the respiratory epithelium and moderate damage to lung tissue.[3] Rats administered, via oral gavage, 10, 20, 40, or 80 mg/kg for 10 consecutive days or 32 mg/kg for 90 consecutive days had inflammation, necrosis, acantholysis, hyperkeratosis, and epithelial hyperplasia of the forestomach.[4]

Chloropicrin was genotoxic in bacterial test systems.[5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for chloropicrin is 0.1 ppm (0.67 mg/m^3).

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β-CHLOROPRENE

CAS: 126-99-8

C_4H_5Cl

Synonyms: Chlorobutadiene; 2-chloro-1,3-butadiene; chloroprene

Physical Form. Colorless liquid

Uses. In the manufacture of synthetic rubber

Exposure. Inhalation; skin absorption

Toxicology. Chloroprene causes central nervous system abnormalities as well as skin and eye irritation. Reproductive, mutagenic, embryotoxic, and carcinogenic effects have been reported.

Exposure of workers to high concentrations for short periods led to temporary unconsciousness; one fatality occurred after a 3- to 4-minute exposure inside an unventilated polymerization vessel containing chloroprene vapor.[1] Experimental exposure of humans to 973 ppm led to nausea and giddiness in resting subjects in 15 minutes and in subjects performing light work in 5–10 minutes.[1] Extreme fatigue and unbearable chest pain occurred after approximately 1 month of exposure to levels ranging from 56 ppm to greater than 334 ppm. Irritability, personality changes, and reversible hair loss also were reported.

Functional disturbances in spermatogenesis and morphologic abnormalities of sperm were observed among workers occupationally exposed to 0.28 and 1.94 ppm chloroprene.[2,3] A threefold excess of miscarriages in the wives of these workers also was reported.

Two Russian studies suggested an increased incidence of lung and skin cancers in chloroprene-exposed workers compared with a variety of control groups.[4] A more recent retrospective cohort mortality study among Russian shoe factory workers found an increase in the mortality from liver cancer that was associated with chloroprene exposure.[5] A US study of cancer mortality among two cohorts of males engaged in the production and/or polymerization of chloroprene concluded that there was no significant excess of lung cancer deaths.[6] However, there was a disproportionately high incidence of lung cancer cases in maintenance workers who had potentially high exposure to chloroprene. Another study of chloroprene workers confirmed a significant increased risk for liver, lung, and lymphatic cancers among maintenance mechanics, who have the highest occupational chloroprene exposure.[7] A dose-response relationship appeared to exist in the cohort of 1213 workers, with low-exposure groups having low standardized mortality ratios (SMRs) and high-exposure groups having the highest risk of cancer.[8] Because most reported effects have involved mixed exposures to multiple substances, and to short-chain polymers of chloroprene, the reported symptoms cannot all be assigned to the monomer alone.[4]

In acute animal studies, the concentrations that killed at least 70% of animals with an 8-hour exposure were 170 ppm for mice, 700 ppm for cats, 2000 ppm for rabbits, and 4000–6000 ppm for rats.[9] Symptoms included inflammation of the mucous membranes of the eyes and nose, followed by central nervous system depression and death from respiratory failure. Repeated exposure of rats 6 hours/day, 5 days/week for 4 weeks caused skin and eye irritation and growth depression at 40 ppm; at 160 and 625 ppm, it resulted in loss of hair, morphologic liver damage, and increased mortality.[10]

In recently completed inhalation studies, mice exposed at 80 ppm for 13 weeks had epithelial hyperplasia of the forestomach and rats exposed at 200 ppm for the same duration had degeneration and metaplasia of the olfactory epithelium, anemia, hepatocellular necrosis, and reduced sperm motility.[11]

Lifetime inhalation exposure of rodents at 80 ppm caused multiple-organ carcinogenicity.[11] Increased incidences of thyroid gland, oral cavity, lung, kidney, and mammary gland tumors occurred in rats, whereas mice had increases in lung, circulatory system (hemangiomas and hemangiosarcomas), Harderian gland, kidney, forestomach, liver, mammary

gland, skin, mesentery, and zymbal gland tumors.

Chloroprene did not cause a significant increase in chromosomal aberrations or sister chromatid exchanges in mice treated *in vivo*. Both positive and negative results have been reported in a number of *in vitro* assays.[8]

The IARC has determined that there is sufficient evidence in experimental animals for the carcinogenicity of chloroprene and that it is possibly carcinogenic to humans.[8]

Exposure of male rats at concentrations of 120–6277 ppm and of male mice at concentrations of 12–152 ppm for 8 hours resulted in sterility or impotence in 13 of 19 rats and in 8 of 14 mice vs. a mean of 0.5 in the two control groups. Degenerative changes in the testes were observed in some of the exposed animals. A significant increase in embryonic mortality was observed in female rats fertilized by males exposed to 1 ppm 4 hours/day for 48 days.[4,8] Hydrocephalus and cerebral herniation occurred in all fetuses from rat dams given oral doses of 0.5 mg/kg during 14 days of pregnancy. Inhalation of 1.11 ppm for 2 days of pregnancy also caused increases in these anomalies.[4,8] In another study, neither embryotoxic nor convincing teratological effects were found after exposing rats at 1, 10, or 25 ppm.[12] Gestational exposure of rabbits to 175 ppm did not result in observable toxicity to either the dam or the offspring.[13]

Contact with skin may cause chemical burns. Conjunctivitis and focal necrosis of the cornea have been reported from eye exposure.[4]

The 2001 ACGIH threshold limit value-time-weighted average (TLV-TWA) for β-chloroprene is 10 ppm (36 mg/m^3) with a notation for skin absorption.

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o-CHLOROSTYRENE

CAS: 2039-87-4

C_8H_7Cl

Synonyms: 2-chlorostyrene

Physical Form. Liquid

Uses. Organic synthesis; preparation of specialty polymers

Exposure. Inhalation

Toxicology. By analogy to styrene, *o*-chlorostyrene is expected to cause central nervous system depression at extremely high concentrations and possibly irritation of the eyes, nose, and mucous membranes.

There are no reports of adverse effects in humans.

In an inhalation study, groups of rats, rabbits, guinea pigs, and one dog were exposed to 101 ppm *o*-chlorostyrene 7 hours/day, 5 days/week for 6 months.[1] There were no significant adverse effects on any species, although microscopic examination of the liver and kidneys in all species showed slight changes.

The 2003 threshold limit value-time-weighted average (TLV-TWA) is 50 ppm (283 mg/m^3) with a short-term excursion level of 100 ppm (425 mg/m^3).

CHLOROTHALONIL

CAS: 1897-45-6

$C_6Cl_4CN_2$

Synonyms: Chloroalonil; 1,3-dicyanotetrachlorobenzene; tetrachlorisophthalonitrile

Physical Form. Colorless, odorless crystals

Uses. Fungicide

Exposure. Inhalation; ingestion; skin absorption

Toxicology. Chlorothalonil is an irritant to the skin and eyes and has been reported to produce allergic contact dermatitis in exposed workers.

Patch testing demonstrated that between 10% and 28% of 88 Japanese farmers were sensitive to chlorothalonil and other pesticides. Thirty-five of these farmers had acute dermatitis. Photosensitization was involved in some cases. Reactions were also observed in greenhouse workers, vegetable farmers, and others with pesticide-induced dermatitis. Four cases of severe recurrent contact dermatitis have been reported in workers exposed to chlorothalonil-containing wood preservatives.[1]

Whether or not chlorothalonil is a true dermal sensitizer in humans or strictly a skin irritant remains controversial.[2] Some investigators suggest that repeated exposure results in an enhanced irritant response, whereas others suggest that it is a potent contact allergen.[2] It is noted that relatively few cases of allergy to chlorothalonil have been reported despite widespread use for over 20 years. Furthermore, at a plant that produces the chemical cases of work-related contact dermatitis have not been reported for years after adoption of good hygienic practices.[2]

The oral LD_{50} of chlorothalonil is 6000 mg/kg in female mice, whereas in rats it is greater than 10,000 mg/kg.[1] In rodent studies chlorothalonil caused lesions in the forestomach and kidney.[3]

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Technical-grade chlorothalonil was tested for possible carcinogenicity in rats and mice. In rats, chlorothalonil was administered in the diet at average doses of 5063 and 10,126 ppm for 80 weeks, followed by observation for 30–31 weeks. Adenomas and carcinomas of the renal tubular epithelium were observed.[4] Mice administered time-weighted average doses of 2688 or 5375 ppm (males) or 3000 or 6000 ppm (females) showed no evidence of carcinogenicity.[4] In other reports chlorothalonil produced renal tubular tumors in male mice and increased incidences of forestomach papillomas and carcinomas in males and females.[5]

Chlorothalonil was not mutagenic in a variety of assays, nor did it bind to DNA.[3] The compound does not appear to have genotoxic potential and probably exerts its carcinogenic action in rodents via a nongenotoxic mechanism.[3] Rodent models may be a poor predictor of carcinogensis in humans because of species differences in metabolic pathways leading to carcinogenesis in the kidney and the lack of a comparable organ (forestomach) in humans.[3]

The IARC has determined that there is sufficient evidence for carcinogenicity of chlorothalonil in experimental animals and inadequate evidence in humans.[5]

An ACGIH threshold limit value has not been adopted for chlorothalonil.

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o-CHLOROTOLUENE

CAS: 95-49-8

C_7H_7Cl

Synonyms: 2-Chloro-1-methylbenzene; 2-chlorotoluene; Halso 99; *o*-tolyl chloride

Physical Form. Colorless liquid

Uses. Solvent; synthesis of dyes, pharmaceuticals, and synthetic rubber compounds

Exposure. Inhalation

Toxicology. *o*-Chlorotoluene causes central nervous system depression in animals and is expected to cause similar effects in humans.

Rats exposed for 6 hours to 4000 ppm became uncoordinated in 1.5 hours, followed in another half-hour by prostration and tremor.[1] Rats exposed to 14,000 ppm exhibited incoordination, vasodilation, labored respiration, and narcosis, but all survived.

In another study, mice, rats, and guinea pigs were exposed to 4400 ppm.[2] Mice developed gasping, ataxia, and convulsions after 30 minutes of exposure. Rats and guinea pigs showed gasping, hyperpnea, ataxia, and convulsions after 45 minutes of exposure. All animals were comatose in 60 minutes. All mice and rats died, as did 7 of 10 guinea pigs.

Moderate skin irritation was noted on rabbit skin after application for 24 hours. A single instillation into the eyes of rabbits produced moderate conjunctival irritation that was reversible by the fifth day of observation.

The 2003 threshold limit value-time-weighted average (TLV-TWA) is 50 ppm (259 mg/m^3).

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CHLORPYRIFOS

CAS: 2921-88-2

$C_9H_{11}Cl_3NO_3PS$

Synonyms: *O*,*O*-diethyl-*O*-(3,5,6-trichloro-2-pyridinyl) phosphorothioate; Dursban; Dowco 179; ENT 27311; Eradex; Lorsban; NA 2783; OMS-0971; Pyrinex

Physical Form. White crystalline solid

Uses. Insecticide

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Chlorpyrifos is an anticholinesterase agent, but it has only moderate capacity to reduce red blood cell cholinesterase.

Signs and symptoms of overexposure are caused by the inactivation of the enzyme cholinesterase, which results in the accumulation of acetylcholine at synapses in the nervous system, skeletal and smooth muscles, and secretory glands. The sequence of the development of systemic effects varies with the route of entry. The onset of signs and symptoms usually is prompt but may be delayed up to 12 hours. Clinical signs include tremor, incoordination, salivation, lacrimation, headache, and decreased body temperature. Exposure to high doses can produce tachycardia, pulmonary edema, loss of bowel control, convulsions, coma, and death. The severity of symptoms does not always correlate with the degree of cholinesterase inhibition.[1–7]

Chlorpyrifos does not have enough vapor pressure to present a vapor hazard; however, if it is dispersed as a mist, particulate inhalation is possible. Five of seven spray workers exposed to 0.5% chlorpyrifos emulsion showed more than 50% reduction in cholinesterase within 2 weeks.[5] Symptoms were not reported.

Human subjects who ingested chlorpyrifos once daily for 4 weeks showed depression of plasma cholinesterase but were symptomless at a dose of 0.1 mg/kg.[5] When four repeated doses were applied to the skin of human volunteers for 12 hours each, doses of 25 mg/kg depressed plasma cholinesterase but caused no symptoms. Chlorpyrifos and its principal metabolite, 3,5,6-trichloro-2-pyridinol, are rapidly eliminated, predominantly in the urine.[8]

An 8.5-year morbidity survey of employees engaged in the manufacture of chlorpyrifos did not show any statistically significant differences in illness or prevalence of symptoms between exposed and unexposed groups.[9] Potentially exposed employees did report symptoms of dizziness, malaise, and fatigue relatively more often than did subjects from the comparison group; however, there was no relationship of these symptoms to exposure levels.

In animal studies, repeated inhalation of chlorpyrifos at 287 $\mu g/m^3$ (near the theoretical maximum vapor concentration) for 13 weeks caused no treatment-related changes in urinalysis, hematology, clinical chemistry, terminal body and organ weights, or pathology.[10] Induction of delayed polyneuropathy in animals occurs only at doses that exceed the LD_{50}.[11] Peripheral neurotoxic effects could occur in humans after massive exposures at almost lethal doses (from which the patient is saved by intensive medical intervention).[6] The possibility that subtle neurobehavioral effects are associated with pesticide exposure cannot be ruled out.[6]

Chlorpyrifos was not carcinogenic in rats fed up to 3.0 mg/kg/day for 2 years.[12] Although many studies reported negative results, genotoxic effects, including induction of micronuclei, increases in sister chromatid exchanges and chromosomal aberrations, have been reported in some studies.[7]

In developmental studies skeletal variations were observed in mice administered gavage doses of 25 mg/kg/day during gestation, a level also causing significant maternal toxicity.[13] Repeated intraperitoneal injection of Dursban (active ingredient chlorpyrifos) to pregnant rats at doses of 0.03, 0.1, or 0.3 mg/kg caused increased incidences of embryolethality, physical abnormalities, and early postnatal neurotoxicity.[14] It was noted that the method of exposure (ip) and solvents present in Dursban may have contributed to the adverse effects. More recent studies with chlorpyrifos indicate that it is especially damaging to the developing brain, targeting diverse events in neural development, including cell proliferation and differentiation, axonogenesis and synaptogenesis, and synaptic function.[15] Developmental neurotoxicity may occur in the absence of overt maternal or fetal toxicity.

The persistent strong odor is most likely due to the sulfur content of the pesticide.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for chlorpyrifos is 0.2 mg/m^3 with a notation for skin absorption.

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CHROMIUM (Metal and Inorganic Compounds, as Cr)
CAS: 7440-47-3 (metal)

Cr

Chromium (III)
CAS: 16065-83-1

Chromium (IV)
CAS: 18540-29-9

Compounds: Chromium can have a valence of 2, 3, or 6. Chromium compounds vary greatly in their toxic and carcinogenic effects. For this reason the ACGIH divides chromium and its inorganic compounds into a number of groupings:

1. *Chromium metals and alloys*: including chromium metal, stainless steels, and other chromium-containing alloys
2. *Divalent chromium compounds* (Cr^{2+}) (chromous compounds): including chromous chloride ($CrCl_2$) and chromous sulfate ($CrSO_4$).
3. *Trivalent chromium compounds* (Cr^{3+})(chromic compounds): including chromic oxide (Cr_2O_3), chromic sulfate ($Cr_2[SO_4]_3$), chromic chloride ($CrCl_3$), chromic potassium sulfate ($KCr[SO_4]_2$), and chromite ore ($FeOCdCr_2O_3$).
4. *Hexavalent chromium compounds* (Cr^{6+}): including chromium trioxide (CrO_3)—the anhydride of chromic acid chromates (e.g., Na_2CrO_4), dichromates, (e.g., $Na_2Cr_2O_7$), and polychromates.

Certain hexavalent chromium compounds have been demonstrated to be carcinogenic on the basis of epidemiological investigations on workers and experimental studies in animals. In general, these compounds tend to be of low solubility in water and thus are subdivided into two subgroups:

a. Water-soluble hexavalent chromium compounds: including chromic acid and its anhydride and the monochromates and dichromates of sodium, potassium, ammonium, lithium, cesium, and rubidium.
b. Water-insoluble hexavalent chromium compounds: including zinc chromate, calcium chromate, lead chromate, barium chromate, strontium chromate, and sintered chromium trioxide.[1]

Physical Form. Most chromium compounds are solids at room temperature.

Uses. In stainless and alloy steels, refractory products, tanning agents, pigments, electroplating, catalysts, and corrosion-resistant products

CHROMIUM METAL AND DIVALENT AND TRIVALENT COMPOUNDS

Exposure. Inhalation

Toxicology. Chromium metal is relatively nontoxic. There is little evidence of significant toxicity from chromic or chromous salts, probably because of poor penetration of skin and mucous membranes. Dermatitis from some chromic salts has been reported.

Four workers engaged in the production of ferrochrome alloys developed a nodular type of pulmonary disease with impairment of pulmonary function; air concentrations of chromium averaged 0.26 mg/m^3, although other fumes and dusts also were present.[2] Chest roentgenograms are said to have revealed only "exaggerated pulmonic markings" in workers exposed to chromite dust.[1] The lungs of other workers exposed to chromite dust have been shown to be the seat of pneumoconiotic changes consisting of slight thickening of interstitial tissue and interalveolar septa, with histologic fibrosis and hyalinization.[3] A refractory plant using chromite ore to make chromite brick had no excess of lung cancer deaths over a 14-year period, and it was concluded that chromite alone probably is not carcinogenic.[4] Exposure to chromium metal does not give rise to pulmonary fibrosis.[1]

Chromite ore roast mixed with sheep fat implanted intrapleurally in rats produced sarcomas coexisting with squamous cell carcinomas of the lungs; the same material implanted in the thigh of rats produced fibrosarcomas.[5] However, the IARC concluded that these studies were inadequate to fully evaluate the carcinogenicity of this compound.[6] Other animal studies have found no increase in the incidence of tumors with chromium metal and chromite ore.[6] The IARC has determined that there is inadequate evidence in humans and animals for the carcinogenicity of metallic chromium and chromium(III) compounds.

Unlike nickel, chromium metal does not produce allergic contact dermatitis.[7] Some patients exhibit positive patch tests to divalent chromium compounds, but these compounds are considerably less potent as sensitizers than hexavalent chromium compounds. A case of chromium (chromic) sulfate-induced asthma in a plating worker, confirmed by specific challenge testing and the presence of IgE antibodies, has been reported.[8]

These compounds do not appear to cause other effects associated with the hexavalent chromium compounds, such as chrome ulcers, irritative dermatitis, or nasal septal perforation.[7]

HEXAVALENT CHROMIUM

Exposure. Inhalation

Toxicology. The water-soluble hexavalent chromium compounds such as chromic acid mist and certain chromate dusts are severe irritants of the nasopharynx, larynx, lungs, and skin; exposure to certain hexavalent chromium compounds, mainly water insoluble, appears to be related to an increased risk of lung cancer.

Hexavalent chromium compounds have been implicated as responsible for such effects as ulcerated nasal mucosa, perforated nasal septa, rhinitis, nosebleed, perforated eardrums, pulmonary edema, asthma, kidney damage, erosion and discoloration of the teeth, primary irritant dermatitis, sensitization dermatitis, and skin ulceration.[9]

Chromic Acid. Workers exposed to chromic acid or chromates in concentrations of 0.11–0.15 mg/m^3 developed ulcers of the nasal septum and irritation of the conjunctiva, pharynx, and larynx, as well as asthmatic bronchitis.[10] A worker exposed to unmeasured but massive amounts of chromic acid mist for 4 days developed severe frontal headache, wheezing, dyspnea, cough, and chest pain on inspiration; after 6 months the worker still experienced chest pain on inspiration and cough.[10]

In an industrial plant in which the airborne chromic acid concentrations measured from 0.18 to 1.4 mg/m^3, moderate irritation of the nasal septum and turbinates was observed after 2 weeks of exposure, ulceration of the septum was present after 4 weeks, and there was perforation of the septum after 8 weeks.[10] A worker exposed to an unmeasured concentration of chromic acid mist for 5 years developed jaundice and was found to be excreting significant amounts of chromium; liver function was mildly to moderately impaired in four other workers with high urinary chromium excretion.[10]

Erosion and discoloration of the teeth has been attributed to chromic acid exposure. Papillomas of the oral cavity and larynx were found in 15 of 77 chrome platers exposed for an average of 6.6 years to chromic acid mist at air concentrations of chromium of 0.4 mg/m^3.[4]

A concentrated solution of chromic acid in the eye causes severe corneal injury; chronic exposure to the mist causes conjunctivitis. Prolonged exposure to chromic acid mist causes dermatitis, which varies from a dry, erythematous eruption to a weeping, eczematous condition.

Chromates. Epidemiological studies from around the world have consistently shown excess risks for lung cancer in workers involved in chromate and chromate pigment production.[6] The epidemiological studies do not clearly implicate specific compounds but do implicate chromium(VI) compounds.[11] (A recent report also implicated insoluble chromium(III) as a cause of lung cancer in

chromate manufacturers, but it may be more likely that insoluble chromium(VI) was involved instead.[11,12]) In one report the relative risk of dying from respiratory cancer among chromate workers was over 20 times the rate for a control population; the latent period was relatively short.[9] In most studies a positive correlation between duration of exposure and lung cancer death was found.[13] Workers employed in chromium-producing industries also had significantly increased nasal and sinus cavity cancers.[14]

Some less soluble hexavalent chromium compounds (lead chromate and zinc chromate pigments; calcium chromate) are carcinogenic in rats, producing tumors at the sites of administration by several routes. Lead chromate also produces renal carcinomas after intramuscular administration in rats.[9]

The IARC has concluded that there is sufficient evidence in humans for the carcinogenicity of chromium(VI) compounds as encountered in the chromate production, chromate pigment production, and chromate plating industries. In experimental animals there is sufficient evidence for the carcinogenicity of calcium chromate, zinc chromates, strontium chromate, and lead chromate.[6]

Chromium(VI) compounds have been consistently genotoxic, inducing a wide variety of effects including DNA damage, gene mutation, sister chromatid exchange, chromosomal aberrations, cell transformation, and dominant lethal mutations.[6]

A variety of reproductive effects including testicular effects, alterations in sexual behavior, and impaired fertility in females have been reported after high doses of chromium(VI) compounds.[11] These effects, reproductive toxicity and testicular damage, were not replicated in a recent series of NTP studies in which mice and rats were exposed to 400 ppm in the diet.[15–17]

Chromium(VI) exposure during gestation caused developmental effects (increased fetal mortality, decreased cranial ossification, and decreased fetal body weight) in rodents in the absence of maternal toxicity.[11]

Chrome ulcer, a penetrating lesion of the skin, occurs chiefly on the hands and forearms where there has been a break in the epidermis and is believed to be due to a direct necrotizing effect of the chromate ion. The ulcer is relatively painless, heals slowly, and produces a characteristic depressed scar. Sensitization dermatitis with varying degrees of eczema has been reported numerous times and is the single most common manifestation of chromium toxicity, affecting not only industrial workers but also the general population.[9]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for chromium metal and chromium(III) compounds is 0.5 mg/m^3 with an A4-not classifiable as a human carcinogen designation; for water-soluble chromium(VI) compounds the TLV-TWA is 0.05 mg/m^3, as Cr, with an A1-confirmed human carcinogen designation, and for insoluble chromium(VI) compounds it is 0.01 mg/m^3, as Cr, also with an A1 designation.

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CHROMYL CHLORIDE

CAS: 14977-61-8

CrO_2Cl_2

Synonyms: Chromium dioxychloride; chromium dioxide dichloride; chromium oxychloride; chromium chloride oxide

Physical Form. Dark red liquid with an unpleasant odor

Uses. In organic oxidations and chlorinations; as a solvent for chromium oxide; in making chromium complexes and dyes

Exposure. Inhalation

Toxicology. Chromyl chloride is a severe irritant.

Although information is not available on exposure levels, the vapor is expected to cause eye, nose, and throat irritation; there may be difficulty in breathing and lung injury.[1] On brief contact with the skin, the liquid will produce second- and third-degree burns; it is very injurious to the eyes. Ingestion causes burning of the mouth and stomach. The toxicity of chromyl chloride is mediated by products formed during hydrolysis; in water it reacts violently to form hydrochloric acid, chromic acid, and chlorine gases.

NIOSH has classified chromyl chloride as an inferred carcinogen based on sufficient evidence of carcinogenicity in humans for chromium and other chromium compounds.[2] Chromyl chloride elicited dose-related mutations in *Salmonella typhimurium*.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for chromyl chloride is 0.025 ppm (0.16 mg/m^3).

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CHRYSENE
CAS: 218-01-9

$C_{18}H_{12}$

Synonyms: 1,2-benzo[*a*]phenanthrene; 1,2-benzphenanthrene; benzo[*a*]phenanthrene; 1,2,5,6-dibenzonaphthalene

Physical Form. Colorless, rhombic plates

Uses. Laboratory reagent; formed during the pyrolysis of organic matter

Exposure. Inhalation; ingestion; skin absorption

Toxicology. There is limited evidence that chrysene is an animal carcinogen.

There is no information regarding the toxicity of chrysene to humans.[1] The LD_{50} for chrysene given intraperitoneally is greater than 320 mg/kg body weight in the mouse.[2]

Chrysene produced skin tumors after skin application to mice and has been shown to be active as a tumor initiator. Local tumors were observed after its subcutaneous injection in mice. Perinatal administration of chrysene to male mice by intraperitoneal injection increased the incidence of liver tumors, malignant lymphoma, and lung tumors.[2]

There are no reports directly correlating human chrysene exposure and tumor development, in part perhaps because chrysene does not occur in isolation but rather occurs as only one component of a mixture of polycyclic aromatic hydrocarbons. There are, however, a number of reports associating human cancer and exposure to mixtures of polycyclic aromatic hydrocarbons that include chrysene as a component, for example, among coke oven workers.[3]

Chrysene was mutagenic to *Salmonella typhimurium* in the presence of an exogenous metabolic system. It induced sister chromatid exchanges in one mouse study and chromosomal aberrations in one hamster study.[2] Chrysene is metabolically activated to a 1,2-diol-3,4-epoxide that is mutagenic and carcinogenic in experimental animals and forms covalent adducts with DNA.[2,4]

The IARC has determined that there is limited evidence that chrysene is carcinogenic to experimental animals.[2] ACGIH has classified chrysene as a confirmed animal carcinogen with unknown relevance to humans; a numerical threshold limit value (TLV) is not recommended.

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COAL DUST

Synonyms: None

Physical Form. Solid

Uses. Coal is a fuel, and is used in the production of coke, coal gas, and coal tar compounds

Exposure. Inhalation

Toxicology. The inhalation of coal dust causes coal worker's pneumoconiosis (CWP).

Simple CWP has no clinically distinguishing symptoms, because many miners have a slight cough and blackish sputum, which are of no help in establishing whether or not the disease is present.[1] Simple CWP is diagnosed according to the number of small opacities present in the chest film. The small opacities may be linear (irregular) or rounded (regular); however, the latter are more commonly seen in CWP and are most frequently located in the upper lung zones.[1] The primary lesion of simple CWP is the coal macule, a focal collection of coal dust particles with a little reticulin and collagen accumulation, measuring up to 5 mm in diameter. Focal emphysema may be associated.

Simple CWP often occurs concomitantly with chronic bronchitis and emphysema.[1] Although CWP is associated with several respiratory impairments, it is not associated with shortened life span; the importance of this benign condition is the fact that it is a precursor of progressive massive fibrosis (PMF).[1] However, simple CWP does not progress in the absence of further exposure.

Any opacity greater than 1 cm in a coal miner is classified as complicated pneumoconiosis or PMF unless there is evidence to suggest another disease such as tuberculosis.[1]

Complicated pneumoconiosis (PMF) is associated with a reduction in ventilatory capacity, low diffusing capacity, abnormalities of gas exchange, low arterial oxygen tension, pulmonary hypertension, and premature death; it may appear several years after exposure has ceased and may progress in the absence of further dust exposure.[1] Macroscopically, the lesions consist of a mass of black tissue that is often adherent to the chest wall. The lesions are of a rubbery consistency and are relatively well defined. Unlike conglomerate silicosis, which consists of matted aggregates of whorled silicotic nodules, the massive lesion of PMF is amorphous, irregular, and relatively homogeneous. In some instances, its center may contain a cavity filled with a black liquid. Cavitation is a consequence of ischemic necrosis or secondary infection by tuberculosis. In PMF, the vascular bed of the affected region is destroyed. Obstructive airway disease is common and is probably a consequence of the distortion and narrowing of the bronchi and bronchioles produced by the conglomerate mass.

The percentage of miners showing definite radiographic evidence of either simple or complicated pneumoconiosis has varied considerably in different geographic areas; factors responsible for this difference include respirable dust levels, the number of years of exposure, and the physical and chemical composition of the coal.[2]

Prevalence of CWP has been associated with coal "rank," with higher-ranking coals consisting of an older coal with a higher percentage of carbon and a higher prevalence of CWP.[3]

A study of 9076 US miners from 1969 to 1971 showed an overall prevalence of CWP of 30%, with PMF occurring in 2.5% of the sample.[2] A more recent study of US coal workers through 1988 has found a reduction in the incidence of pneumoconiosis coinciding with a reduction in workplace exposures to 2 mg/m^3 after 1969.[3] In Britain, the prevalence of all categories of CWP in working miners has fallen from 13.4% in 1959–1960 to 5.2% in 1978; for PMF, the rate in 1978 was 0.4%.[4]

Various studies have examined the incidence of gastric cancer with coal dust exposure because various carcinogenic substances have been identified in coal and because coal dust may reach the gastrointestinal tract through the pulmonary clearance system.[5] Although

early reports have found an increased standardized mortality ratio for gastric cancer, a recent matched case-control study found no evidence of a dose-response relationship between coal mining and gastric cancer. Evidence from epidemiological studies for an association between coal dust and lung cancer has not been consistent, with both excess and deficits reported.[6] There is no exposure-response relation with duration of exposure, cumulative exposure, or radiographic evidence of pneumoconiosis.

In limited studies coal dust did not increase the incidence of tumors in rats. There was no evidence of mutagenicity after exposure of rodents by inhalation or oral gavage.[6]

The IARC has determined that there is inadequate evidence in experimental animals and in humans for the carcinogenicity of coal dust.[6]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for bituminous or lignite coal dust is 0.9 mg/m^3, as respirable particulate; a TLV-TWA of 0.4 mg/m^3, as respirable particulate, is recommended for miners exposed to anthracite coal dust.

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COAL TAR PITCH VOLATILES

CAS: 65996-93-2

Synonyms: CTPV; particulate polycyclic organic matter (PPOM); particulate polycyclic aromatic hydrocarbons (PPAH); polynuclear aromatics (PNAs)

Physical Form. As stated by ACGIH:[1]

> The pitch of coal tar is the black or dark brown amorphous residue that remains after the redistillation process. The volatiles contain a large quantity of lower molecular weight polycyclic hydrocarbons. As these hydrocarbons (naphthalene, fluorene, anthracene, acridine, phenanthrene) sublime into the air there is an increase of benzo(*a*)pyrene (BaP or 3,4-benzpyrene) and other higher weight polycyclic hydrocarbons in the tar and in the fumes. Polycyclic hydrocarbons, known to be carcinogenic, are of this large molecular type.

Sources/Uses. Occur as emissions from coke ovens, from coking of coal tar pitch, and from Soderberg aluminum reduction electrolytic cells; used for base coatings and paints; for roofing and paving; and as a binder for carbon electrodes

Exposure. Inhalation

Toxicology. Epidemiological evidence suggests that workers intimately exposed to the products of combustion or distillation of bituminous coal are at increased risk of cancer at many sites, including lungs, kidney, and skin.[2]

The chemical composition and particle size distribution of coal tar pitch volatiles (CTPV) from different sources are significant variables in determining toxicity.[3,4]

In a study of 22,010 US male aluminum reduction workers with over 5 years' employment in the industry, there was a slight positive association with lung cancer [standardized mortality ratio (SMR) = 121], which was somewhat stronger in Soderberg workers (SMR = 162).[4] There was a slight, but not statistically significant, excess of leukemia (SMR = 170) and lymphoma (SMR = 125) in potroom workers.

In more detailed analysis of the mortality experience of this cohort up to year end 1977, the results of other studies relative to an excess of lung cancer were not confirmed, but there were indications of a higher than expected mortality in pancreatic cancer, lymphohematopoietic cancers, genitourinary cancer, nonmalignant respiratory disease, and benign and unspecified neoplasms.[6]

A case-cohort study of aluminum production plant workers showed a clear excess of lung cancer risk in men who had worked in Soderberg potrooms in jobs with high exposure to CTPV, and that the risk was not due to confounding by smoking.[7] The rate ratio for lung cancer rose with cumulative exposure to CTPV measured as benzene-soluble material to 2.25 at 10–19 mg/m^3-years benzene-soluble matter but did not rise with further exposure.

A study in Canada of 5891 men in two aluminum reduction plants found the mortality from lung cancer related to "tar-years" of exposure; the SMR for persons exposed for more than 21 years to the higher levels of tars was 2.3 times that of persons not exposed to tars.[8] A follow-up study of this cohort through 1977 showed excess deaths from respiratory disease; pneumonia and bronchitis; malignant neoplasms of the stomach and esophagus, bladder, and lung; malignant neoplasms (all sites); Hodgkin disease; and hypertensive disease. Mortality from malignant neoplasms of the bladder and lung was related to the number of tar-years and to years of exposure.[9]

Exposure to coke oven emissions is a cause of lung and kidney cancer. A major study of US coke oven workers showed that mortality from lung cancer for full topside workers is 9 times the expected rate; for partial topside workers, it is almost 2.5 times the expected rate; and for side oven workers, it is 1.7 times the expected rate.[10] All of these rates are based on 5 or more years of exposure in the job category. As the length of employment increases, so does the mortality experience. For example, for employees with 20 or more years of employment topside, the lung cancer rate is 20 times the expected rate. In addition to the risk of lung cancer, the relative risk of mortality from kidney cancer for all coke oven workers is 7.5.[11]

A retrospective cohort study of 6635 male workers employed for more than 15 years in seven Chinese factories found that the SMRs for lung and liver cancer among those highly exposed to CTPV were 4.3 and 2.25, respectively.[12]

Certain industrial populations exposed to coal tar products have a demonstrated risk of skin cancer. Substances containing polycyclic hydrocarbons or polynuclear aromatics (PNAs), which may produce skin cancer, also produce contact dermatitis (e.g., coal tar pitch, cutting oils).[4] Although allergic dermatitis is readily induced by PNAs in guinea pigs, it only rarely is reported in humans from occupational contact with PNAs. Incidences in humans have resulted largely from the therapeutic use of coal tar preparations.[6]

Components of pitch and coal tar produce cutaneous photosensitization; skin eruptions usually are limited to areas exposed to ultraviolet light.[4,13,14] Most of the phototoxic agents will induce hypermelanosis of the skin; if chronic photodermatitis is severe and prolonged, leukoderma may occur.[13] Some oils containing PNAs have been associated with follicular and sebaceous gland changes, which commonly take the form of acne.[4]

Coal tar fumes were mutagenic in a modified Ames test.[15] Fumes generated at 316°C contained significantly higher concentrations of PAHs than those generated at 232°C, and the mutagenic activity generally paralleled the PAH content.

Biological monitoring of 1-hydroxypyrene (a PAH metabolite) in urine has been a useful indicator of PAH exposure in coke oven workers.[16]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for coal

tar pitch volatiles is 0.2 mg/m^3 as benzene solubles, with an A1-confirmed human carcinogen designation.

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COBALT
CAS: 7440-48-4

Co

Synonyms: None

Physical Form. Gray solid

Uses. Alloys; carbides; high-speed steels; paints, electroplating

Exposure. Inhalation

Toxicology. Cobalt causes skin irritation, allergic contact dermatitis, and occupational asthma; interstitial pulmonary fibrosis is associated with exposure to hard metal dust (tungsten and cobalt).

In the occupational setting, exposure to cobalt alone occurs primarily in the production of cobalt powders.[1] With other industrial exposures, such as hard metal exposure, additional

agents modulate the toxicity of cobalt. Three types of lung disease have been reported in the cemented tungsten carbide industry: (1) an interstitial fibrotic process, (2) an interstitial pneumonitis that often disappears when exposure ceases, and (3) an obstructive airways syndrome. The latter may result from simple irritation, but in addition, a distinct form of occupational asthma occurs.[2] Cobalt, which is used as a binder for the tungsten carbide crystals, has been implicated as the etiologic agent.[3,4]

Among 12 workers who were engaged in the manufacturing of, or grinding with, tungsten carbide tools and who developed interstitial lung disease, there were 8 deaths; serial chest roentgenograms over a period of 3–12 years revealed gradually progressive densities of a linear and nodular nature that gradually involved major portions of both lungs. Cough, production of scanty mucoid sputum, dyspnea on exertion, and reduced pulmonary function occurred early in the course of the disease.[4] Disease is seldom seen without at least 10 years of exposure, but shorter periods have been reported.[3]

The obstructive airways syndrome appears to be an allergic response and is characterized by wheezing, cough, and shortness of breath while at work.[2,4] There is no evidence that this type of disease progresses to interstitial fibrosis. In a report of nine cases, the syndrome did not develop until after 6–18 months of exposure.[5]

On screening 1039 tungsten carbide workers, interstitial lung disease was observed in 0.7% and work-related wheezing occurred in 10.9%.[6]

Occupational exposure to cobalt dust has been associated with cardiomyopathy characterized by functional effects on the ventricles and enlargement of the heart.[7]

Cobalt and its compounds produce an allergic dermatitis of an erythematous papular type that usually occurs in skin areas subjected to friction, such as the ankle, elbow flexures, and sides of the neck.[8] Ocular effects have included congestion of the conjunctiva.[9]

Animal studies have reported developmental effects (stunted fetuses and decreased pup weight and viability) after oral exposure to cobalt at doses that also produced maternal toxicity.[10]

Testicular atrophy was reported in rats exposed to 19 mg cobalt/m^3 (as cobalt sulfate) for 16 days.[11] Male mice exposed for 13 weeks at 1.14 mg cobalt/m^3 had a decrease in sperm motility, and at 11.4 mg cobalt/m^3 there was testicular atrophy; at the high dose female mice had a significant increase in length of the estrous cycle.[11]

Rhabdomyosarcomas developed in rats injected intramuscularly with the powder of either pure cobalt metal or cobalt oxide.[12] In other studies implantation of cobalt caused local fibrosarcomas in rabbits, but inhalation studies in hamsters did not reveal any increase in tumors from cobalt oxide.[9] Lifetime exposure to cobalt sulfate by inhalation resulted in increased incidence of alveolar/bronchiolar neoplasms and a spectrum of inflammatory, fibrotic, and proliferative lesions in the respiratory tract of male and female rats and mice.[13]

Epidemiological studies to determine the carcinogenicity of cobalt in humans have been confounded by concurrent exposure to other known carcinogens such as nickel and arsenic and small study populations.[14] A retrospective cohort study of 874 women exposed to cobalt in two Danish porcelain factories did not demonstrate a significant increased risk of developing lung cancer compared with the reference group.[15] A significant increase in lung cancer risk was found in workers simultaneously exposed to cobalt and tungsten carbide when exposures during the last 10 years were ignored.[16]

The IARC has determined that there is sufficient evidence that cobalt metal powder and cobaltous oxide are carcinogenic in experimental animals and that they are possible human carcinogens.[17]

In mammalian cells *in vitro* cobalt compounds have caused DNA strand breaks, sister chromatid exchanges, and aneuploidy, but not chromosomal aberrations.[17] Cobalt salts are generally nonmutagenic in prokaryotic assays.[18]

The 2003 ACGIH threshold limit value-

time-weighted average (TLV-TWA) for elemental cobalt and inorganic compounds is 0.02 mg/m^3 with an A3-confirmed animal carcinogen designation with unknown relevance to humans notation.

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COBALT HYDROCARBONYL
CAS: 16842-03-8

C_4HCoO_4

Synonyms: Cobalt carbonyl hydride; tetracarbonylhydrocobalt

Physical Form. Flammable gas with an offensive odor

Uses. Catalyst in organic reactions

Exposure. Inhalation

Toxicology. Cobalt hydrocarbonyl is expected to be a pulmonary irritant.

The 30-minute LC_{50} in rats was determined to be 165 mg/m^3.[1]

Definitive toxicity data for cobalt hydrocarbonyl do not exist because of the rapid decomposition in air of the chemical to a solid particulate. In most cases, exposures are primarily to inorganic cobalt compounds.

By analogy to nickel carbonyl, acute effects from animal exposures are expected to be pulmonary edema, congestion, and hemorrhage. In humans, nickel carbonyl causes an acute flulike syndrome that subsides and is followed after 12–36 hours by an acute respiratory syndrome. Exposure to cobalt hydrocarbonyl may be expected to produce similar effects.

Irritation may occur from skin or eye exposure.[2]

The 2003 threshold limit value-time-weighted average (TLV-TWA) is 0.1 mg/m^3 as Co.

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COPPER (Dust and Fume)
CAS: 7440-50-8

Cu, CuO

Synonyms: None

Physical Form. Reddish solid

Sources. Copper and brass manufacture; welding of copper-containing metals

Exposure. Inhalation

Toxicology. Copper fume causes irritation of the upper respiratory tract and metal fume fever (MFF), an influenza-like illness.

Respiratory, gastrointestinal, and dermal effects have been observed in workers exposed to copper dust and fumes.[1] Exposure to concentrations of 1–3 mg/m^3 for short periods resulted in altered taste response but no nausea; levels from 0.02 to 0.4 mg/m^3 produced no complaints.

Typical MFF, a 24- to 48-hour illness characterized by chills, fever, aching muscles, dryness in the mouth and throat, and headache, has been reported in several workers exposed to copper fume.[2,3] With MFF, leukocytosis is usually present with counts of 12,000–16,000/mm^3; recovery is usually rapid, and there are no sequelae.[4] Most workers develop an immunity to these attacks, but it is quickly lost, and attacks tend to be more severe on the first day of the workweek.[4]

It has recently been noted that if copper-induced MFF does occur, it is a very rare event.[5] Despite extensive use of copper in many industries, only a handful of MFF cases are reported in the literature.[5] Further limitations of these reports include possible contamination of the fume by other substances more likely to have caused MFF, atypical symptoms and complaints, and lack of consistency among types of work associated with symptoms. One reason that MFF may have rarely been described after copper exposure is that aerosolized copper particulates formed during welding, thermal cutting, and other hot work are mostly greater than respirable or submicron size. Studies of air in a brass foundry found that only 5% of the total copper exposure was respirable (aerosol less than or equal to 1 μm), whereas 40% of the zinc oxide exposures were to an aerosolized particulate of respirable size.[5]

Copper dust may cause respiratory irritation.[1] Gastrointestinal effects including anorexia, nausea, and occasional diarrhea have been attributed to swallowing of the dust.[1]

Lung damage after chronic exposure to fumes in industry has not been described.[6] The higher incidence of respiratory cancer reported in copper smelters is due to the presence of arsenic in the ore.[6]

Although unlikely in an occupational setting, ingestion of copper salts may cause vomiting, abdominal pain, diarrhea, lethargy, acute hemolytic anemia, renal and liver damage, neurotoxicity, increased blood pres-

sure and respiratory rates, coma, and death.[7] Transient irritation of the eyes has followed exposure to a fine dust of oxidation products of copper produced in an electric arc.[8]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for copper is 0.2 mg/m^3 for the fume and 1 mg/m^3 for dusts and mists as Cu.

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COTTON DUST, RAW

Synonyms: None

Physical Form. Fibers

Source. Cotton processing

Exposure. Inhalation

Toxicology. Raw cotton dust causes a respiratory syndrome termed byssinosis.

The initial symptoms are chest tightness, cough, wheezing, and dyspnea in varying degrees of severity on the first day of the workweek (grade 1 byssinosis).[1–3] Symptoms usually disappear an hour or so after the individual leaves work but may recur on the first day of each workweek. With continued exposure the symptoms also appear on subsequent days of the workweek (grade 2 byssinosis) There usually is a decrease in the FEV_1 and in vital capacity on the first day of the workweek after 3–4 hours of exposure; the changes in airway resistance and decreased flow rates have been attributed to narrowing of small airways due to bronchoconstriction. Eventually, obstructive airway disease, which is irreversible, occurs (grade 3 byssinosis).

Follow-up of cotton textile workers in China found that workers who consistently reported reversible symptoms such as chest tightness at work had significantly greater 15-year loss of FEV_1, suggesting that long-term cotton dust exposure was associated with permanent obstructive impairments.[4]

Although a loss in lung function has been documented in cotton textile workers, no clear evidence of increased mortality has been reported.[5] A review of 2895 consecutive autopsies showed no significant differences in the prevalence of emphysema, interstitial fibrosis, or cor pulmonale between 283 employees of a cotton textile mill and the general population.[6] In another postmortem study of 49 cotton workers, the incidence of emphysema was associated with cigarette smoking, with 16 of 36 smokers showing centrilobular emphysema vs. 1 of 13 nonsmokers.[7] Another study of women with advanced byssinosis confirmed the association between emphysema and cigarette smoking rather than cotton dust exposure.[8]

Two additional studies of cotton workers also found no excess mortality from respiratory disease but differed in other findings. In the first report of 3458 British cotton industry

worker, mortality from respiratory disease was reduced overall, but for subjects who initially reported byssinotic symptoms, the mortality from respiratory disease was slightly raised, and it increased with length of service.[9] The mortality from lung cancer was lower than expected, and it decreased with length of service. A mortality study of 1065 women employed in Finnish cotton mills did not confirm low mortality from respiratory cancer.[10] Instead, an increase in lung (3 vs. 1.9 expected) and gastrointestinal (13 vs. 6.6 expected) cancers was reported. Cotton dust exposure also appeared to increase the morbidity of renal disease and rheumatoid arthritis. Exposure to textile dust increased the risk of sinonasal cancer (squamous cell tumors and adenomas) among women in a case control study in France.[11] There was some evidence of a dose-response relationship, but because subjects had been exposed to various fibers (cotton, wool, synthetic) no specific association with type of fiber could be made.

A syndrome known as "mill fever," which may or may not be related to the development of byssinosis, has been described in some persons unaccustomed to breathing cotton dust.[2] Shortly after exposure, there is development of malaise, cough, fever, chills, and upper respiratory symptoms; these may recur daily for days to months until acclimatization takes place and symptoms disappear. Tolerance may be lost temporarily after a period of absence from exposure, or if exposure to a greater concentration of dust occurs. The exact prevalence of "mill fever" among new employees is unknown, but estimates range from 10% to 80%.[1]

Epidemiological studies have indicated that prevalence of byssinosis among cotton workers can be correlated with the average concentration of lint-free dust of particle size under 15 μ in diameter and with the number of years of exposure.[2] Specifically, in a follow-up study of 66 cotton textile workers, with an additional 10 years of exposure, the prevalence of byssinosis increased from 23% to 43% in the female workers and from 23% to 52% in the male workers.[10]

There is little evidence of a threshold below which zero prevalence is found.[2] The slopes of the prevalence-dustiness curves obtained by different investigators vary considerably.[2]

Gram-negative bacterial endotoxin has been implicated as one of the agents responsible for respiratory illnesses due to cotton dust exposure.[12]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for cotton dust is 0.2 mg/m^3.

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CRESOL (All Isomers)
CAS: 1319-77-3

ortho-Cresol
CAS: 95-48-7

meta-Cresol
CAS: 108-39-4

para-Cresol
CAS: 106-44-5

C_7H_8O

Synonyms: Cresylic acid; tricresol; methylphenol; *o*-cresol; *m*-cresol; *p*-cresol; hydroxytoluene

Physical Form. *Ortho-* and *para* isomers are solids; the *meta* isomer and isomer mixtures are yellowish liquids

Uses. Antiseptics; disinfectants; solvent; insecticides; resins; flame-retardant plasticizers

Exposure. Skin absorption; inhalation

Toxicology. All isomers of cresol cause skin and eye burns; exposure also may cause impairment of kidney and liver function, as well as central nervous system and cardiovascular disturbances.

Skin and eye contact are the major concerns of occupational exposure.[1] Signs and symptoms related to skin contact are a burning sensation, erythema, skin peeling, localized anesthesia, and, occasionally, ochronosis, a darkening of the skin.[1] Hypersensitivity also has been reported.[2]

Cresols are rapidly absorbed through the skin, producing systemic effects.[1] About 20 ml of a 90% cresol solution accidentally poured over an infant's head caused chemical burns, cyanosis, unconsciousness, and death within 4 hours.[3] Histopathologic examination showed hepatic necrosis, cerebral edema, acute tubular necrosis of the kidneys, and hemorrhagic effusions from the peritoneum, pleura, and pericardium. The blood contained 12 mg cresol/100 dl.

Inhalation of appreciable amounts of cresol vapor is unlikely under normal conditions because of the low vapor pressure; however, hazardous concentrations may be generated at elevated temperatures.[1] Seven workers exposed to cresol vapor at unspecified concentrations for 1.5–3 years had headaches, which were frequently accompanied by nausea and vomiting.[1] Four of the workers also had elevated blood pressure, signs of impaired kidney function, blood calcium imbalance, and marked tremors. Eight of ten subjects exposed to 1.4 ppm *o*-cresol vapor experienced upper respiratory tract irritation.[1]

Several cases of ingestion have shown cresol to be corrosive to body tissues and to cause toxic effects on the vascular system, liver, kidneys, and pancreas.[1]

Rats survived 8 hours of inhaling air saturated with the vapor.[4] Irritation of the nose and eyes and some deaths were observed in mice exposed to saturated concentrations 1 hour/day for 10 days.[5] Animal experiments have produced varying results with regard to concentrations necessary to produce death.[1] In general, the *ortho* and *para* isomers are considered equal in toxicity, with the *meta* isomer regarded as the least toxic.[1]

At doses that were maternally toxic, *o*- and *p*-isomers induced slightly elevated incidences of minor variations in the offspring of exposed rats and rabbits.[6]

Cresol isomers promoted dimethylbenzan-

thracene-induced papillomas in mice when applied as 20% solutions in benzene twice weekly for 11 weeks; no carcinomas were produced.[7]

Cresol mixtures and the *o*- and *p*-isomers have been found to be weakly genotoxic in some *in vitro* assays inducing sister chromatid exchange and chromosomal aberrations in Chinese hamster ovary cells.[6] Results were negative with the *meta*-isomer, as were all *in vivo* assays.

In the eyes of rabbits, undiluted cresols caused permanent opacification and vascularization; a drop of a 33% solution applied to rabbit eyes and removed with irrigation within 60 seconds caused only moderate injury, which was reversible.[8]

In rat liver tissue, *p*-cresol was 5- to 10-fold more toxic than the *o*- or *m*-isomers as determined by the degree of cell killing.[9] Furthermore, the toxicity of *p*-cresol was dependent on the formation of a reactive intermediate, and it was suggested that the mechanism of toxicity for *p*-cresol may differ from that of the *o*- and *m*-isomers.

The odor of cresol is recognized at concentrations as low as 5 ppm.[2] The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for all isomers of creosol is 5 ppm (22 mg/m^3) with a notation for skin absorption.

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CROTONALDEHYDE
CAS: 4170-30-3

$CH_3CH{=}CHCHO$

Synonyms: β-Methyl acrolein; 2-butenal; crotonic aldehyde

Physical Form. Colorless liquid

Uses. Intermediate for the production of scorbic acid; formerly used in the manufacture of *n*-butyl alcohol; formed during the combustion of fossil fuels

Exposure. Inhalation

Toxicology. Crotonaldehyde is an irritant of the eyes, mucous membranes, and skin.

Exposure of humans to 4 ppm for 10 minutes caused lacrimation and upper respiratory irritation; at 45 ppm there was conjunctival irritation after a few seconds.[1,2]

In eight cases of corneal injury reported from industrial exposure to crotonaldehyde, healing was complete in 48 hours; the severity of exposure was not specified.[3]

Rats did not survive exposure to 1650 ppm for 10 minutes; effects included respiratory distress, an excitatory stage, and terminal convulsions; autopsy revealed bronchiolar damage.[2] Pulmonary edema has also been observed in rats after fatal exposure to 1500 ppm for 30 minutes or 100 ppm for 4 hours.

Administered in the drinking water for 113 weeks, 42 mg/l crotonaldehyde induced neoplastic lesions in rats; 2 of 27 animals had hepatocellular carcinomas and 9 of 27 had neoplastic lesions.[4] Altered liver cell foci occurred in 23 of the 27 animals. The increased incidence of neoplastic and preneoplastic lesions was not observed at the higher dose (421 mg/l). Crotonaldehyde produced variable results in a variety of genetic assays.[5]

The IARC has determined that there is inadequate evidence in humans and in experimental animals for the carcinogenicity of crotonaldehyde.[5] Overall crotonaldehyde is not classifiable as to its carcinogenicity to humans.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for crotonaldehyde is 2 ppm (5.7 mg/m^3).

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CUMENE

CAS: 98-82-8

$C_6H_5C_3H_7$

Synonyms: Cumol; 2-phenylpropane; isopropylbenzene

Physical Form. Colorless liquid

Uses. As thinner for paints and lacquers; as component of high-octane aviation fuel; in production of styrene; in organic synthesis

Exposure. Inhalation; skin absorption

Toxicology. Cumene is an eye and mucous membrane irritant. At high concentrations, it causes narcosis in animals; it is expected that severe exposure will produce the same effect in humans.

Concentrations lethal to humans are not expected to be encountered at room temperature because of the low volatility of cumene.[1] If inhalation of high concentrations of the vapor did occur, dizziness, incoordination, and unconsciousness could be expected.[2] In animals, cumene narcosis is characterized by slow induction and long duration, suggesting a cumulative action.[3] There are no reports of systemic effects in humans.

The LC_{50} for rats was 8000 ppm for a 4-hour exposure.[4] The LC_{50} for mice was 2040 ppm for a 7-hour exposure; the effect was central nervous system depression.[3] A 20-minute exposure to concentrations ranging from 2000 to 8000 ppm caused neurobehavioral effects in mice including gait disturbances, impaired psychomotor coordination, decreased arousal and rearing, and changes in posture.[5]

Repeated inhalation by rabbits and rats of 2000 ppm caused ataxia and lethargy.[6] Rats exposed to 1202 ppm 6 hours/day, 5 days/week for 13 weeks had increased relative and absolute adrenal weights; increased relative and absolute kidney weights also occurred in exposed females.[7] No significant changes were noted in rats exposed 8 hours/day to 500 ppm

for 150 days.[2] In rats, guinea pigs, monkeys, and dogs, exposed at either 224 ppm 8 hours/day, 5 days/week for 6 months or 30 ppm continuously for 90 days, there were no adverse effects on symptoms, body weight, or histology.[8]

Cumene was not a developmental toxicant in either rats or rabbits after exposure to levels (1200 ppm and 2300 ppm, respectively) associated with maternal toxicity.[9] Most genotoxic tests with cumene have been negative.[10]

The LD_{50} for penetration of rabbit skin was 12.3 ml/kg after 14 days.[4] Contact of the liquid with the skin causes erythema and irritation.[11] Eye contamination may produce conjunctival irritation.[1]

It generally is agreed that cumene has no damaging effect on the hematopoietic system, despite its chemical similarity to benzene.[5] Furthermore, cumene is not anticipated to be a significant carcinogenic hazard because it is metabolically similar to toluene, a substance that showed no carcinogenic activity in 2-year inhalation studies.[10]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 50 ppm (246 mg/m^3) with a notation for skin absorption.

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CYANAMIDE
CAS: 420-04-2

CH_2N_2

Synonyms: Carbodiimide; cyanoamine; hydrogen cyanamide; cyanogen nitride; carbamonitrile

Physical Form. Crystalline solid

Uses. Fumigants, metal cleaners, production of synthetic rubber, chemical synthesis

Exposure. Ingestion; inhalation

Toxicology. Cyanamide is an irritant of the eyes, mucous membranes, and skin; it is an inhibitor of aldehyde dehydrogenase and can cause an "antabuse" effect with ethanol ingestion.

Cyanamide is severely irritating and caustic to the eyes, skin, and respiratory tract.[1]

Concurrent exposure to cyanamide and ethanol produces tachycardia, decreased

diastolic blood pressure, hypertension, increased respiration rate, and symptoms of alcohol intoxication, owing to a buildup of acetaldehyde.[2]

In a 6-month study of rats, oral doses of 2.7 or 25 mg/kg/day caused no hepatic changes.[3] A two-generation study of reproduction and fertility in rats used oral doses of 2, 7, or 25 mg/kg/day.[4] Maternal toxicity was observed. Decreases in dam weight, number of corpora lutea, number of implantations, and number of neonates was attributable to the toxic effects in the dams. There were no findings in the F_1 generation.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for cyanamide is 2 mg/m^3.

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CYANIDES
NaCN
CAS: 143-33-9

KCN
CAS: 151-50-8

$Ca(CN)_2$
CAS: 592-01-8

Synonyms/compounds: Sodium cyanide; potassium cyanide; calcium cyanide ("black cyanide")

Physical Form. Powders, granules, or flakes

Uses. Extraction of gold and silver; electroplating; hardening of metals; coppering; zincing; bronzing; manufacture of mirrors; reclamation of silver from photographic film; pesticides

Exposure. Inhalation; skin absorption; ingestion

Toxicology. The alkali salts of cyanide can cause rapid death due to metabolic asphyxiation.

Cyanide ion exerts an inhibitory action on certain metabolic enzyme systems, most notably cytochrome oxidase, the enzyme involved in the ultimate transfer of electrons to molecular oxygen.[1] Because cytochrome oxidase is present in practically all cells that function under aerobic conditions, and because the cyanide ion diffuses easily to all parts of the body, cyanide quickly halts practically all cellular respiration. The venous blood of a patient dying of cyanide is bright red and resembles arterial blood because the tissues have not been able to utilize the oxygen brought to them.[2] Cyanide intoxication produces lactic acidosis, the result of an increased rate of glycolysis and production of lactic acid.[3]

If large amounts of cyanide have been absorbed, collapse usually is instantaneous, the patient falling unconscious, often with convulsions, and dying almost immediately. Symptoms of intoxication from less severe exposure include weakness, headache, confusion, and occasionally nausea and vomiting.[1,2] The respiratory rate and depth usually are increased initially, at later stages respiration becoming slow and gasping. Coma and convulsions occur in some cases. If cyanosis is present, it usually indicates that respiration either has ceased or has been very inadequate for a few minutes. In one case of nonfatal ingestion of 600 mg of potassium cyanide, the clinical course was marked by acute pulmonary edema and lactic acidosis.[3]

Most reported cases of occupational cyanide poisoning have involved workers with a mixture of repeated acute or subacute expo-

sures and chronic or prolonged low-level exposures, making it unclear whether symptoms simply resulted from multiple acute exposures with acute intoxication. Some symptoms persisted after cessation of such exposures, perhaps because of the effect of anoxia from inhibition of cytochrome oxidase. Symptoms from claimed "chronic" exposure are similar to those reported after acute exposures, such as weakness, nausea, headache, and vertigo.[1] A study of 36 former workers in a silver-reclaiming facility, who were repeatedly exposed to cyanide, demonstrated some residual symptoms 7 or more months after cessation of exposure; frequent headache, eye irritation, easy fatigue, loss of appetite, and epistaxis occurred in at least 30% of these workers.[4] Changes in thyroid chemistry, without manifestations of hypothyroidism, have also been reported in cyanide-exposed individuals.

Cyanide solutions or cyanide aerosols generated in humid atmospheres have been reported to cause irritation of the upper respiratory tract (primarily nasal irritation) and skin.[1] Skin contact with solutions of cyanide salts can cause itching, discoloration, or corrosion, most likely due to the alkalinity of the solutions. Skin irritation and mild systemic symptoms (e.g., headache, dizziness) have been caused by solutions as dilute as 0.5% potassium cyanide.[1]

Skin contact with aqueous cyanide solutions for long periods has caused caustic burns; these cases may be fatal because of significant skin absorption.[1]

Administered in the diet for 13 weeks to rats at 12.5 mg/kg/day, sodium cyanide caused a number of reproductive effects including decreases in testis weight and spermatid counts in males and alterations in estrous and proestrous cycles in females.[5] Adverse developmental effects have been observed in rodents at maternally toxic doses.[6]

No studies are available to evaluate the carcinogenic risk of cyanide exposure in humans or animals.[6] The cyanide salts are not mutagenic in a variety of genotoxic assays.[6]

At high levels, cyanide acts so rapidly that its odor has no value as a warning.[2] At lower levels, the odor may provide some warning, although many individuals are unable to recognize the scent of "bitter almonds."[3]

The 2003 ACGIH ceiling-threshold limit value (C-TLV) for cyanide salts, as CN, is 5 mg/m^3 with a notation for skin absorption.

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CYANOGEN
CAS: 460-19-5

$(CN)_2$

Synonyms: Carbon nitride; dicyanogen; nitriloacetonitrile; oxalonitrile; prussite

Physical Form. Gas with almond-like odor

Uses. Organic synthesis; fuel gas for welding and cutting heat-resistant metals; rocket and missile propellant; fumigant

Exposure. Inhalation; eye or skin contact

Toxicology. Cyanogen reacts with water, acids, and acid salts to produce hydrogen cyanide, which causes death from metabolic asphyxiation.

Exposure of humans to 16 ppm caused eye and nose irritation.[1] A concentration of 270 ppm hydrogen cyanide has long been said to be immediately fatal to humans. A more recent study, however, states that the estimated LC_{50} to humans for a 1-minute exposure is 3404 ppm; 270 ppm would be fatal after 6–8 minutes, 181 ppm after 10 minutes, and 135 ppm after 30 minutes.[2]

If large amounts of cyanide have been absorbed, collapse usually is instantaneous, the patient falling unconscious, often with convulsions, and dying almost immediately.[2,3] Symptoms of intoxication from less severe exposure include weakness, headache, confusion, vertigo, fatigue, anxiety, dyspnea, and occasionally nausea and vomiting.[2–4] The respiratory rate and depth usually are increased initially, and at later stages respiration becomes slow and gasping. Coma and convulsions occur in some cases. If cyanosis is present, it usually indicates that respiration either has ceased or has been very inadequate for a few minutes. Chronic overexposure may cause dizziness, loss of appetite, and weight loss.[5]

Cyanide ion exerts an inhibitory action on certain metabolic enzyme systems, most notably cytochrome oxidase, the enzyme involved in the ultimate transfer of electrons to molecular oxygen.[2] Because cytochrome oxidase is present in practically all cells that function under aerobic conditions, and because the cyanide ion diffuses easily to all parts of the body, cyanide quickly halts practically all cellular respiration. The venous blood of a patient dying of cyanide is bright red and resembles arterial blood because the tissues have not been able to utilize the oxygen brought to them.[3] Cyanide intoxication produces lactic acidosis, probably the result of an increased rate of glycolysis and the production of lactic acid.[4]

Studies in rats suggested that cyanogen is 10-fold less acutely toxic than hydrogen cyanide.[1] In rats and monkeys exposed to 11 or 25 ppm cyanogen for 6 hours/day, 5 days/week for 6 months, there were no effects on hematologic or clinical chemistry values.[6] Mean body weights were reduced in rats at the higher level.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 10 ppm (21 mg/m^3).

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CYANOGEN CHLORIDE
CAS: 506-77-4

ClCN

Synonyms: Chlorine cyanide; chlorocyanogen; chlorocyanide

Physical Form. Colorless liquid or gas

Uses. Organic synthesis; poison gas used by military

Exposure. Inhalation

Toxicology. Cyanogen chloride is a severe irritant of the eyes and respiratory tract and can also cause death from metabolic asphyxiation.

In humans concentrations of 159 ppm and 48 ppm have been reported as fatal after 10 min and 30 min, respectively.[1] A concentration of 20 ppm was considered intolerable after 1 minute, and 1 ppm for 10 minutes was irritating. Symptoms of exposure include severe irritation of the eyes and respiratory tract, with hemorrhagic exudate of the bronchi and trachea and pulmonary edema. Repeated exposures may also cause dizziness, loss of appetite, mental deterioration, and weight loss.[2]

In addition to the irritant effects, cyanogen chloride may also cause interference with cellular metabolism via the cyanide radical. Cyanide ion exerts an inhibitory action on certain metabolic enzyme systems, most notably cytochrome oxidase, the enzyme involved in the ultimate transfer of electrons to molecular oxygen.[3] Because cytochrome oxidase is present in practically all cells that function under aerobic conditions, and because the cyanide ion diffuses easily to all parts of the body, cyanide quickly halts practically all cellular respiration. The venous blood of a patient dying of cyanide is bright red and resembles arterial blood because the tissues have not been able to utilize the oxygen brought to them.[4] Cyanide intoxication produces lactic acidosis, probably the result of increased rate of glycolysis and production of lactic acid.[5]

In animal studies reported LC_{50} values were 2200 ppm for 1 minute in monkeys, 2700 ppm for 3 minutes in rats, and 3000 ppm for 7 minutes in rabbits.[2]

The 2003 threshold limit value-ceiling (TLV-C) is 0.3 ppm (0.75 mg/m^3).

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CYCLOHEXANE
CAS: 110-82-7

C_6H_{12}

Synonyms: Hexahydrobenzene; benzene hexahydride; hexamethylene

Physical Form. Colorless liquid

Uses. Chemical intermediate; solvent for fats, oils, waxes, resins, and rubber

Exposure. Inhalation

Toxicology. Cyclohexane is irritating to the eyes and mucous membranes; at high concentrations it causes narcosis in animals, and it is expected that severe exposure will produce the same effect in humans.

A concentration of 300 ppm is detectable by odor and is somewhat irritating to the eyes and mucous membranes.[1] At higher concentrations, the vapor may cause dizziness, nausea, and unconsciousness.[2] Unlike benzene, cyclohexane is not associated with hematologic changes.

Rabbits exposed to 786 ppm cyclohexane for 50 periods of 6 hours each showed minor microscopic changes in the liver and kidneys; lethargy, light narcosis, increased respiration, and diarrhea; some deaths were observed during a total of 60 hours of exposure to 7444 ppm; 1-hour exposure to 26,752 ppm caused rapid narcosis, tremor, and, rarely, opisthotonos and was lethal to all exposed rabbits.[3] In mice, exposure to 18,000 ppm produced tremors within 5 minutes, disturbed equilibrium by 15 minutes, and recumbency at 25 minutes.[2] Lethal concentrations administered by inhalation or orally to animals caused generalized vascular damage with severe degenerative changes in the heart, lung, liver, kidney, and brain.[2]

Inhalation exposure of mice at 7000 ppm 6 hrs/day, 5 days week for 14 weeks caused hyperreactivity and diminished response to an auditory alerting stimulus during exposures and significantly increased liver weights at the end of exposures; rats similarly exposed also had a significantly increased incidence of hepatic centrilobular hypertrophy.[4] Repeated intraperitoneal administration of 1.5 g/kg caused evidence of renal tubular injury in rats; effects were attributed to cyclohexanol, the main metabolite of cyclohexane.[5]

No evidence of developmental toxicity was observed in rats or rabbits exposed to 7000 ppm during gestation; reductions in body weight gain were observed in maternal rats.[6]

In multigeneration reproduction study in rats decreased pup weights occurred in the F_1 and F_2 generation at the 7000-ppm exposure level.[7]

Concentrations of cyclohexanol in urine and cyclohexane in whole blood and serum have shown significant correlations with occupational exposure levels.[8]

Cyclohexane defats the skin on repeated contact.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for cyclohexane is 300 ppm (1030 mg/m^3).

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CYCLOHEXANOL
CAS: 108-93-0

$C_6H_{11}OH$

Synonyms: Hexahydrophenol; cyclohexyl alcohol

Physical Form. Colorless, viscous liquid

Uses. Solvent for oils, resins, ethyl cellulose; manufacture of soap, plastics

Exposure. Inhalation; skin absorption

Toxicology. Cyclohexanol causes irritation of the eyes, nose, and throat; at high concentrations it causes narcosis in animals, and it is expected that severe exposure will produce the same effect in humans.

Human volunteers exposed to a vapor concentration of 100 ppm for 3–5 minutes experienced eye, nose, and throat irritation.[1] Headache and conjunctival irritation have resulted from prolonged exposure to "excessive" but undefined concentrations.[2]

Rabbits exposed 6 hours/day to 272 ppm over a 10-week period showed slight eye irritation; at 997 ppm additional effects were salivation, lethargy, narcosis, mild convulsive movements, and some deaths.[3] Lethal doses of cyclohexanol produced slight necrosis of the myocardium and damage to the lungs, liver, and kidneys.[3] The application of 10 ml of cyclohexanol to the skin of a rabbit for 1 hour/day for 10 days induced narcosis, hypothermia, tremors, and athetoid movements; necrosis, exudative ulceration, and thickening of the skin occurred in the area of contact.[2] Ten microliters applied directly to the cornea of rabbits caused moderate to severe irritation.[4]

Mice fed diets containing 1% cyclohexanol during gestation produced offspring with an increased mortality during the first 3 weeks of life.[2]

The 2003 threshold limit value-time-weighted average (TLV-TWA) is 50 ppm (206 mg/m^3) with a notation for skin.

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CYCLOHEXANONE
CAS: 108-94-1

$C_6H_{10}O$

Synonyms: Pimelic ketone; hexanon; sextone

Physical Form. Colorless liquid

Uses. Industrial solvent for cellulose acetate resins, vinyl resins, rubber, and waxes; solvent-sealer for polyvinyl chloride; in printing industry; coating solvent in audio and videotape production

Exposure. Inhalation; skin absorption

Toxicology. Cyclohexanone causes eye, nose, and throat irritation; at high concentrations, it produces lethargy and narcosis in animals, and it is expected that severe exposure will cause the same effect in humans.

In most human subjects, exposure to 25 ppm of the vapor for 5 minutes did not cause effects, but 50 ppm was irritating, especially to the throat; exposure to 75 ppm resulted in more

noticeable eye, nose, and throat irritation.[1] One anecdotal case suggested that exposure to cyclohexanone at high levels for many years may be associated with epileptic seizures.[2]

Rabbits exposed to 190 ppm for 6 hours/day for 50 days showed slight liver and kidney injury. At 309 ppm there was slight conjunctival irritation, and at 1414 ppm lethargy was observed. At 3082 ppm effects were incoordination, salivation, labored breathing, narcosis, and some deaths.[3] Five of six rats survived exposure to 2000 ppm for 4 hours, but 4000 ppm caused coma and death of all six. Narcosis, hypothermia, and decreased respiration were observed in guinea pigs exposed to 4000 ppm for 6 hours.[4] Recovery from narcosis was slow, and 3 of 10 animals died within 4 days of exposure.

Rats and mice administered cyclohexanone in their drinking water for 2 years showed marginal evidence of carcinogenic activity.[5] Male rats receiving 3300 ppm had a 13% incidence of adrenal cortex adenomas versus 2% in controls; the incidence of this neoplasm did not increase in the higher dose males or in any of the female rats. Mice had a statistically significant increase in incidence of lymphomas-leukemias among the females given 6500 ppm, but not among the group given the higher doses. Thus a dose-related trend in increased neoplasms was not observed among any of the groups.

The IARC has determined that there is inadequate evidence for the carcinogenicity of cyclohexanone in experimental animals and that it is not classifiable as to its carcinogenicity to humans.[6]

Rats exposed on gestation days 5–20 by inhalation to concentrations of up to 500 ppm for 7 hours/day showed no significant fetotoxic effects.[7] Depression of both maternal and fetal body weights, but no incidence of teratogenicity, occurred in rats exposed through inhalation at 1430 ppm during days 9–16 of gestation.[8]

Eye contact with liquid cyclohexanone may cause corneal injury.[9] The liquid is a defatting agent, and prolonged or repeated skin contact may produce irritation or dermatitis.[9] Allergic contact dermatitis has been reported in a patient with repeated direct contact with 100% cyclohexanone solution.[10]

The main metabolite of cyclohexanone is cyclohexanol, which is excreted in the urine.[11] A good correlation has been shown between postshift urinary cyclohexanol levels (corrected for creatinine) and occupational exposure to cyclohexanone.[11]

Cyclohexanone has an odor similar to peppermint, and harmful concentrations are not likely to be voluntarily tolerated.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for cyclohexanone is 25 ppm (100 mg/m^3) with a notation for skin absorption.

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CYCLOHEXENE

CAS: 110-83-8

C_6H_{10}

Synonym: 1,2,3-Tetrahydrobenzene

Physical Form. Colorless liquid

Uses. Manufacture of adipic acid, maleic acid, hexahydrobenzoic acid, and aldehyde; stabilizer for high-octane gasoline

Exposure. Inhalation

Toxicology. Cyclohexene is regarded as a mild respiratory irritant and central nervous system depressant by analogy to the observed effects of chemically similar substances.

No acute or chronic effects have been reported in humans.

Mice lost their righting reflex at approximately 9000 ppm, and 15,000 ppm was lethal.[1]

Dogs inhaling cyclohexene vapor (concentration not stated) exhibited symptoms characterized by muscular quivering and incoordination.[2] A 6-month inhalation study of various species repeatedly exposed at 75, 150, 300, or 600 ppm showed a lower weight gain for rats exposed at the highest level.[3] Increased alkaline phosphatase was found with exposures, but no other biochemical or hematologic abnormalities were observed.

The liquid defats the skin on direct contact.

Cyclohexene was not mutagenic in *Salmonella typhimurium* with or without metabolic activation.[4]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for cyclohexene is 300 ppm (1010 mg/m^3).

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CYCLOHEXIMIDE

CAS: 66-81-9

$C_{15}H_{23}NO_4$

Synonyms: Actidione, Acti-aid, Naramycin

Physical Form. Colorless crystals

Uses. Fungicide, growth regulator

Exposure. Ingestion; skin contact

Toxicology. Cycloheximide is a teratogen and reproductive toxin in experimental animals.

There is no information concerning toxic effects in humans, although the probable lethal oral dose for humans is 5–50 mg/kg.

The lowest LD_{50} reported for cycloheximide is 2 mg/kg after oral administration in the rat.[1] In animal experiments, cycloheximide is irritating to the skin and eyes. Animals given toxic doses exhibit salivation, bloody diarrhea, tremors, and excitement leading to death from cardiovascular collapse.[2]

Several studies in rats, mice, and rabbits demonstrate that cycloheximide is embryotoxic, fetotoxic, and teratogenic.[3] Intraperitoneal administration of doses as low as 250 µg/kg on day 10 of gestation produced central nervous system, craniofacial, and cardiovascular system abnormalities in rats. Musculoskeletal abnormalities were produced in mice after intraperitoneal administration of doses as low as 30 mg/kg on day 9 of gestation. Subcutaneous administration of 5 mg/kg cycloheximide on day 11 caused postimplantation mortality in the mouse. Effects on fertility were observed in pregnant rabbits administered as little as 5 µg/kg on day 1 of gestation.

Cycloheximide is genotoxic in *Escherichia coli* with metabolic activation and in the mouse sperm morphology assay. Carcinogenicity bioassays in the mouse and rat are inconclusive.[3]

The ACGIH has not established a threshold limit value (TLV) for cycloheximide.

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CYCLOHEXYLAMINE

CAS: 108-91-8

$C_6H_{13}N$

Synonyms: Aminocyclohexane; aminohexahydrobenzene; CHA; hexahydroaniline; hexahydrobenzenamine

Physical Form. Colorless to slightly yellow liquid with a strong, fishy odor

Uses/Sources. Production of rubber-processing chemicals; corrosion inhibitor in boiler feed water; production of insecticides, plasticizers, and dry cleaning soaps; a metabolite of the sweetener cyclamate

Exposure. Inhalation; eye/skin contact

Toxicology. Cyclohexylamine is an irritant of the mucous membranes, eyes, and skin.

In three cases of acute human exposure from industrial accidents, symptoms included light-headedness, drowsiness, anxiety and apprehension, and nausea; slurred speech and vomiting also occurred in one case.[1] In human patch tests, a 23% solution caused severe irritation and possible sensitization. However, guinea pig sensitization tests did not confirm a potential for sensitization.[2]

In a multispecies study, rabbits, guinea pigs, and rats were exposed 7 hours/day, 5 days/week to levels of 150, 800, and 1200 ppm.[1] At 1200 ppm all animals except for one rat died after a single exposure. At 800 ppm fractional mortality occurred after repeated exposures. At 150 ppm four of five rats and two guinea pigs survived 70 hours of exposure, but one rabbit died after only 7 hours. Effects were irritation of the respiratory tract and eyes with the development of corneal opacities.

When the undiluted liquid was applied to the skin of guinea pigs and kept in contact under an occluding cuff, the LD_{50} was between 1 and 5 ml/kg; edema, necrosis, and persistent eschars were observed.[2] One drop of a 50% aqueous solution in the eye of a rabbit caused complete destruction of the eye.

Cyclohexylamine has long been known to be pharmacologically active and has sympathomimetic effects on the heart and blood pressure.[3] However, it is not particularly potent.[4]

Cyclohexylamine is a metabolite of the artificial sweetener sodium cyclamate, with the amount of conversion varying considerably from person to person.[5]

Cyclohexylamine has been studied for carcinogenicity in two studies in mice, one of which was a multigeneration study, and in four studies in rats.[6] There were no differences in tumor incidence between treated and control animals. In a 2-year multigeneration study in rats, testicular atrophy was statistically significant at 50 and 150 mg/kg/day, but not at 100 mg/kg/day.[7] Effects on testes were also observed in rats fed 400 mg/kg/day for up to 13 weeks; the Sertoli cell was the primary target.[8]

Several studies have shown no evidence of mutagenicity or teratogenicity.[6] Chromosome damage was induced in bone marrow cells of rats by intraperitoneal injection of 10–50 mg/kg per day for 5 days and in peripheral blood cells of fetal lambs treated in utero with 50–250 mg/kg.[9,10]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for cyclohexylamine is 10 ppm (41 mg/m^3).

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CYCLOPENTADIENE
CAS: 542-92-7

C_5H_6

Synonyms: 1,3-Cyclopentadiene; *p*-pentine; pentole; pyropentylene

Physical Form. Colorless liquid

Uses. In manufacture of resins; in organic synthesis

Exposure. Inhalation; minor skin absorption

Toxicology. Cyclopentadiene is an irritant; repeated exposures have caused mild liver and kidney injury in experimental animals.

In human volunteers, the vapor was irritating at both 250 and 500 ppm.[1]

The oral LD_{50} in rats was 0.82 g/kg.[2] Rats exposed 7 hours/day to 500 ppm for 35 days (over a period of 53 days) developed centrilob-

ular, cloudy swelling of liver cells and cloudy vacuolization of renal tubular epithelium.[1] Dogs exposed 39 times to 400 ppm for 6 hours followed by 16 exposures at 800 ppm had no ill effects, as determined by observation, clinical tests, or histologic examination.[1] Repeated daily exposure in four species at 250 ppm for 6 months also caused no symptoms. Applied to the skin of rabbits, the liquid caused marked irritation, exudates in the pleural and peritoneal cavities, and hyperemia of the kidneys.[1] The dermal LD_{50} was 6.72 ml/kg for the rabbit.[2]

The 2003 threshold limit value-time-weighted average (TLV-TWA) is 75 ppm (203 mg/m^3).

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CYCLOPENTANE

CAS: 287-92-3

C_5H_{10}

Synonym: Pentamethylene

Physical Form. Flammable, colorless liquid

Uses. As a laboratory reagent; in the manufacture of pharmaceuticals; found in solvents and in petroleum ether; propellant pressurizing agent

Exposure. Inhalation

Toxicology. Cyclopentane is a central nervous system (CNS) depressant and irritant.

Only limited information is available on human exposures. Symptoms of acute exposure to high concentrations are expected to be excitement, loss of equilibrium, stupor, coma, and respiratory failure.[1]

Because cyclopentane is not sufficiently stable to occur naturally in large quantities, most exposures involve a mixture of substances.[1] In the Italian shoe industry, exposure to glue solvents containing up to 18% cyclopentane has been associated with polyneuropathy.[2] However, it is assumed that *n*-hexane is present in these solvents and accounts for the polyneuropathy.

In animal experiments high concentrations initially cause stimulation of the CNS and then CNS depression.[3] In mice, 15 minutes at 60,000 ppm or 10 min at 80,000 produced anesthesia; deaths occurred at concentrations near those required to produce anesthesia, indicating a small margin of safety between narcotic and fatal concentrations. Mice exposed 6 hours/day for 90 days to 10,200 ppm had no substance-related abnormalities in clinical, neurofunctional, or pathologic examinations.[3]

In another report repeated exposures of rats to 8000 ppm 6 hours/day for 12 weeks resulted in decreased body weight gains in females; no effects were found in males or females exposed to up to 1100 ppm 6 hours/day for 3 weeks.[1]

Applied to the skin of guinea pigs cyclopentane produced slight erythema and dryness.[1] Instilled in rabbit eyes it is mildly irritating.[3]

Cyclopentane was not mutagenic in the Ames bacterial assay; it was also negative *in vitro* in the mouse lymphoma assay and in the micronucleus test.[3]

Cyclopentane is considered a severe fire hazard with a lower flammability limit of 15,000 ppm. The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for cyclopentane is 600 ppm.

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CYMENE
o-Cymene
CAS: 527-84-4

m-Cymene
CAS: 535-77-3

p-Cymene
CAS: 99-87-6

$C_{10}H_{14}$

Synonyms: Isopropyltoluene; isopropylmethylbenzene

Physical Form. Colorless liquid with a sweet aromatic odor

Uses. As a diluent for lacquers, varnishes, and dyes; in the production of resins; as a component of fragrances; also found as a by-product in the manufacture of sulfite paper pulp

Exposure. Inhalation

Toxicology. Cymene, which may occur in *ortho*, *meta*, or *para* forms, is an irritant of the skin and mucous membranes and may cause central nervous system effects; in animals subcutaneous injection has produced hematologic changes.

In a very early report, *p*-cymene produced headache and nausea in volunteers who ingested 3–4 g/day for 2–3 days.[1] A severe case of blood dyscrasia was found in a man who had been exposed to 340 ppm *p*-cymene for 20 years while working in a sulfite pulp mill.[2] There was also exposure to a variety of other substances during this time, including acetone, sulfur dioxide, acetaldehyde, methyl alcohol, formic acid, and terpenes. No similar cases of hematologic effects following human exposure to *p*-cymene have been reported.

The lowest lethal concentration for rats was 5000 ppm for 45 minutes.[3] At this concentration, signs included dyspnea, twitching of the whiskers, and ataxia, which were followed by hyperreactivity to auditory stimuli. Other signs included rigid tails, carpopedal spasm, generalized quivering, profuse salivation, and hypothermia. In mice, the LD_{50} was 4370 ppm; effects were characteristic of central nervous system excitation, such as tremor and convulsions, which lasted for 2–3 hours.[1] Inhibitory effects of the central nervous system followed over the next 48 hours and included lethargy, shallow breathing, and coma.

Rats exposed to 50 or 250 ppm *p*-cymene 6 hours/day, 5 days/week for 4 weeks had a significantly decreased yield of synaptosomal protein in the brain, suggesting a decrease in the density and total number of synapses.[4]

Subcutaneous injection of rabbits with 2 ml of *p*-cymene for 2 days caused an increased number of immature hematopoietic cells in the peripheral blood.

On the skin, *p*-cymene may cause erythema, dryness, and defatting. However, 4% *p*-cymene in petroleum did not produce irritation in 25 humans after a 48-hour closed patch test or after 10 daily applications to the same spot on the backs of subjects.[5] Undiluted *p*-cymene applied to rabbit skin for 24 hours under occlusion was moderately irritating. The LD_{50} by skin absorption is greater than 5 g/kg in rabbits.

A threshold limit value (TLV) has not been established for *o*-, *m*-, or *p*-cymene.

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DDT
CAS: 50-29-3

$C_{14}H_9Cl_5$

Synonyms: 1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)ethane; dichlorodiphenyltrichloroethane

Physical Form. White crystalline solid

Uses. Insecticide; use banned in many temperate-climate countries, but still widely used in the tropics

Exposure. Inhalation; skin absorption; ingestion

Toxicology. DDT affects the nervous system at high doses and causes paresthesias, tremor, and convulsions.

Ingestion by humans of 10 mg/kg is sufficient to cause effects in some, and convulsions have frequently occurred after ingestion of 16 mg/kg; 285 mg/kg has been taken without fatal results.[1] The onset of effects, usually occurring 2 or 3 hours after ingestion, is characterized by paresthesias of the tongue, lips, and face; the subject soon develops tremor, a sense of apprehension, dizziness, confusion, malaise, headache, and fatigue; in severe intoxication, convulsions may occur and there may be paresis of the hands.[1] Ingestion of very large doses induces vomiting.[1] Recovery is well advanced or complete in 24 hours except in the most serious cases; three persons who each ingested an estimated 20 g of DDT showed a residual weakness of the hands after 5 weeks. There are no confirmed reports of fatalities occurring exclusively from ingestion of pure DDT. Heavy exposure to the dust may cause skin and eye irritation.[1]

Although chronic poisoning in humans has not been described, continued absorption of DDT by humans results in storage of DDT and its metabolites, including DDE [2,2-bis(*p*-chlorophenyl)-1,1-dichloroethylene], in fat.[2–4] In a study of 20 workers exposed to DDT for 11–19 years and with a calculated daily intake of 18 mg/person [calculated from DDA (2,2-bis(*p*-chlorophenyl)acetic acid) content in fat and DDA excretion in urine], the sum of isomers and metabolites of DDT in the fat was 38–647 ppm (compared with an average of 8 ppm for the general population); although DDE was the major excretory product in the general population, DDA was the major excretory product in DDT-exposed workers.[2]

Large oral doses of DDT in rats caused focal and centrilobular necrosis of the liver.[1] However, in clinical evaluation and laboratory studies of 31 workers exposed to equivalent oral intakes of 3.6–18 mg daily for an average of 21 years, there was no evidence of hepatotoxicity; an observed increase in activity of hepatic microsomal enzymes was not accompanied by clinical evidence of detriment to general health.[5]

The hepatocarcinogenicity of DDT by the oral route has been demonstrated and confirmed in several strains of mice. Liver cell tumors have been produced in both sexes and in CF mice were found to have metastasized to the lungs.[6] However, the tumorigenic potential of DDT was negligible in monkeys after dosing for 15–22 years. Of 35 monkeys administered 20 mg DDT/kg, 5 days/week for 130 months, only 1 developed hepatocellular carcinoma after a latency period of 20 years.[7] Despite numerous studies, there is no conclusive, unequivocal, or consistent evidence linking

DDT exposure to human cancers.[8] The IARC has determined that there is sufficient evidence for the carcinogenicity of DDT in experimental animals and that it is possibly carcinogenic to humans.[6]

Reproductive and developmental toxicity have been reported in animal studies.[8] Effects are attributed to hormone-altering actions of DDT isomers and/or metabolites.

In mice, exposure to DDT during gestation and in the neonatal stage has also caused developmental neurotoxicity, in the form of behavioral deficits in the learning process, that persisted into adulthood. Human studies have suggested that alterations in functions that are hormonally controlled such as duration of lactation, maintenance of pregnancy, and fertility may occur from DDT exposure.[8]

DDT has given both positive and negative results in a wide variety of genotoxic assays. In general, it appears that DDT is not a significant genotoxic hazard at environmentally relevant concentrations.[8]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for DDT is 1.0 mg/m^3 with an A3 confirmed animal carcinogen with unknown relevance to humans designation.

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DECABORANE
CAS: 17702-41-9

$B_{10}H_{14}$

Synonyms: Decaboron tetradecahydride, boron hydride

Physical Form. Colorless to white crystalline solid

Uses. In rocket propellants; in polymer synthesis; corrosion inhibitor; fuel additive; mothproofing agent

Exposure. Inhalation; skin absorption

Toxicology. Decaborane affects the nervous system and causes signs of both hyperexcitability and narcosis.

In humans, the onset of symptoms is frequently delayed for 24–48 hours after exposure; dizziness, headache, and nausea are common; other symptoms of mild intoxication include light-headedness, drowsiness, incoordination, and fatigue; more severe intoxication results in tremor, localized muscle spasms, and convulsive seizures.[1–3] Muscle spasm usually subsides after 24 hours, whereas light-headedness and fatigue may remain for up to 3 days.[3]

The 4-hour inhalation LC_{50} for mice was 26 ppm; signs included restlessness, depressed breathing, generalized weakness, and corneal

opacities.[4] Rats exhibited normal activity during 4-hour exposures to concentrations ranging up to 95 ppm.

Exposure of rabbits to 56 ppm for 6 hours was fatal; effects included dyspnea, coarse movements of the head, weakness, rigid hindquarters, absence of eye reflexes, and convulsive seizures.[5] By percutaneous application, the rabbit LD_{50} was 113 mg/kg.[6] The hazard from skin absorption is considered to be high.[7]

Cumulative toxic effects occurred in various animal species receiving repeated small doses of decaborane by oral, intraperitoneal, or cutaneous routes.[7] The rate of recovery was markedly delayed in some animal species surviving repeated doses compared with those that had received a single, large dose. In dogs repeatedly given oral doses of 3 mg/kg, the effects on the central nervous system were not pronounced but there was damage to the liver and kidneys.

Intravenous administration of 4–10 mg/kg produced bradycardia and an initial transient hypertensive effect in the anesthetized dog.[8]

Toxicity is thought to occur from the decomposition of decaborane to a stable intermediate that in turn inhibits intracellular pyridoxal phosphate-requiring enzymes.[9]

Rapid olfactory fatigue excludes odor as a satisfactory early warning device.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for decaborane is 0.05 ppm (0.25 mg/m^3) with a short-term excursion limit of 0.15 pm (0.75 mg/m^3) and a notation for skin absorption.

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DECALIN
CAS: 91-17-8

$C_{10}H_{18}$

Synonyms: Decahydronaphthalene; bicyclo(4.4.0)decane; naphthane

Physical Form. Colorless liquid

Uses. Solvent for naphthalene, fats, resins, oils; alternate for turpentine in lacquers, shoe polishes, and waxes; component in motor fuels and lubricants

Exposure. Inhalation

Toxicology. Decalin is an irritant of the eyes and mucous membranes; in animals it causes species- and sex-specific kidney and liver damage.

No serious poisonings with decalin in humans have been reported.[1] Inhalation of 100 ppm produces upper respiratory irritation.[2] Contact with the liquid produced vesicular eczema, accompanied by intense itching, in a worker exposed to decalin and some detergents.[3]

The LC_{50} in rats was estimated to be

710 ppm for a 4-hour exposure, and in mice the LC_{50} was 1085 ppm, also for a 4-hour exposure.[2,4] A 4-hour inhalation exposure of eight rats at 1000 ppm caused tremors, convulsions, and death in three of the animals.[5]

Subchronic exposure of rats, mice, and guinea pigs to 50 or 250 ppm, 6 hours/day for 1 month produced different effects in the different species. Rats exhibited increased cytoplasmic hyaline droplet formation in the renal tubule epithelium, whereas mice exposed to the higher concentration developed hepatocellular cytoplasmic vacuolization. Guinea pigs had signs of alveolar irritation that was not dose related.[5]

An additional, longer-term study of dogs, rats, and female mice exposed to 5 or 50 ppm for 90 days was also conducted.[2] No distinct exposure-related effects were noted in dogs or in female rats; mild, reversible liver damage was noted in mice. In male rats, decalin exposure produced nephropathy.

Recent studies found clear evidence of carcinogenicity of decalin in male rats exposed for 2 years at 100 and 400 ppm, based on increased incidences of renal tubule neoplasms; increased incidences of pheochromocytoma of the adrenal medulla were also considered to be exposure related.[6] Neither neoplasms or chemical-related kidney lesions occurred in female rats. Equivocal evidence of carcinogenicity was reported in female mice exposed at 25, 100, and 400 ppm for 2 years, based on marginally increased incidences of hepatocellular and uterine neoplasms. Nonneoplastic lesions of the liver, including centrilobular hypertrophy and necrosis, were significantly increased in male mice exposed at 400 ppm.

Additional studies of decalin exposure in rats have characterized the specific sequence of renal alterations: first the variable occurrence of light-microscopically evident proximal convoluted tubule epithelial cell necrosis, presumably a reflection of cellular injury associated with excessive protein accumulation (hyaline droplets); then the occurrence of granular casts at the junction of the inner and outer bands of the outer zone of the medulla; and finally, chronic nephrosis, occurring secondary to tubular obstruction by granular casts.[7] It is not known how this excessive protein accumulation (specifically, α_{2u}-globulin, a low-molecular-weight glycoprotein) results in renal tubular cell death, but it does not appear to be caused through an autolytic process induced by lysosomal enzyme leakage. Studies have shown that although decalin exposure induced enlarged lysosomes in renal tubular cells of treated male rats, the lysosomes remained intact.[8]

Other reports have confirmed the species- and sex specificity for kidney toxicity by decalin. Relevance to human exposure has not been established.[8]

Decalin was not mutagenic in bacterial assays in vitro but caused a small but significant increase in micronucleated normochromatic erythrocytes in male mice treated *in vivo*.[6]

The mild terpinelike odor of decalin may not provide adequate warning of exposure.

A threshold limit value (TLV) has not been established for decalin.

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DEMETON

CAS: 8065-48-3

$C_8H_{19}O_3PS_2$

Synonyms: Mixture of *O*,*O*-diethyl *S*-(and *O*)-2-[(ethylthio)ethyl] phosphorothioates; Mercaptofos; Demox; Systox

Physical Form. Pale yellow to light brown, oily liquid

Uses. Acaricide; insecticide

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Demeton is an anticholinesterase agent.

At least four fatal, several severe nonfatal, and a number of mild cases of demeton intoxication have been reported. Both animal experiments and human exposures suggest that the toxicity and potency of demeton is similar to that of parathion.[1] Signs and symptoms of overexposure are caused by the inactivation of the enzyme cholinesterase, which results in the accumulation of acetylcholine at synapses in the nervous system, skeletal and smooth muscle, and secretory glands.[1–3] The sequence of the development of systemic effects varies with the route of entry. The onset of signs and symptoms is usually prompt but may be delayed up to 12 hours. After inhalation, respiratory and ocular effects are the first to appear, often within a few minutes of exposure. Respiratory effects include tightness in the chest and wheezing caused by bronchoconstriction and excessive bronchial secretion; laryngeal spasms and excessive salivation may add to the respiratory distress; cyanosis may also occur. Ocular effects include miosis, blurring of distant vision, tearing, rhinorrhea, and frontal headache.

After ingestion, gastrointestinal effects such as anorexia, nausea, vomiting, abdominal cramps, and diarrhea appear within 15 minutes to 2 hours. After skin absorption, localized sweating and muscular fasciculations in the immediate area occur usually within 15 minutes to 4 hours; skin absorption is somewhat greater at higher ambient temperatures and is increased by the presence of dermatitis.[1–3]

With severe intoxication by all routes, an excess of acetylcholine at the neuromuscular junctions of skeletal muscle causes weakness aggravated by exertion, involuntary twitchings, fasciculations, and eventually paralysis. The most serious consequence is paralysis of the respiratory muscles. Effects on the central nervous system include giddiness, confusion, ataxia, slurred speech, Cheyne–Stokes respiration, convulsions, coma, and loss of reflexes. The blood pressure may fall to low levels, and cardiac irregularity including complete heart block may occur. Complete symptomatic recovery usually occurs within 1 week; increased susceptibility to the effects of anticholinesterase agents persists for up to several weeks. Daily exposure to concentrations that are insufficient to produce symptoms after a single exposure may result in the onset of symptoms. Continued daily exposure may be followed by increasingly severe effects.

In animal studies, exposure to 3 mg demeton/m^3 for 2 hour resulted in no illness in rats during the first exposure, tremors during the second exposure, lacrimation and tremors during the third exposure, and death in 10 of 17 animals during the fourth exposure.[4]

Administered to mice between days 7 and 12 of gestation as a single intraperitoneal dose

of 7 or 10 mg/kg or as three consecutive doses of 5 mg/kg, demeton was found to be embryotoxic (decreased fetal weight and higher mortality). A few minor skeletal abnormalities were produced at the 5 mg/kg dose level.[4]

Demeton was mutagenic in bacterial assays.[4] A single dose injected intraperitoneally induced chromosomal aberrations in the bone marrow of Syrian hamsters.[5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for demeton is 0.01 ppm (0.11 mg/m^3) with a notation for skin absorption.

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DIACETONE ALCOHOL
CAS: 123-42-2

$(CH_3)_2C(OH)CH_2COCH_3$

Synonyms: 4-Hydroxyl-4-methyl-2-pentanone; diacetonyl alcohol; diacetone; dimethyl acetonyl carbinol

Physical Form. Colorless to yellow liquid

Uses. Solvent for pigments, cellulose, resins, oils, fats, and hydrocarbons; hydraulic brake fluid; antifreeze

Exposure. Inhalation; minor skin absorption

Toxicology. Diacetone alcohol causes irritation of the eyes and respiratory tract; at high concentrations it causes narcosis in animals, and it is expected that severe exposure will cause the same effect in humans.

Most human subjects exposed to 100 ppm for 15 minutes complained of eye, nose, and throat irritation; exposure to 400 ppm also caused chest discomfort.[1,2]

Animals exposed to 2100 ppm for 1–3 hours exhibited restlessness, mucous membrane irritation, and drowsiness.[3] Rats exposed to 1500 ppm for 8 hours survived.[4] Injection of 3 ml/kg or intragastric administration of 5 ml/kg diacetone alcohol in rabbits caused respiratory depression, narcosis, and death.[5] A temporary decrease in the number of erythrocytes in the blood of rats was observed for 1–4 days after intragastric administration of 2 ml/kg of diacetone alcohol; hepatic lesions characterized by vacuolization and granulation of the parenchymal cells were noted, but recovery was complete in 7 days.[6]

The liquid defats the skin and may produce dermatitis with prolonged or repeat contact; in the eyes, it causes moderate to marked irritation and transient corneal damage.[3]

The odor threshold of diacetone alcohol is 0.28 ppm, which should provide adequate warning of exposure.[7]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for diacetone alcohol is 50 ppm (238 mg/m^3).

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2,4-DIAMINOTOLUENE

CAS: 95-80-7

$C_7H_{10}N_2$

Synonyms: TDA; 2,4-TDA; toluene-2,4-diamine; 3-amino-*p*-toluidine; 1,3-diamino-4-methylbenzene

Physical Form. Crystalline solid

Uses. Intermediate in the production of toluene diisocyanate, which is used to produce polyurethane; in the production of dyes

Exposure. Inhalation; skin absorption

Toxicology. Diaminotoluene (TDA) is a skin and eye irritant; in animals it is carcinogenic and a reproductive toxin.

Although details are not available, extremely high exposure levels are said to cause central nervous system effects, liver damage, and chemical cyanosis from the production of methemoglobin.[1] On the skin TDA produces dermatitis, blistering, and uticaria; in the eye it causes irritation and lacrimation. Repeated or prolonged contact may result in sensitization.[1]

Tests in symptomatic polyurethane foam workers indicate that TDA does not produce asthma.[2]

TDA was tested for carcinogenicity in the diet of F344 rats at time-weighted average doses of 79, 176 (males), and 171 (females) ppm TDA for 103 weeks.[3] Rats of both sexes had hepatocellular carcinomas or neoplastic nodules. The significance of these tumors in both sexes was supported by a high incidence of associated nonneoplastic lesions of the liver. Female rats also had carcinomas or adenomas of the mammary gland in a dose-related manner and at a higher incidence than in controls. In mice fed dietary levels of 100 or 200 ppm TDA for 101 weeks females had excess hepatocellular carcinomas, whereas no tumor excess occurred in the male mice.

After *in vivo* administration in rats TDA induced formation of both DNA and hemoglobin adducts in a dose-dependent manner.[4] TDA was mutagenic in bacterial assays.[1]

TDA was a reproductive toxin in male rats. Administration of 15 mg/kg body weight/day for 10 weeks resulted in a significant reduction in spermatogenesis, reduced weights of seminal vesicles and epididymides, diminished circulating testosterone, and an elevation in serum luteinizing hormone.[1] A study of 84 TDA-exposed workers found no differences in sperm count, sperm morphology, or other reproductive parameters compared with nonexposed workers.[5]

A threshold limit value (TLV) for TDA has not been assigned.

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DIAZOMETHANE

CAS: 334-88-3

CH_2N_2

Synonyms: Azimethylene; diazirine

Physical Form. Yellow gas

Uses. Powerful methylating agent for acidic compounds such as carboxylic acids, phenols, enols; not manufactured for sale and distribution because of toxicity and explosivity

Exposure. Inhalation

Toxicology. Diazomethane is a severe pulmonary irritant.

Exposure to the gas is extremely dangerous, causing irritation of the eyes, chest pain, cough, fever, and severe asthmatic attacks. A chemist briefly exposed to an unknown concentration in a laboratory developed a violent cough and shortness of breath, leading to severe pulmonary edema; symptoms completely subsided within 2 weeks.[1] In a fatal incident, another chemist exposed to an unknown concentration of diazomethane, as well as other irritant gases, experienced immediate respiratory distress leading to pneumonitis and death on the fourth day after exposure.[1]

A physician exposed to diazomethane from a laboratory spill noted only a faint odor but immediately experienced severe headache, cough, mild anterior chest pain, generalized aching of muscles, and a sensation of overwhelming tiredness.[2] Within 5 minutes he was stuporous, and on admission to a hospital he was markedly flushed and feverish; he recovered in approximately 48 hours. Subsequent exposure to trace amounts of the gas produced wheezing, cough, and malaise, leading to the suspicion that this substance may also have a sensitizing effect on the respiratory system. Skin exposure has produced irritation and denudation.[3]

Exposure of cats to 175 ppm for 10 minutes resulted in pulmonary edema and hemorrhage, with death occurring in 3 days.[1] Limited animal studies indicate that diazomethane is carcinogenic in mice (increased incident of lung tumors after skin application) and rats (exposure to the gas caused lung tumors).[4] The IARC has determined that there is limited evidence of carcinogenicity in animals and that the agent is not classifiable as to its carcinogenicity to humans (Group 3).[5]

The warning properties of diazomethane are poor.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for diazomethane is 0.2 ppm (0.34 mg/m^3).

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DIBENZ[*a*,*b*]ANTHRACENE
CAS: 53-70-3

$C_{22}H_{14}$

Synonyms: DBA; dibenzo[*a*,*b*]anthracene; 1,2:5,6-dibenzanthracene

Physical Form. Colorless solid

Sources. Dibenz[*a*,*b*]anthracene (DBA) is a major component of polynuclear aromatic hydrocarbons, also known as polycyclic aromatic hydrocarbons, and is usually bound to small particulate matter present in urban air, industrial and natural combustion emissions, and cigarette smoke.

Exposure. Inhalation

Toxicology. DBA produced carcinomas in animals after oral or dermal exposure and injection site tumors after subcutaneous or intramuscular administration.

Mammary carcinomas and forestomach papillomas were observed in mice after gavage administration.[1,2] DBA has also been shown to cause skin papillomas and carcinomas in mice when applied dermally 3 times/week for a lifetime.[3–5] Subcutaneous injection of 1 µmol of DBA three times weekly for 20 doses induced injection site sarcomas in 100% of female Sprague-Dawley rats by 33 weeks.[6]

The genetic toxicity of DBA has been evaluated in a variety of short-term genetic toxicology assays and was positive in most systems.[5] DBA undergoes metabolism to form several reactive intermediates. The 3,4-dihydrodiol metabolite of DBA is thought to be further metabolized to a 3,4-diol-1,2-epoxide, the ultimately mutagenic metabolite. Thus the genotoxicity of DBA is dependent on metabolic activation, either exogenously supplied or endogenously present, and the ratio of enzymatic activation and detoxication pathways. The carcinogenic properties could also depend on methyl substitution of DBA and the formation of an aralkylating metabolite.[6]

Most human exposure to DBA in the environment or workplace occurs when it is particle bound and a component of complex mixtures of polycyclic aromatic hydrocarbons. Thus it has not been possible to study the effects of human exposure to DBA alone.

The IARC considers that there is sufficient evidence that DBA is carcinogenic in experimental animals and that it is probably carcinogenic to humans.[7]

No threshold limit value (TLV) has been assigned for DBA.

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DIBORANE
CAS: 19287-45-7

B_2H_6

Synonyms: Boroethane; boron hydride

Physical Form. Gas

Uses. High-energy fuel; reducing agent; initiator of polymerization of ethylene, vinyl, and styrene; source of boron for the semiconductor industry

Exposure. Inhalation

Toxicology. Diborane is a pulmonary irritant.

In humans, overexposure results in a sensation of tightness in the chest, leading to precordial pain, shortness of breath, nonproductive cough, and sometimes nausea.[1–4] Prolonged exposure to low concentrations causes headache, light-headedness, vertigo, chills, and, less frequently, fever. Fatigue or weakness occurs and may persist for several hours; tremor or muscular fasciculations occur infrequently and are usually localized and of short duration. Diborane gas has not been found to have significant effects on contact with skin or mucous membranes, although high concentrations may cause eye irritation.[5]

The LC_{50} for rats was 50 ppm for 4 hours; in other animal experiments, acute exposure caused pulmonary edema and hemorrhage and temporary damage to the liver and kidneys.[6] Repeated exposure of dogs at about 5 ppm for 6 hours/day resulted in death after 10–25 exposures; 1 of 2 animals survived repeated exposure at 1–2 ppm for 6 months.[7] Repeated respiratory insult was thought to be the underlying cause of death.

In more recent studies the LD_{50} for male mice was 31.5 ppm for a 4-hour exposure.[8] After exposure at 15 ppm for up to 8 hours, decreased body weight and severe inflammatory changes in the lungs were seen in the mice. Cellular infiltration, bleeding, edema, and congestion occurred in mice with the longest exposures. At a dose of 5 ppm for 2 or 4 weeks, increases in leukocytes and erythrocytes were observed in addition to inflammatory changes in the lungs.[8] At concentrations of 0.2 or 0.7 ppm 6 hours/day, 5 days/week for 2 or 4 weeks, there was slight infiltration of polymorphous neutrophils in the peribronchiolar region.[9] In rats subacute exposures of 0.11 or 0.96 ppm 6 hours/day, 5 days/week for 8 weeks induced dose-related changes in the lungs, including increased neutrophil and macrophage counts without evidence of histopathologic damage.[10]

The threshold of odor detection is approximately 3.3 ppm; the repulsive odor is described as rotten eggs, sickly sweet, musty, or foul.[6]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for diborane is 0.1 ppm (0.11 mg/m^3).

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1,2-DIBROMO-3-CHLOROPROPANE

CAS: 96-12-8

$C_3H_5Br_2Cl$

Synonyms: DBCP; dibromochloropropane

Physical Form. Colorless to yellow liquid

Uses. Formerly as an agricultural nematocide (use banned in the US in 1977)

Exposure. Inhalation; skin absorption

Toxicology. 1,2-Dibromo-3-chloropropane (DBCP) is a mild central nervous system depressant and causes sterility in male workers due to a selective effect on seminiferous tubules.

DBCP has caused oligospermia and aspermia in male workers.[1] Initial documentation of these effects occurred in workers engaged in the production of DBCP at an agricultural chemical plant in Lathrop, California. Of 27 exposed male workers, 11 had abnormally low sperm counts of less than 1 million/ml; all had been exposed for at least 3 years. None with sperm counts above 40 million had been exposed for more than 3 months.[2]

Subsequent studies in this and three other DBCP plants showed a total of more than 100 cases of oligospermia or aspermia. Exposures in one plant were estimated at 100–600 ppb.[1]

A larger clinical-epidemiological study of these men was undertaken to determine the exposure-effect relationships involved. Of 142 nonvasectomized men providing semen samples, 107 had been exposed to DBCP and 35 had not been exposed. There was a clear-cut difference in both the distribution of sperm counts and the median counts between the exposed men and the nonexposed men. Of the exposed men, 13.1% were azoospermic, 16.8% were severely oligospermic, and 15.8% were mildly oligospermic.[3] A follow-up study reported some recovery among 30 azoospermic and oligospermic workers who had a minimum of 18 months of exposure during 1976–1977.[4] Of the 26 azoospermic subjects who voluntarily participated in follow-up, 19 (73.0%) showed evidence of spermatogenesis recovery. Thirteen azoospermic subjects recovered to normospermic levels; however, their mean most recent sperm count (44.4 million/ml) was significantly lower than the mean (88.8 million/ml) of the 17 oligospermic subjects who recovered to normospermic levels. The lack of spermatogenesis recovery was definitively shown to be job- and, possibly, age-related. The follicle-stimulating hormone level in 1977 was significantly associated with azoospermia, as well as the likelihood of return to normospermia among the azoospermic subjects. After 17 years of follow-up, it was determined that sperm count recovery tended to be evident within 36–45 months of last exposure, with no improvement after that.[5]

A recent cohort study of 26,000 workers from 12 countries outside the US found that after a median exposure to DBCP of 3 years, 64% of the men overall, and 90% of the men studied from the Philippines, had azoospermia or oligospermia.[6] The percentage of men with no children was 28.5% overall.

Male exposure to DCBP has also been associated with an increased frequency of spontaneous abortions in wives of exposed workers, but congenital abnormalities have not been reported among children of workers who received sufficient DBCP exposure to induce oligospermia.[7,8]

Other effects reported by exposed workers include headache, nausea, light-headedness, and weakness.[8]

In animal studies, effects of exposure include increased mortality, gonadal atrophy, and carcinomas. The LC_{50} for rats was 368 ppm for 1 hour and 103 ppm for 8 hours.[9] Irritation of the eyes and respiratory tract was observed at levels of 60 ppm and higher. Moderate depression of the central nervous system was manifested as sluggishness and ataxia.

In rats of both sexes given 50–66 exposures to 12 ppm over 70–90 days, 40–50% of the animals died.[9] Although death was attributed to lung infection, the most striking observation in males at autopsy was severe atrophy and degeneration of the testes. There were also degenerative changes of the seminiferous tubules, reduction in sperm count, and abnormal development of sperm cells. Other effects were mild damage to the liver and kidneys.

The liquid applied undiluted to the eye of a rabbit caused transient irritation.[9] An LD_{50} of 1.4 g/kg was obtained when the material was applied undiluted for 24 hours to the rabbit skin. Repeated application (20 times) to the skin of a rabbit caused slight crustiness. However, the dermis and subcutaneous tissue showed extensive necrosis.

In a study of carcinogenesis, DBCP was orally administered to rats and mice 5 times/week at maximally tolerated doses and at half those doses.[10–12] As early as 10 weeks after initiation of treatment, there was a high incidence of squamous cell carcinomas of the stomach in both species. In female rats there were also mammary adenocarcinomas. Chronic inhalation resulted in carcinomas of the respiratory tract in mice and multiple site tumors in rats.[13]

Cohort studies have reported excess lung, liver, bilary, and cervical cancer but are limited by small numbers, insufficient follow-up time, multiple pesticide exposures, and lack of exposure data.[14] The IARC has determined that there is sufficient evidence in experimental animals for the carcinogenicity of DBCP and that it is possibly carcinogenic to humans.[14]

DBCP is a genotoxic in microbial and mammalian assays.[8] The mechanism for DBCP-induced testicular toxicity may be related to direct DNA damage. Binding of DBCP metabolites to testicular cell DNA has been demonstrated. Alternatively, inhibition of sperm carbohydrate metabolism could also account for DBCP toxicity to epididymal sperm.

The odor of DBCP was detected at 1.7 ppm, the only level tested.[8]

The ACGIH has not established a threshold limit value (TLV) for 1,2-dibromo-3-chloropropane.

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2-*N*-DIBUTYLAMINOETHANOL

CAS: 102-81-8

$(C_4H_9)_2NCH_2CH_2OH$

Synonyms: DBAE; β-*N*-dibutylaminoethyl alcohol; *N*,*N*-dibutylethanolamine

Physical Form. Colorless liquid

Uses. Organic syntheses

Exposure. Inhalation; skin absorption

Toxicology. 2-*N*-dibutylaminoethanol (DBAE) is a skin and eye irritant. Effects in humans have not been reported.

Rats exposed at 70 ppm had tremors, convulsive seizures, and eye and nasal irritation within 4 hours of exposure. On subsequent days of 6-hour exposures, mild tremors were evident, and one death in five animals occurred on the fourth day. Effects at the end of 5 days included a 57% average body weight loss, a 2-fold increase in liver- and kidney-to-body weight ratios, a 10-fold increase in total serum bilirubin, an elevated hematocrit, and a slight increase in clotting times.[1] Exposure at 33 ppm for 5 days resulted in growth failure but no mortality; animals at this exposure level appeared essentially normal, except for some occasional nose rubbing, suggestive of mild irritation. Rats exposed for 6 months to 22 ppm were comparable to controls throughout the exposure period.

At high oral dose levels (4–8 g/kg), rats exhibited periods of inactivity, followed by tremors, incoordination, clonicotonic convulsions, and death. At lower dose levels (0.5–1.0 g/kg), animals appeared lethargic during the first day. On the day after dosing, surviving rats appeared normal, except for mild diarrhea. The acute oral LD_{50} for neutralized DBAE was 1.78 g/kg. No histopathologic changes in the heart, liver, kidneys, adrenals, spleen, brain, or testes were observed in rats euthanized 24 hours after a dose of 1.2 g/kg.

The LD_{50} by percutaneous absorption was 1.68 g/kg for the rabbit.[2] Applied to the skin of rabbits, the liquid caused necrosis within 24 hours, and instilled in rabbit eyes, it produced corneal necrosis.

In vitro studies show that DBAE inhibits acetylcholinesterase.[3]

Dibutylaminoethanol was negative in *Salmonella* mutagenicity tests.[4]

The nauseating odor of DBAE may provide adequate warning of overexposure, because it is unlikely that individuals would stay in badly contaminated areas for any length of time.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for

dibutylaminoethanol is 0.5 ppm (3.5 mg/m^3) with a notation for skin absorption.

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2,6-DI-*tert*-BUTYL-*p*-CRESOL
CAS: 128-37-0

$C_{15}H_{24}O$

Synonyms: BHT; butylated hydroxytoluene; DBPC; 2,6-bis(1,1-dimethylethyl)-4-methylphenol

Physical Form. White, crystalline solid

Uses. Antioxidant used to preserve fat-containing foods and stabilize rubber, plastics, petroleum

Exposure. Ingestion

Toxicology. 2,6-Di-*tert*-butyl-*p*-cresol or BHT is of relatively low acute toxicity in animals, and there is no evidence of either acute or chronic effects among exposed workers.

Oral LD_{50} values in the range of 2 g/kg body weight have been reported in mice and rats.[1] Oral administration to mice at lethal doses produces weight loss, dyspnea, and enlarged lungs with pulmonary edema and hemorrhage. Repeated administration of BHT causes impaired function and histologic changes in the liver, kidneys, and thyroid and impaired coagulation of the blood. On the skin or eye of rabbits it is slightly irritating, but it has no sensitizing effect in guinea pigs.

Several chronic feeding studies have been conducted in mice and rats. Results have been either no difference in tumor incidence or increased pulmonary tumors (mice) or pituitary adenomas (rats) at the low dose but not the high dose.[2–4]

The IARC has determined that there is limited evidence for the carcinogenicity of BHT in experimental animals.[5]

BHT has given primarily negative results in a large number of in vivo and in vitro genotoxic assays.[1]

No significant reproductive effects were observed in three-generation toxicity studies in mice administered up to 0.4% in the diet.[6]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 2,6-di-*tert*-butyl-*p*-cresol is 2 mg/m^3.

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DIBUTYL PHENYL PHOSPHATE

CAS: 2528-36-1

$C_{14}H_{23}PO_4$

Synonyms: DBPP; phosphoric acid, dibutyl phenyl ester

Physical Form. Slightly yellow liquid

Uses. Component in hydraulic fluids

Exposure. Inhalation; skin absorption

Toxicology. Dibutyl phenyl phosphate (DBPP) has caused skin irritation in humans after repeated or prolonged contact.

Skydrol 500B-4 fire-resistant hydraulic fluid, a proprietary phosphate ester mixture composed principally of DBPP and tributyl phosphate, was evaluated in an inhalation study.[1] Rats were exposed to respirable levels of 5, 100, and 300 mg/m^3 for 6 hours/day, 5 days/week. After 6 weeks of exposure, 10 rats/sex/group were euthanized and assessed for indications of toxicity. Another 15 rats/sex/group were studied after a total of 13 weeks of exposure. The only clinical sign of toxicity was a reddish nasal discharge with accompanying oral salivation in mid- and high-exposure animals of both sexes, indicative of an irritant response. Reduced body weights, increased liver weights, and decreased erythrocyte counts, hemoglobin levels, and hematocrit values were observed in high-exposure female rats after 13 weeks of Skydrol exposure. High-exposure male rats also had increased liver weights and decreased hematocrit values after 13 weeks.

DBPP was administered to male and female rats in their diets in separate subchronic (91 day) and two-generation reproduction studies.[2] Dose levels were 5, 50, and 250 mg/kg/day in both studies. In the reproduction study, cross-fostering was performed between some high-exposure and control litter offspring and dams after a second mating of F_0 animals. Compared with control animals, body weights were consistently lower in high-exposure adult animals in both studies. High-exposure rats in the subchronic study had decreased erythrocyte counts and hematocrit and hemoglobin levels. They also had increased liver weights. In the reproduction study, mating and fertility indices were comparable among the parental animals in both generations, but survivability among high-exposure pups reared by control dams appeared to be decreased. Urinary bladder histopathologic changes, consisting of mononuclear cell infiltration and transitional epithelial hyperplasia, were noted in mid- and high-exposure rats from both studies. The no observable adverse effect level in both of these studies was 5 mg/kg/day.

DBPP was tested for its potential to cause organophosphorus compound-induced delayed neurotoxicity (OPIDN) in the adult hen.[3] The acute oral LD_{50} of DBPP was estimated to be 1,500 mg/kg and was used as a test dose. Hens were given two doses of DBPP 21 days apart and killed 21 days after the second dose. None of the hens given DBPP exhibited nerve damage or clinical signs that were different from untreated control animals. The results suggest that DBPP is unlikely to cause OPIDN with any single sublethal dose.

DBPP is not considered to be a primary irritant or a sensitizing agent based on patch testing of 50 human volunteers.[4] Repeated or prolonged contact with the skin has caused drying and cracking of exposed skin.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 0.3 ppm (3.5 mg/m^3) with a notation for skin absorption.

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DIBUTYL PHOSPHATE
CAS: 107-66-4

$(n\text{-}C_4H_9O)_2(OH)PO$

Synonyms: Dibutyl hydrogen phosphate; di-*n*-butyl phosphate

Physical Form. Pale amber liquid

Uses. Organic catalyst; antifoaming agent

Exposure. Inhalation

Toxicology. Dibutyl phosphate is an irritant of the eyes and mucous membranes.

Data on effects in humans are sparse; workers exposed to unspecified concentrations of vapor complained of respiratory irritation and headache.[1] It is a moderately strong acid and could be expected to be irritating on contact.

In rats, the oral LD_{50} is 3.2 g/kg.[2] Pregnant rats orally treated with dibutyl phosphate at 250, 500, or 1000 mg/kg on days 7–17 of gestation failed to show any evidence of maternal and fetal toxicities including teratogenic effects.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for dibutyl phosphate is 1 ppm (8.6 mg/m^3) with a short-term excursion limit of 2 ppm (17 mg/m^3).

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DIBUTYL PHTHALATE
CAS: 84-74-2

$C_{16}H_{22}O_4$

Synonyms: DBP; butyl phthalate; 1,2-benzenedicarboxylic acid dibutyl ester; phthalic acid dibutyl ester

Physical Form. Colorless or slightly colored oily liquid

Uses. Plasticizer in the production of polymer products; in cosmetics; manometer fluid; insect repellant

Exposure. Inhalation; ingestion

Toxicology. Dibutyl phthalate (DBP) is of low-order acute toxicity; reproductive and developmental effects have been reported in animal studies.

A chemical worker who accidentally swallowed 1 g (about 140 mg/kg) developed nausea, dizziness, headache, pain and irritation in the eyes, conjunctivitis, and toxic nephritis. He recovered completely after 2 weeks.[1]

There were no positive reactions to 5% DBP among 53 subjects given a 48-hour closed-patch test.[2] Cosmetic formulations containing up to 9% DBP ranged from nonirritating to slightly irritating in various patch test procedures. Sensitization and photosensitization did not occur.[3]

The single-dose oral LD_{50} has been estimated to be between 20,000 and 25,000 mg/kg for the rat, with some deaths occurring at 10,000 mg/kg.[4] Signs of acute toxicity in animals include depression of activity, labored breathing, and lack of coordination.[5] Rats exposed to concentrations as low as 0.5 mg/m^3 of DBP mist for 6 hours per day for 6 months had smaller weight gains and greater brain and lung weights than controls.[6] At 50 mg/m^3, the effects were more pronounced. In some rodent studies DBP exposure induced hepatomegaly and hepatic peroxisomes.[5,7] (It has been noted that studies with nonhuman primates have shown no similar hepatic effects with phthalate esters, suggesting that humans may not be sensitive to the hepatic effects of peroxisome proliferators.[7])

Undiluted DBP instilled in rabbit eyes caused no observable irritation up to 48 hours after instillation.[8]

Reduced testes weights and histologic evidence of testicular injury were found in rats and guinea pigs but not hamsters or mice fed 2 g/kg/day DBP for 10 days, indicating a species-specific response.[9] The basis of this species variation may be related to species differences in the ability to conjugate monobutyl phthalate, the primary metabolite of DBP, with glucuronic acid.[7]

In a continuous breeding study, mice given 1.0% DBP in their diets for 7 days before and during a 98-day cohabitation period had significant reproductive effects, including a reduction in the numbers of litters per pair and in the proportion of pups born alive.[10] Reduced fertility in males is related to testicular atrophy and seminiferous tubule damage.

Oral administration of DBP in pregnant animals causes a number of developmental effects including an increased number of resorptions, increased fetal deaths, decreased fetal weights, neural tube defects, cleft palate, skeletal abnormalities, and altered reproductive development in the offspring.[11–14] Fetotoxic effects occur in the absence of maternal toxicity. Teratogenic effects occur at high doses, and susceptibility to teratogenesis varies with developmental stage and period of administration. Doses causing developmental toxicity are thought to far exceed any reasonable human exposure conditions.[15]

Carcinogenesis was not observed in 18-month or longer feeding studies in rats.[3] DBP was not mutagenic in bacterial assays but did induce mutations in mouse lymphoma cells.[16] After *in vivo* administration to mice there was no increase in micronucleated erythrocytes.[16]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 5 mg/m^3.

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DICHLOROACETYLENE

CAS: 7572-29-4

Cl_2C_2

Synonyms: Acetylene, dichloro; dichloroethyne

Physical Form. Liquid

Uses/Sources. By-product in synthesis of vinylidene chloride; decomposition product of trichloroethylene under alkaline conditions

Exposure. Inhalation

Toxicology. Dichloroacetylene is a neurotoxin; it is carcinogenic in experimental animals.

Exposure of humans to dichloroacetylene in a variety of settings has caused headache, dizziness, nausea, vomiting, eye irritation, mucous membrane irritation, and neurological disorders, manifested as paresis and neuralgia in several cranial and cervical nerves.[1–5] In some cases the cranial nerve involvement persisted for several days to years. Extreme nausea occurred among individuals exposed to levels as low as 0.5–1.0 ppm.[3] In an early report two deaths occurred several days after dichloroacetylene exposure; autopsy revealed cerebral edema.[4]

After a single exposure of rabbits to 17 ppm for 6 hours, the sensory trigeminal nucleus was severely affected.[6] Other effects included tubular and focal necrosis in the collecting tubules of the kidney and fatty degeneration of the liver.[6,7]

In a carcinogenicity inhalation study, rats and mice were exposed to 9 ppm 6 hours/day, 1 day/week for 12 months; 2 ppm 6 hours/day, 1 day/week for 18 months; or 2 ppm 6 hours/day, 2 days/week for 18 months.[8] There was a significant increase in cystic kidney tumors in all exposed animals. Male mice were the most susceptible, with kidney tumors in 90% of exposed animals. Female rats showed an excess of malignant lymphomas.

The selective renal carcinogenicity of dichloroacetylene may be due to a bioactivation mechanism that involves glutathione *S*-conjugate formation, translocation to the kidneys, and subsequent renal metabolism to yield reactive electrophiles presumably responsible for carcinogenicity.[9]

The IARC stated that there is limited evidence for the carcinogenicity of dichloroacetylene in experimental animals and that dichloroacetylene is not classifiable as to its carcinogenicity to humans.[10]

The 2003 ACGIH ceiling-threshold limit value (C-TLV) for dichloroacetylene is 0.1 ppm (0.39 mg/m^3) with an A3-animal carcinogen designation.

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o-DICHLOROBENZENE

CAS: 95-50-1

$C_6H_4Cl_2$

Synonyms: 1,2-Dichlorobenzene; dichlorobenzol; dichloricide

Physical Form. Clear liquid

Uses. Organic synthesis (primarily 3,4-dichloroaniline); solvent; insecticide; dye manufacture

Exposure. Inhalation

Toxicology. *o*-Dichlorobenzene is a skin and eye irritant. At high doses, it causes central nervous system depression and liver and kidney damage in animals. Heavy exposure is expected to produce the same effects in humans.

In humans, eye irritation is not usually evident below 20 ppm but becomes noticeable at 25–30 ppm and painful to some at 60–100 ppm if exposures are for more than a few minutes duration.[1] Some acclimation may occur but not to a great extent. Workers exposed to concentrations ranging from 1 to 44 ppm and averaging 15 ppm showed no indication of injury or of untoward hematologic effect.[2] Accidental exposure of 26 subjects to unspecified levels 8 hours/day for 4 days caused eye, nose, and throat irritation.[3] Ten of the 26 subjects reported dizziness, severe headache, fatigue, and nausea. Chromosome studies showed significant alterations in the leukocytes of exposed workers, which appeared reversible 6 months later.

The liquid left on the skin may produce blistering, and later the area may become pigmented.[2] Sensitization dermatitis has been reported.[2]

Rats died from exposure to 977 ppm for 7 hours but survived when exposed for only 2 hours; animals survived exposure to 539 ppm for 3 hours but at necropsy showed marked centrilobular necrosis of the liver, as well as cloudy swelling of the tubular epithelium of the

kidney.[2] During exposure rats exhibited drowsiness, unsteadiness, eye irritation, difficulty in breathing, and anesthesia. Several species of animals exposed for periods of 6 or 7 months to 93 ppm for 7 hours daily showed no adverse effects.[2]

Studies with male F344 rats have shown that *o*-dichlorobenzene was more toxic to the liver and kidneys than the *meta*- and *para*-isomers after a single administration.[4] In addition to isomer specificity, strain-specific differential toxicity has also been demonstrated, with Sprague-Dawley rats being relatively resistant to the acute hepatic toxicity of *o*-dichlorobenzene.[5]

Repeated dermal application to rats was fatal.[6] The liquid instilled in the rabbit eye produced apparent distress and slight conjunctival irritation.[2]

There was no evidence of carcinogenicity in rats or mice receiving 60 or 120 mg/kg by gavage 5 times per week for 2 years.[7] The IARC has determined that there is evidence suggesting lack of carcinogenicity of *o*-dichlorobenzene in experimental animals and that there is inadequate evidence for carcinogenicity in humans.[8]

In *in vivo* genotoxic assays *o*-dichlorobenzene induced micronuclei in the bone marrow of mice and was found to bind covalently to DNA, RNA, and proteins.[8] Furthermore, a significant and persistent increase in chromosomal aberrations was observed in the peripheral blood of accidentally exposed workers.

No developmental toxicity was evident in rats or rabbits exposed during gestation by inhalation to concentrations up to 400 ppm.[9]

The odor of *o*-dichlorobenzene is perceptible to most people at 2–4 ppm.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for *o*-dichlorobenzene is 25 ppm (150 mg/m^3) with a short-term excursion limit of 50 ppm (301 mg/m^3).

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***p*-DICHLOROBENZENE**

CAS: 106-46-7

$C_6H_4Cl_2$

Synonyms: 1,4-Dichlorobenzene; *p*-chlorophenyl chloride; paracide

Physical Form. Colorless or white crystals

Uses. Disinfectant and deodorant; chemical intermediate; moth control

Exposure. Inhalation

Toxicology. *p*-Dichlorobenzene vapor is an irritant of the eyes and upper respiratory tract and is toxic to the liver. It is carcinogenic in experimental animals.

In five cases of intoxication by inhalation from household or occupational exposure to *p*-dichlorobenzene used as a mothproofing agent, one person with only moderate exposure suffered severe headache, periorbital swelling, and profuse rhinitis, which subsided 24 hours after cessation of exposure.[1] The other four persons who had more prolonged and heavy exposure developed anorexia, nausea, vomiting, weight loss, and hepatic necrosis with jaundice; two died, and another developed cirrhosis. Although these five cases were temporarily associated with known exposure to *p*-dichlorobenzene in four different settings, it is unclear how thoroughly other potential causes for these findings were excluded.

In 58 workers exposed for an average of 4.8 years (range 8 months to 25 years) to *p*-dichlorobenzene at levels of 10–725 ppm, there was no evidence of hematologic effects despite the structural similarity to benzene, a potent bone marrow depressant. Painful irritation of the eyes and nose was noted at levels between 50 and 80 ppm, and pain was severe at 160 ppm.

Solid particles of *p*-dichlorobenzene in the human eye cause pain.[2] The solid material produces a burning sensation when held in contact with the skin, but the resulting irritation is slight; warm fumes or strong solutions of *p*-dichlorobenzene may irritate the intact skin slightly on prolonged or repeated contact.[2,3] A case of allergic purpura induced by *p*-dichlorobenzene has been reported.[4]

In a study of workers engaged in synthesizing or otherwise handling *p*-dichlorobenzene, it was concluded that urinary excretion of 2,5-dichlorophenol (a metabolite of *p*-dichlorobenzene) can serve as an index of exposure.[5]

Administration of *p*-dichlorobenzene to rats for 13 weeks caused renal tubular cell degeneration in males receiving 300 mg/kg or more; in mice hepatocellular degeneration was observed in both sexes at doses above 600 mg/kg, but renal damage did not occur at doses up to 1800 mg/kg for 13 weeks.[6]

In male rats given *p*-dichlorobenzene by gavage at 150 or 300 mg/kg for 2 years, there was a significant dose-related increased incidence of tubular cell adenocarcinomas of the kidney; no excess was observed in female rats or in either sex of mice.[6] It has been proposed that *p*-dichlorobenzene causes an increase in protein droplet formation in the kidney of male rats leading to cell death and subsequent cell proliferation that may play a critical role in the carcinogenesis process.[7] The presence of α_{2u}-globulin is essential for the development of this syndrome, and rats that do not synthesize this protein, such as the NCI-Black-Reiter, do not develop renal disease after exposure.[8] Furthermore, the mechanism is not considered relevant to humans.[9]

p-Dichlorobenzene also increased the incidence of hepatocellular adenomas and carcinomas, as well as nonneoplastic liver lesions in male and female mice dosed at 600 mg/kg for 2 years. The National Toxicology Program study concluded that there was clear evidence of carcinogenicity for male rats and for both male and female mice.[6]

In a long-term inhalation study in male and female rats and female mice, there was no evidence of carcinogenicity after exposure at 75 or 500 ppm for 5 hours/day, 5 days/week for 76 weeks (rats) or 57 weeks (mice).[10] Although there has been a report of five cases of blood dyscrasias, including leukemia, among individuals exposed to *o*- or *p*-dichlorobenzene, the IARC has concluded that the human data are inadequate to evaluate the carcinogenicity of dichlorobenzenes but the *para*-isomer is possibly carcinogenic to humans.[9]

Exposure of rats to *p*-dichlorobenzene vapor concentrations up to 538 ppm for 2 generations resulted in F_0 and F_1 adult toxicity, including reduced body weights in both sexes and kidney effects (hyaline droplet neuropathy and renal tubular cell hyperplasia) in males, but

no effects on reproduction. Postnatal toxicity in F_1 and F_2 litters was observed at the high dose.[11]

p-Dichlorobenzene is not genotoxic in both *in vivo* and *in vitro* assay systems.[12]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for *p*-dichlorobenzene is 10 ppm (60 mg/m^3) with an A3-animal carcinogen designation.

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3,3′-DICHLOROBENZIDINE
CAS: 91-94-1

$C_{12}H_{10}Cl_2N_2$

Synonyms: DCB; 4,4′-diamino-3,3′-dichlorobiphenyl; *o*, *o*′-dichlorobenzidine

Physical Form. Colorless crystals

Uses. Used in the production of yellow and red pigments for the printing ink, textile, paper, paint, rubber, plastic, and related industries

Exposure. Inhalation; skin absorption

Toxicology. 3,3′-Dichlorobenzidine (DCB) is carcinogenic in several animal species.

The acute LD_{50} of DCB in rats has been estimated to be 7100 mg/kg for the free base and 3800 mg/kg for the dihydrochloride salt.[1] Considering these high LD_{50} values, acute lethality in man after oral exposure is not expected to be very likely.[2]

Dermatitis was cited as the only verified health problem encountered by workers in contact with DCB at a DCB manufacturing plant.[1] Applied to the skin of rabbits DCB dihydrochloride caused no discernable reaction; instilled in the rabbit eye 20 mg (as 0.1 ml of 20% corn oil suspension) produced erythema, pus, and corneal opacity. No effects were reported when 100 mg of the free base was placed in rabbit eyes.

Existing animal data shows that DCB induces tumors at a variety of sites in several animal species.[2]

Of 111 rats given 20 mg of DCB by injection or gastric intubation 6 days/week for 10–20 months, 17 had tumors of the zymbal gland (a specialized sebaceous gland adjacent to the external ear canal), 13 had mammary tumors, 8 had skin tumors, 5 had malignant lymphomas, 3 had urinary bladder tumors, 3 had salivary gland tumors, and 2 had intestinal tumors; no tumors were found in 130 control rats.[3]

Of 44 male rats fed 1000 ppm for 12 months, 9 developed granulocytic leukemia and 8 developed zymbal gland tumors; mammary gland tumors were found in rats of both sexes.[4]

In hamsters, 0.3% DCB in the diet produced transitional cell carcinomas of the bladder and some liver cell tumors.[5] Liver tumors were also found in mice exposed to DCB.[3] Female dogs fed 8 mg/kg/day for a period of 6–7 years had hepatocellular carcinomas and papillary transitional cell carcinomas of the urinary bladder; tumors were absent in untreated controls.[6]

Four of four beagle dogs administered DCB by capsule for 7 years had bladder papillary transitional cell carcinoma and three had liver carcinoma; untreated controls had no liver or bladder neoplasms.[2]

There are no reports in which DCB exposure has been conclusively linked to cancer in humans.[1] However, DCB exposure may have been a factor in some cases of bladder cancer attributed to benzidine, because these substances are often produced together, and DCB also bears a close structural similarity to benzidine.[7] A British plant handling 3,3′-dichlorobenzidine had a site incidence of bladder cancer 2–3 times that predicted for males employed between 1972 and 1987; the cause of this apparent excess could not be identified because of potential exposure to many other chemicals.[8] Since that time, the incidence of bladder cancer appears to have fallen to background levels and has been attributed to an alteration in hygiene standards.[8]

Studies in several test systems have shown DCB to be genotoxic *in vitro* and *in vivo* and suggest that this effect most likely mediates the carcinogenicity of the chemical.[2] *In vitro*, DCB has induced sister chromatid exchanges, unscheduled DNA synthesis, and positive responses in bacterial *Salmonella* assays; *in vivo* DCB induced micronuclei in polychromatic erythrocytes in male mice and fetuses.[9–12]

Because of demonstrated potent carcinogenicity in multiple animal species, evidence of genotoxicity, and structural relationship to the known bladder carcinogen benzidine, DCB should be regarded as a probable human carcinogen and exposure by any route should be avoided.[2]

3,3′-Dichlorobenzidene has no threshold limit value (TLV) exposure limit and is classified as an A3, confirmed animal carcinogen with unknown relevance to humans, and a notation for skin absorption.

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DICHLORODIFLUOROMETHANE

CAS: 75-71-8

CCl_2F_2

Synonyms: Freon 12; Refrigerant 12; Isotron; Halon; Genetron 12; Frigen 12

Physical Form. Colorless gas

Uses. Refrigerant; aerosol propellant; plastics; blowing agent

Exposure. Inhalation

Toxicology. Dichlorodifluoromethane causes central nervous system depression at very high concentrations.

Volunteers exposed to 200,000 ppm for a short time experienced significant eye irritation as well as central nervous system effects.[1] The effects disappeared within minutes after return to fresh air. Exposure at 110,000 ppm for 11 minutes caused a marked decrease in consciousness, amnesia, and cardiac arrhythmias; at 40,000 ppm for 80 minutes, there was generalized paresthesia, tinnitus, apprehension, and slurred speech.[1] Two volunteers exposed to 10,000 ppm for 2.5 hours showed slight psychomotor impairment.[2]

Chronic exposure of volunteers to 1000 ppm 8 hours/day for 17 days caused no subjective symptoms, no cardiac abnormalities, and no pulmonary function abnormalities.[3]

Sniffing aerosols of fluorochlorinated hydrocarbons has caused sudden death from cardiac arrest probably due to cardiac arrhythmias from sensitization of the myocardium to epinephrine.[4]

Refrigerator repairers exposed to dichlorodifluoromethane and chlorodifluoromethane (peak exposures 1300–10,000 ppm) showed no clear connection between exposure and cardiac arrhythmia as determined by ambulatory electrocardiograms.[5] The investigators suggest that subjects with compromised cardiac function may be more susceptible to the arrhythmogenic potential of fluorocarbons but that in general, a higher exposure concentration, on the order of 100,000–200,000 ppm may be necessary to provoke cardiac arrhythmias.

In rats, when dichlorodifluoromethane was administered at various concentrations with 20% oxygen for 30 minutes, the following effects were observed: 200,000 ppm, no observable effects; 300,000 ppm, muscular twitching and tremor; 800,000 ppm, coma, corneal reflexes absent; 800,000 ppm for 4 and 6 hours was not lethal and the animals suffered no permanent effects.[6] In a recent report 3- to 20-minute exposure of rats to concentrations of 140,000–470,000 ppm induced in a dose-dependent manner acute neurobehavioral effects ranging from operant performance deficits, to motor and equilibrium deficits, to anesthesia with occasional convulsions.[7]

Chronic exposure of rats 6 hours/day for

90 days at 10,000 ppm and of dogs at 5000 ppm caused no adverse effects as determined by observation, clinical tests, or histologic examination.[8]

A variety of reproductive, carcinogenic, and mutagenic studies have found no significant effects.[1,9]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for dichlorodifluoromethane is 1000 ppm (4950 mg/m^3).

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1,3-DICHLORO-5,5-DIMETHYLHYDANTOIN

CAS: 118-52-5

$C_5H_6Cl_2O_2N_2$

Synonyms: Dactin; Halane; DCDMH

Physical Form. White powder

Uses. Chlorinating agent; disinfectant; laundry bleach; in water treatment; intermediate for drugs; insecticides; polymerization catalyst

Exposure. Inhalation

Toxicology. 1,3-Dichloro-5,5-dimethylhydantoin powder in contact with water yields hypochlorous acid, which is an irritant of the eyes and mucous membranes.

There is a single report of a worker exposed to concentrations exceeding 0.2 mg/m^3 experiencing cough and chest discomfort.[1]

The LD_{50} for rats when administered orally as a 10% aqueous suspension was 542 mg/kg; at necropsy, gastrointestinal hemorrhages were found.

The substance was mutagenic in *Drosophila* testing.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 1,3-dichloro-5,5-dimethylhydantoin is 0.2 mg/m^3 with a short-term excursion limit (TLV-STEL) of 0.4 mg/m^3.

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1,1-DICHLOROETHANE
CAS: 75-34-3

CH_3CHCl_2

Synonyms: Ethylidene dichloride

Physical Form. Colorless liquid

Uses. Cleansing agent; degreaser; solvent for plastics, oils, and fats; grain fumigant; chemical intermediate; formerly used as an anesthetic

Exposure. Inhalation

Toxicology. At high concentrations 1,1-dichloroethane causes central nervous system depression.

There have been no reported cases of human overexposure by inhalation. In the past, 1,1-dichloroethane was used as an anesthetic at levels of approximately 25,000 ppm.[1] Use was discontinued when it was discovered that cardiac arrhythmias might be induced. Cardiovascular toxicity has not been reported in animals after exposure.

Rats survived exposure to 32,000 ppm for 30 minutes but died after 2.5 hours of exposure.[2] The most consistent findings in animals were pathologic changes in the kidney and liver at exposure to concentrations of above 8000 ppm for up to 7 hours, and at much higher concentrations, near 64,000 ppm, there was damage to the lungs as well. No adverse clinical effects were noted in rats, rabbits, or guinea pigs exposed to 1000 ppm for 13 weeks, after a prior 13-week exposure to 500 ppm.[3] Under the same conditions renal injury was apparent in cats, as evidenced by increased serum urea and creatinine levels.

No histopathological alterations were noted in the liver, kidneys, or lungs of male mice that ingested up to 2500 mg/liter 1,1-dichloroethane in drinking water for 52 weeks.[4]

A significant increase in endometrial stromal polyps, a benign neoplasm, occurred in female mice administered up to 3.3 g/kg/day 1,1-dichloroethane by gavage for 78 weeks.[5] There was also a dose-related trend for the incidence of hemangiosarcomas and mammary adenocarcinomas in female rats and hepatocellular carcinoma in male mice. High mortality in all animal groups obscured results. The National Cancer Institute determined that there was no conclusive evidence for carcinogenicity, but 1,1-dichloroethane should be treated with caution by analogy to other chloroethanes shown to be carcinogenic in laboratory animals.[5,6]

The liquid applied to the intact or abraded skin of rabbits produced slight edema and very slight necrosis after the sixth of 10 daily applications. When the liquid was instilled in the eyes of rabbits, there was immediate, moderate conjunctival irritation and swelling, which subsided within a week.[2]

Although the liquid may be absorbed through the skin, it is apparently not absorbed in amounts sufficient to produce systemic injury.

Exposure of rats to 6000 ppm, 7 hours/day, on days 6–15 of gestation was associated with an increased incidence of delayed ossification of sternebrae.[7] Maternal toxicity was limited to decreased weight gain.

1,1-Dichloroethane did not act as a tumor initiator or as a complete carcinogen in a rat liver foci assay.[8] Positive results were seen for tumor promotion in the presence of an initiator. It has produced both positive and negative results in *Salmonella* assays.

Odor cannot be relied on to provide warning of overexposure.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 1,1-dichloroethane is 100 ppm (405 mg/m^3).

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1,2-DICHLOROETHYLENE

CAS: 540-59-0

cis-1,2-Dichloroethylene
CAS: 156-59-2

trans-1,2-Dichloroethylene
CAS: 156-60-5

$C_2H_2Cl_2$

Synonyms: Acetylene dichloride; dichloroacetylene; 1,2-dichloroethene

Physical Form. Colorless liquid

Uses. 1,2-Dichloroethylene is used as a solvent for organic materials and as an intermediate in the synthesis of other chlorinated compounds; it may be produced by the chlorination of acetylene but is often produced as a by-product in the manufacture of other chlorinated compounds.

Exposure. Inhalation; ingestion; skin

Toxicology. 1,2-Dichloroethylene causes central nervous system depression at high concentrations; liver, lung, and heart damage have been reported in animal studies.

1,2-Dichloroethylene is a mixture of two geometric isomers, *cis* and *trans*; the proportion of the *cis* isomer to the *trans* isomer varies from mixture to mixture, depending on the manufacturer's specifications. The properties of the mixture are expected to be similar to those of the individual isomers.

There has been only one report of industrial poisoning, a fatality caused by very high vapor inhalation in a small enclosure.[1] The isomeric concentration of the vapor was not reported, nor were the level and duration of the exposure or symptoms of toxicity. In another early report, exposure to the *trans* isomer at 2200 ppm caused nausea, drowsiness, fatigue, vertigo, and increased intracranial pressure in two human subjects.[1]

In mice, the LC_{50} for a single 6-hour inhalation exposure was 22,000 ppm for the *trans* isomer.[2]

A very limited rat study reported the following after inhalation of the *trans* isomer: 8 hours at 3000 ppm was associated with pathologic changes in the heart, described as fibrous swelling of the myocardium and hyperemia; at 1000 ppm for 1 day, pathologic changes in the lungs included pulmonary capillary hyperemia, alveolar septal distension, and pulmonary edema; hematologic effects at this level included a reduction in the number of circulating leukocytes and erythrocytes; pathologic changes in the liver consisted of lipid accumulation and fatty degeneration following an 8-hour exposure at 200 ppm.[3]

In another report, the acute oral LD_{50} for *trans*-1,2-dichloroethylene administered by gavage was 8000 mg/kg for male rats and 9900 mg/kg for female rats.[4] Signs associated with lethal doses included those of pulmonary hyperemia and central nervous system depression including ataxia, loss of righting reflex, and depressed respiration.

Rats receiving approximate daily doses of 500, 1500, or 3000 mg of *trans*-1,2-dichloroethylene in their drinking water for 90 days had no significant adverse effects as deter-

mined by hematologic, serological, or urinary parameters.[4] There were no compound-related gross or histologic effects, although there were dose-dependent increases in kidney weights and ratios in treated females. The authors concluded that toxicity from exposure to *trans*-1,2-dichloroethylene in drinking water at 1 µg/l is low and probably does not constitute a serious health hazard. It should be noted, however, that adequate information is not available on possible chronic effects.

Administered by inhalation to rats 6 hours/day on days 7–16 of gestation, 12,000 ppm *trans*-1,2-dichloroethylene caused fetal toxicity in the form of reduced fetal weights; overt maternal toxicity was also observed at this dose and was expressed as a significant reduction in weight gain and in feed consumption.[5] Increased incidences of alopecia, lethargy, salivation, and ocular irritation were also observed in the treated dams. *trans*-1,2-Dichloroethylene was not considered to be uniquely toxic to the rat conceptus.

Mild burning of the eyes after acute exposure to either *trans*-1,2-dichloroethylene vapor or aerosol was reported by two subjects in a 1936 self-experimentation study. However, dichloroethylene has been used in combination with ether as a general anesthetic in at least 2000 cases with no evidence of ocular toxicity.[6]

In genotoxic assays the *cis* isomer induced chromosomal aberrations in mouse bone marrow cells after intraperitoneal injections.[7] Neither isomer was mutagenic in bacterial assays, nor did they produce chromosomal aberrations or sister chromatid exchanges in mammalian cells *in vitro*.[7]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 1,2-dichloroethylene is 200 ppm (793 mg/m^3).

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DICHLOROETHYL ETHER
CAS: 111-44-4

$C_4H_8Cl_2O$

Synonyms: bis(2-Chloroethyl) ether; BCEE; chlorex; 1-chloro-2-(β-chloroethoxy)ethane

Physical Form. Colorless liquid

Uses. Solvent for resins, wax, oils, turpentine; insecticide

Exposure. Inhalation; skin absorption

Toxicology. Dichloroethyl ether is a severe respiratory and eye irritant; high levels cause narcosis in animals, and severe exposure is expected to cause the same effects in humans. The inhalation hazard is limited by its relatively low volatility; skin absorption is more hazardous.

In experimental human exposure, 500 ppm caused intolerable irritation to the eyes and

nose with cough, lacrimation, and nausea; at 100 ppm there was some irritation, whereas at 35 ppm there were no effects.[1]

In guinea pigs, concentrations of 500–1000 ppm were fatal after 5–8 hours of exposure; effects were immediate lacrimation and nasal irritation, followed by unsteadiness and coma; autopsy findings were pulmonary edema, pulmonary hemorrhage, and occasional complete consolidation.[1] Fatalities occurred when 300 mg/kg was applied dermally to guinea pigs as a pure liquid for 24 hours.

Repeated oral administration of 300 mg/kg daily to both sexes of two strains of mice for 80 weeks induced a significant elevated incidence of tumors, mostly hepatomas.[2] Four other limited studies in rats and mice using oral gavage, subcutaneous or intraperitoneal injection, and skin painting failed to confirm these findings.[3] The IARC has determined that there is limited evidence in animals and inadequate evidence in humans for the carcinogenicity of dichloroethyl ether.[4]

In general, positive results have been obtained in mutagenicity studies.[3]

Skin application to animals resulted in erythema and necrosis, and application to the eye resulted in corneal necrosis.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for dichloroethyl ether is 5 ppm (29 mg/m^3) with a short-term excursion limit of 10 ppm (58 mg/m^3) and a notation for skin absorption.

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DICHLOROFLUOROMETHANE

CAS: 75-43-4

$CHFCl_2$

Synonyms: Dichloromonofluoromethane; fluorodichloromethane; Freon 21; Refrigerant 21; FC-21

Physical Form. Colorless gas

Uses. Refrigerant gas; propellant gas

Exposure. Inhalation

Toxicology. Dichlorofluoromethane at high concentrations causes asphyxia and cardiac sensitization in animals; repeated or prolonged exposure to lower concentrations results in liver damage.

Acute or chronic effects from human exposure have not been reported. In liquid form this substance may cause frostbite.

Exposure of guinea pigs to 400,000 ppm with 18% oxygen was fatal, and death was preceded by dyspnea, tremor, and convulsive movements, but not narcosis.[1] Animals died at 102,000 ppm with congested lungs, kidneys, and liver but survived 52,000 ppm, showing tremor, incoordination, and irregular breathing.[1]

In rats, 90 day exposures to 1000 and 5000 ppm caused bilateral hair loss, extensive liver damage, and excessive mortality.[2] The chronic toxicity of dichlorofluoromethane appears to be quite different from difluorinated methanes and more similar to the hepatotoxin chloroform.[3] In mice 100,000 ppm induced arrhythmias and sensitized the heart to epinephrine.

After exposure at 10,000 ppm on days 6 through 15 of gestation, 15 of 25 pregnant female rats had no viable fetuses or implantation sites on the uterine wall.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for dichlorofluoromethane is 10 ppm (42 mg/m^3).

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1,1-DICHLORO-1-NITROETHANE
CAS: 594-72-9

$CH_3CCl_2NO_2$

Synonyms: Ethide

Physical Form. Colorless liquid

Uses. Fumigant insecticide

Exposure. Inhalation

Toxicology. 1,1-Dichloro-1-nitroethane is a pulmonary, skin, and eye irritant in animals; it is expected that severe exposure will cause the same effects in humans.

No effects in humans have been reported.

Exposure of rabbits to 2500 ppm for 40 minutes was fatal, but exposure to 170 ppm for 30 minutes was nonlethal; autopsy revealed pulmonary edema and hemorrhage, with damage to the heart, liver, and kidneys. At high concentrations, effects included lacrimation, increased nasal secretion, sneezing, cough, pulmonary rales, and weakness. Application of the liquid to the skin of rabbits caused irritation and edema.[1,2] This compound is considerably more irritating to skin and mucous membranes of animals than 1-chloro-1-nitropropane and exhibits greater toxicity by inhalation.[3]

In *Salmonella typhimurium* assays 1,1-dichloro-1-nitroethane was mutagenic in the TA100 and TA97 stains but not in TA1535 or TA98.[4]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 1,1-dichloro-1-nitroethane is 2 ppm (12 mg/m^3).

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2,4-DICHLOROPHENOL
CAS: 120-83-2

$C_6H_3OHCl_2$

Synonyms: DCP; 2,4-DCP; 1,3-dichloro-4-hydroxybenzene; 2,4-dichlorophenic acid

Physical Form. White solid

Uses. Intermediate in production of herbicidal chlorophenoxy acids such as 2,4-dichlorophenoxyacetic acid

Exposure. Inhalation

Toxicology. 2,4-Dichlorophenol (2,4-DCP) is an uncoupler of oxidative phosphorylation; toxic manifestations include central nervous system depression followed by increased respiration, hyperthermia, increased blood pressure, progressive weakness, and cyanosis.

A number of occupational fatalities have been associated with acute dermal exposure to heated liquid 2,4-DCP.[1] In one case report, an accidental death was attributed to absorption of 2,4-DCP through the skin.[2] A 33-year-old man splattered portions of his right thigh and right arm with a pure solution of 2,4-DCP while disposing of industrial waste. He washed himself without undressing, and shortly thereafter (within 20 min) he experienced a seizure and collapsed. Resuscitation efforts failed. It was determined that less than 10% of his body surface was contaminated, which resulted in blood concentrations of 24.3 mg/l. Other drugs, including ethanol, were not detected in a toxicological screen. The authors suggest that the blood level of 2,4-DCP in this case is in accordance with lethal blood concentrations of phenol that have been reported.

The oral LD_{50} in rats was 2830 mg/kg.[3] Typical effects associated with acute lethal oral doses have included restlessness and increased respiratory rate, which appear quickly, followed shortly by tremors, convulsions, dyspnea, coma, and death.[4] The primary toxic mechanism is the uncoupling of oxidative phosphorylation.[4]

In an NTP report, exposure of rats to concentrations as high as 2000 mg/kg/day in the diet for up to 13 weeks did not cause mortality; 2600 mg/kg/day did not affect survival of mice at this duration, but all mice died when exposed to 5200 mg/kg for 4 weeks.[5] Renal tubular necrosis was found in mice at the highest dose level, but no effect was seen in mice fed 2600 mg/kg/day or in rats fed 2000 mg/kg for 13 weeks.

Both erythroid and myelocytic elements of bone marrow were depleted in rats fed 500 mg/kg/day for 13 weeks.[4] Mice fed 325 mg/kg/day or more for 13 weeks had dose-related increases in hepatic necrosis.[6]

Feeding tests with rats and mice, for periods up to 103 weeks, at doses as high as 440 mg/kg/day for rats and 1300 mg/kg/day for mice showed no evidence of carcinogenic activity due to 2,4-DCP.[5]

Topical application of 0.3% dimethylbenzanthracene in benzene as an initiator followed by twice-weekly application of 20% 2,4-DCP in benzene to mice produced papillomas in 75% and carcinomas in 6% at 24 weeks; 62% had carcinomas after 39 weeks.[7] There is no evidence that 2,4-DCP acting alone induces papillomas or carcinomas.[4]

The IARC has determined that there is evidence suggesting lack of carcinogenicity of 2,4-DCP in experimental animals.[8]

Female rats were given 3, 30, or 300 ppm in drinking water from 3 weeks of age through breeding and parturition (Group 1) or for 24 months (Group 2).[9] Animals from Group 1 were bred to untreated males at 90 days of age; litter sizes at 300 ppm were significantly smaller than controls. The percentage of stillborn pups increased at all doses. In Group 2, liver weights were significantly increased in the 300 ppm group. Spleen weights were higher and thymuses were smaller than in the control group. Delayed-type hypersensitivity responses in treated animals were significantly suppressed compared with controls. Tumor incidence, latency, or type was not different from controls.

In mammalian cells *in vitro* 2,4-DCP produced chromosomal aberrations and induced unscheduled DNA synthesis; it was negative for sister chromatid exchange *in vivo* and was mostly negative in bacterial assays.[3]

Oral exposure of pregnant rats to 750 mg/kg/day for 10 gestational days induced slightly decreased fetal weight, delayed ossification of sternal and vertebral arches, and some early embryonic deaths.[10] Maternal deaths also occurred at this dose, indicating that 2,4-DCP was not selectively toxic to embryos or fetuses. No effects were noted in dams or offspring exposed at 375 mg/kg/day.

A threshold limit value (TLV) has not been established for 2,4-dichlorophenol.

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2,4-DICHLOROPHENOXYACETIC ACID
CAS: 94-75-7

$C_8H_6Cl_2O_3$

Synonyms: 2,4-D; Hedonal; component of Agent Orange

Physical Form. Crystalline solid

Uses. Herbicide

Exposure. Inhalation; ingestion; skin absorption

Toxicology. 2,4-Dichlorophenoxyacetic acid (2,4-D) causes signs of both hypo- and hyperexcitation of the central nervous system.

One fatal case of poisoning involved a suicidal person who ingested not less than 6500 mg and experienced violent convulsions; there were no significant findings at autopsy.[1] In another fatality from suicidal ingestion of a mixture of 2,4-D and two other related herbicides, progressive hypotension, coma, tachypnea, and abdominal distension preceded death. An autopsy revealed nonspecific findings. Concentrations of 2,4-D measured in blood and urine were 520 and 670 mg/l, respectively.[2] A single dose of 3.6 g of 2,4-D administered intravenously to a patient for treatment of disseminated coccidioidomycosis caused stupor, hyporeflexia, fibrillary twitching of some muscles, and urinary incontinence; 24 hours after the dose, the patient still complained of profound muscular weakness, which subsided after an additional 24 hours.[3,4]

Contact of the material with the skin may cause dermatitis.[3,4] Dermal absorption and ingestion of aerosol droplets trapped in the nose appear to be the primary routes of entry in spraying operations.

Peripheral neuropathy has been reported to occur occasionally after exposure to 2,4-D, but more frequently after exposure to another phenoxyherbicide, 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) or its contaminants including 2,3,7,8-TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin).[5] A study of workers employed in the manufacture of 2,4-D and 2,4,5-T found a statistically significant increased frequency of mild slowing of nerve conduction velocity in the sural sensory and median motor nerves; there were no associated symptoms.[6]

Several case-control studies of soft tissue sarcoma and lymphoma have suggested an increased risk among workers exposed to phenoxyacetic acid herbicides, including 2,4-D.[7,8] In one study involving primarily 2,4-D exposure, there was an increased risk for malignant lymphoma of the non-Hodgkin type but not for soft tissue sarcomas.[9] The IARC has deemed the evidence implicating 2,4-D to be inadequate.[7] Concomitant exposure to other known carcinogenic substances and insufficient accumulation of person-years of observation are two of the primary limiting factors in establishing the risks associated with 2,4-D exposures.[10,11] Large cohort studies of agricultural and forestry workers exposed to these herbicides have not subsequently confirmed any increased incidence of malignancy.[7,12] For 878 chemical workers potentially exposed to 2,4-D at any time between 1945 and 1983, an analysis by production area, duration of exposure, and cumulative dose showed no patterns suggestive of a causal association between 2,4-D exposure and any particular cause of death.[13] Particular attention was given to deaths from brain neoplasms in this cohort, because a recent unpublished study reported an increased incidence of astrocytomas in male rats fed 45 mg/kg/day in the diet for 2 years. No brain neoplasms were observed.[13] Four additional years of mortality follow-up on this cohort through 1986 has not revealed any patterns suggestive of a causal association between 2,4-D exposure and any particular cause of death, including cancer.[14] A case-control study of Vietnam war-era veterans with soft tissue sarcoma did not find an association with potential exposure to Agent Orange (a 1:1 mixture of 2,4-D and 2,4,5-T).[15] A subsequent mortality study of these veterans did find an elevated standardized proportionate mortality ratio for soft tissue sarcoma, but it was not based on adequate numbers of deaths or adequate exposure data.[16]

A review of epidemiological studies of chlorophenoxy herbicides found no consistent or conclusive evidence linking 2,4-D to human carcinogenesis. It was further stated that, in general, animal studies, conducted under current test guidelines, have also shown no evidence of carcinogenicity supporting the results of epidemiological studies.[17]

There were no indications of genotoxic potential for 2,4-D acid, or any of its derivatives, in bacterial assays, in unscheduled DNA synthesis assay, or in mouse bone marrow micronucleus tests.[18,19]

A two- to threefold increased risk of birth defects among children of Vietnam war veterans exposed to Agent Orange has been suggested by several epidemiological studies, but these studies have been criticized on a number of grounds, including exposure assessment, outcome verification, and potential for recall bias.[20] Animal studies have not demonstrated clear-cut adverse effects of phenoxyherbicide exposure on reproductive outcomes.[20,21]

2,4-D is readily absorbed through the skin; therefore, measurements of ambient air concentrations do not necessarily reflect the total absorbed dose.[22] Immunochemical determination of 2,4-D in urine has provided effective measurement of human exposure levels.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 2,4-D is 10 mg/m^3.

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1,3-DICHLOROPROPENE
CAS: 542-75-6

$C_3H_4Cl_2$

Synonyms: 1,3-DCP; α-chloroallyl chloride; 1,3-dichloropropylene; Telone; Telone II; DD fumigants

Physical Form. Clear to amber-colored liquid

Uses. Widely used as a preplanting soil fumigant for the control of nematodes

Exposure. Inhalation; skin absorption

Toxicology. 1,3-Dichloropropene (1,3-DCP) is an irritant of the eyes, mucous membranes, and skin; exposures in animals have been associated with contact hypersensitivity and damage to the nasal tissues, lungs, liver, kidneys, and urinary bladder. It is considered to be carcinogenic to experimental animals.

A truck spill in 1985 resulted in exposure of an estimated 80 people.[1,2] Signs and symptoms were headache in six persons, mucous membrane irritation in five, dizziness in five, and chest discomfort in four. Eleven of 41 persons tested had slightly elevated SGOT and/or SGPT values. In 28 persons interviewed 12 weeks after exposure, complaints were headache in 12, abdominal discomfort in 6, chest discomfort in 5, and malaise in 5. In one case the diagnosis was pneumonia, based on persistent dyspnea and cough.

In a report of two firefighters who were simultaneously exposed at a chemical spill, lymphomas appeared simultaneously 6 years later and the individuals died within several months of each other.[3] The IARC noted that because firefighters are exposed to a large number of chemicals, the role of 1,3-dichloropropene could not be evaluated.[4,5]

Accidental ingestion of 1,3-DCP by a 27-year-old-worker resulted in gastrointestinal distress, adult respiratory distress syndrome, hematologic and hepatorenal impairment, and death within 40 hours due to multiorgan failure.[6] Initial symptoms, on hospital admittance, included acute gastrointestinal distress, sweating, tachypnea, and tachycardia. The chemical was toxicologically identified by gas chromatography, and initial blood levels were 1.13 µmol/l in blood and 0.20 µmol/l in urine.

The oral LD_{50} was 713 mg/kg in male rats and 470 mg/kg in females.[7] (LD_{50} values as low as 100 mg/kg have been reported for rats; this range in values is attributed to different rat strains and from differences in the 1,3-DCP formulations used.[8]) Exposure to 1000 ppm for 2 hours was lethal to rats, whereas brief exposure at this concentration caused severe eye irritation and loss of consciousness.[9]

Acute dermal application of dilute or full-strength DCP rapidly produced erythema and edema in rats, rabbits, and guinea pigs.[8] Delayed-type hypersensitivity reactions and contact sensitization have also been reported in guinea pigs and humans.[8]

A carcinogenicity study in rats and mice using a technical grade of 1,3-dichloropropene administered by oral gavage 3 times/week for 104 weeks produced tumors of the urinary bladder, lung, and forestomach in mice and of the liver and forestomach in rats.[10] The IARC has determined that there is sufficient evidence for animal carcinogenicity of technical-grade 1,3-dichloropropene but inadequate evidence for carcinogenicity to humans.[5]

In a subsequently published report, an inhalation carcinogenicity study with technical-grade material, rats and mice were exposed to 0, 5, 20, or 60 ppm 6 hours/day, 5 days/week for up to 2 years.[11] There were morphologic changes in the nasal tissue of rats exposed to 60 ppm and mice exposed to 20 and 60 ppm. Mice exposed to 20 or 60 ppm had hyperplasia of the epithelial lining of the urinary bladder. Rats showed no increased tumor incidence. Male mice showed an increased incidence of bronchioloalveolar adenomas in the 60 ppm group.

Rats of both sexes were exposed in an inhalation reproduction study to technical-grade 1,3-dichloropropene at 0, 10, 30, or 90 ppm for 6 hours/day, 5 days/week, for two generations.[12] There were no adverse effects on reproductive and neonatal parameters. Parental effects were focal hyperplasia and/or focal degenerative changes in the olfactory epithelium at 90 ppm.

A number of genotoxic effects have been reported for 1,3-DCP including increased DNA strand breaks, sister chromatid exchanges, and mitotic aberrations in Chinese hamster cells.[8,13] It did not induce dominant lethal mutations in the germ cells of male CD rats after inhalation of 150 ppm.[14]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 1,3-

dichloropropene is 1 ppm (4.5 mg/m^3) with a notation for skin absorption and an A3-confirmed animal carcinogen with unknown relevance to humans designation.

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2,2-DICHLOROPROPIONIC ACID

CAS: 75-99-0

CH_3CCl_2COOH

Synonyms: Dalapon; Dalzpon; Dowpon-M

Physical Form. Colorless liquid; the commercial herbicide is light tan powder

Uses. Herbicide marketed as the sodium salt or a mixture of the sodium and magnesium salts used to control grasses in a wide variety of crops and in a number of noncrop applications, such as along drainage ditches and railroads and in industrial areas.

Exposure. Inhalation

Toxicology. 2,2-Dichloropropionic acid is expected to be an irritant of the eyes, skin, and respiratory tract.

Exposure at 2–7 ppm for an unspecified time produced minimal respiratory irritation.[1] The dry powder or a concentrated solution can be irritating to the eyes or skin if not removed by washing.[2]

Acute toxicity data indicate that it has a low order of toxicity in mammals, with a range of oral LD_{50} values of 4–9 g/kg.[2] Short-term multiple-dose studies suggest that the toxicity of the compound is not cumulative. Cattle that received a 1 g/kg daily oral dose for 10 days showed some signs of toxicity but rapidly recovered when dosing ceased. Slight cloudy swelling of the convoluted tubules and hypertrophy or swelling of the glomerular cells of the kidney were the only findings in a bull calf receiving 1 g/kg/day. Dogs were dosed by gavage for an 81-day period, initially with 50 mg/kg/day, with dosages adjusted upward until the animals were receiving 1000 mg/kg/day. Vomiting ensued at this high dose level, and the study was terminated at 81 days. Except for vomiting, no other signs of toxicity were evident. Extensive hematologic and biochemical parameters were all normal, as were the organ-to-body weight ratios.

In a 97-day rat study, there were no effects in male rats fed Dalapon in the diet at levels up to 115 mg/kg/day. In female rats, there were slight, statistically significant increases in average kidney weights at the 34.6 mg/kg/day level. At 346 or 1150 mg/kg/day, both male and female rats showed growth retardation, increased liver and kidney weights, and slight histopathologic changes in the liver and kidneys.

A 1-year study was conducted with dogs that showed significant increases in the average kidney weight in animals receiving 100 mg/kg/day but not in those receiving 50 mg/kg/day. All other parameters were comparable to controls.

Significant increases were noted in the kidney weight of rats receiving 50 mg/kg/day for 2 years but not in those receiving 15 or 5 mg/kg/day. In a 2-year mouse study, increased liver weights were noted at 200 mg/kg/day in the diet. No associated lesions were noted on histologic examination of the livers. There were also increased incidences of benign lung adenomas and cystadenomas of the harderian gland in male mice fed Dalapon for 2 years. No tumors were found in rats fed Dalapon for 2 years.

In a three-generation reproduction study in rats, no reproductive effects were found in rats administered Dalapon in the diet at levels up to 3000 ppm (150 mg/kg/day). The mean weight of pups was depressed when pregnant rats received 1000 or 1500 mg/kg/day in the diet during days 6 through 15 of gestation but not when they received 500 mg/kg/day. No other effects on the fetuses were observed.

Dichloropropionic acid was not mutagenic in a variety of assays. The 2003 threshold limit value-time-weighted average (TLV-TWA) is 1 ppm (5.8 mg/m^3).

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DICHLOROTETRAFLUOROETHANE

CAS: 76-14-2

$C_2Cl_2F_4$

Synonyms: Refrigerant 114; CFC-114; Freon 114; 1,2-dichloro-1,1,2,2-tetrafluoroethane

Physical Form. Colorless gas

Uses. Refrigerant; aerosol propellant; solvent; fire extinguisher

Exposure. Inhalation

Toxicology. Dichlorotetrafluoroethane causes asphyxia at extremely high concentrations.

Although dichlorotetrafluoroethane has

not been directly implicated, sniffing aerosols of other fluorochlorinated hydrocarbons has caused sudden death due to cardiac arrest, probably a result of sensitization of the myocardium to epinephrine.[1] The liquid spilled on the skin may cause frostbite.

Exposure to 200,000 ppm for 16 hours was fatal to dogs; single 8-hour exposures produced tremor and convulsions but no fatalities; repeated exposures at 140,000–160,000 ppm for 8 hours caused incoordination, tremor, and occasionally convulsions, but all dogs survived.[2] At 47,000 ppm for 2 hours, guinea pigs developed irregular respiration.[2] At 25,000 ppm, 1 of 12 dogs developed serious arrhythmia after intravenous epinephrine.[1]

Chronic administration of 10,000 ppm to rats and 5000 ppm to dogs, 6 hours/day for 90 days, caused no effects as determined by clinical, biochemical, and histologic examinations.[3]

A 40% solution applied to rabbit skin was without effect. Repeated spraying caused irritation of the mucous membrane of rabbit eyes.[2]

Dichlorotetrafluoroethane is considered to have little or no mutagenic or carcinogenic potential.[4]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for dichlorotetrafluoroethane is 1000 ppm (6990 mg/m^3).

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DICHLORVOS

CAS: 62-73-7

$C_4H_7Cl_2O_4P$

Synonyms: 2,2-Dichlorovinyl dimethyl phosphate; DDVP

Physical Form. Oily liquid

Uses. Insecticide

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Dichlorvos (DDVP) is an anticholinesterase agent.

Signs and symptoms of overexposure are caused by the inactivation of the enzyme cholinesterase, which results in the accumulation of acetylcholine at synapses in the nervous system, skeletal and smooth muscle, and secretory glands.[1,2] The sequence of the development of systemic effects varies with the route of entry. The onset of signs and symptoms is usually prompt but may be delayed up to 12 hours. After inhalation, respiratory and ocular effects are the first to appear, often within a few minutes of exposure. Respiratory effects include tightness in the chest and wheezing owing to bronchoconstriction and excessive bronchial secretion; laryngeal spasm and excessive salivation may add to the respiratory distress; cyanosis may also occur.[3] Ocular effects include blurring of distant vision, tearing, rhinorrhea, and frontal headache. After ingestion, gastrointestinal effects such as anorexia, nausea, vomiting, abdominal cramps, and diarrhea appear within 15 minutes to 2 hours. After skin absorption, localized sweating and muscular fasciculations in the immediate area occur usually within 15 minutes to 4 hours; skin absorption is somewhat greater at higher ambient temperatures and is increased by the presence of dermatitis.[1,2]

With severe intoxication by all routes, an excess of acetylcholine at the neuromuscular junctions of skeletal muscle causes weakness

aggravated by exertion, involuntary twitchings, fasciculations, and, eventually, paralysis. The most serious consequence is paralysis of the respiratory muscles. Effects on the central nervous system include giddiness, confusion, ataxia, slurred speech, Cheyne–Stokes respiration, convulsions, coma, and loss of reflexes. The blood pressure may fall to low levels, and cardiac irregularities including complete heart block may occur.

Complete symptomatic recovery usually occurs within a week; increased susceptibility to the effects of anticholinesterase agents persists for up to several weeks after exposure. Daily exposure to concentrations that are insufficient to produce symptoms after a single exposure may result in the onset of symptoms. Continued daily exposure may be followed by increasingly severe effects.

In a study of 13 workers exposed for 12 months to an average concentration of DDVP of 0.7 mg/m^3, the erythrocyte cholinesterase activity was reduced by approximately 35%, whereas the serum cholinesterase activity was reduced by 60%. The results of other tests and of thorough medical examination conducted at regular intervals were entirely normal.[4]

DDVP has been shown to cause a persistent irritant contact dermatitis in one worker with negative patch tests and appears to be capable of inducing an allergic contact dermatitis.[5,6]

Although several epidemiological studies have suggested a positive association between dichlorvos exposure and cancer, conclusions are limited because all have involved small study groups and exposure to several agents.[7] In animal studies chronic gavage administration of dichlorvos caused a dose-related increase in papillomas of the forestomach in mice and a dose-related increase in mononuclear-cell leukemia and an increased incidence of pancreatic acinar cell adenomas in male rats.[8] The IARC has determined that there is sufficient evidence for the carcinogenicity of DDVP in experimental animals and inadequate evidence in humans.[8]

DDVP was not genotoxic in various *in vivo* mammalian assays.[8] It was mutagenic in bacterial assays and in some cultured mammalian cell assays.

Developmental toxicity has not been demonstrated in a variety of animal species even in the presence of maternal toxicity.[8]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for dichlorvos is 0.1 ppm (0.90 mg/m^3) with a notation for skin absorption.

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DICYCLOPENTADIENE
CAS: 77-73-6

$C_{10}H_{12}$

Synonyms: Bicyclopentadiene; 1,3-cyclopentadiene dimer; 3*a*,4,7,7*a*-tetrahydro-4,7-methanoindene; DCPD

Physical Form. Colorless crystals when pure or as a clear liquid

Uses. As a chemical intermediate in the manufacture of pesticides; in the production of resin coatings, adhesives, and fuel additives

Exposure. Inhalation

Toxicology. Dicyclopentadiene is an irritant to the eyes, skin, and upper respiratory tract; at high concentrations it is a central nervous system depressant.

Voluntary human exposure to 1 ppm for 7 minutes produced mild eye and throat irritation; olfactory fatigue occurred in one subject within 24 minutes, but no fatigue occurred during a 30-minute exposure at 5.5 ppm.[1] Workers accidentally exposed to vapors for 5 months experienced headaches during the first 2 months of exposure but lacked symptoms the next 3 months, indicating a certain degree of adaptation.

Animal studies show considerable difference in sensitivity for the various species. The 4-hour LC_{50} for guinea pigs and rabbits was approximately 770 ppm; rats were slightly more sensitive with a 4-hour LC_{50} of 660 ppm, and mice were the most sensitive species, with a 4-hour LC_{50} of 145 ppm. All species followed a general pattern of eye irritation, loss of coordination, and, if death ensued, convulsions. For example, dogs exposed at 773 ppm had irritation of the eyes, nose, and extremities within 60 minutes; at 458 ppm, tremors occurred within 15 minutes, and signs of irritation, including lacrimation, were apparent within 50 minutes; 272 ppm produced tremors within 3 hours.

Rats repeatedly exposed to 332 ppm for 6 hours/day for 10 days succumbed. At autopsy, there was hemorrhage of the lungs and blood in the intestines, and, in females, there was also hemorrhage of the thymus. Rats exposed at the two lower concentrations (146 and 72 ppm) exhibited no adverse clinical signs, and no gross lesions were apparent at necropsy. Subchronic exposure of rats 7 hours/day for 3 months caused some kidney damage and lung involvement in the form of chronic pneumonia and bronchiectasis at both 74 and 35 ppm.

No consistent adverse effects were found in dogs exposed to 32, 23, or 9 ppm, 7 hours/day for 89 days. Minimal changes in biochemical test values were reported at the highest exposure level, but no dose-related pathologic changes were noted among any of the groups.

Reproductive toxicity was observed in rats administered 100 mg/kg by gavage in a continuous breeding protocol experiment: fewer F_1 pups were born live, and lower F_1 pup weights and higher F_1 pup mortality were observed. Increased liver and kidney weights were found at necropsy.[2] These effects occurred at levels that also produced systemic toxicity, suggesting that dicyclopentadiene is not selectively a reproductive toxin.

Undiluted dicyclopentadiene caused minor irritation when applied to the skin of rabbits, and only trace injury occurred when instilled in the eye.

Dicyclopentadiene has a camphorlike odor with a 100% recognition threshold of 0.02 ppm; however, there may not be noticeable irritation below 10 ppm.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for dicyclopentadiene is 5 ppm (27 mg/m^3).

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DICYCLOPENTADIENYL IRON

CAS: 102-54-5

$C_{10}H_{10}Fe$

Synonyms: Ferrocene; biscyclopentadienyl iron

Physical Form. Orange crystalline solid or orange needles

Uses. In ultraviolet stabilizers and smoke depressants for polymers; to increase the burn rate of rocket propellants; to prevent erosion of space capsule shields; to improve the viscosity of lubricants; to catalyze polymerization reactions; to catalyze combustion; some derivatives used as hematinic agents

Exposure. Inhalation; ingestion

Toxicology. Dicyclopentadienyl iron causes changes in blood parameters and hepatic cirrhosis.

The toxicological properties of dicyclopentadienyl iron have not been extensively investigated. However, it has been used as a preventive and therapeutic iron deficiency drug, and its utilization is listed as tolerable.

In rats, the inhalation LD_{50} is greater than 150 mg/m^3; various oral LD_{50} values ranging from 1000 to 2000 mg/kg have been cited.[1] For mice, LD_{50} values of 600–1550 mg/kg have been reported. There were no fatalities in rats administered 10 treatments of 200 mg/kg over a 2-week period.

Repeated inhalation exposure of F344/N rats and B6C3F1 mice at 0, 2.5, 5.0, 10, 20, or 40 mg of vapor for 6/hours/day for 2 weeks caused exposure-related lesions in the nasal turbinates of both species.[2] The lesions were primarily centered in the olfactory epithelium and were morphologically diagnosed as subacute, necrotizing inflammation. Exposure-related effects on organ weights were also seen; rats had decreased liver weights, whereas in mice, liver, spleen, kidney, and brain weights were decreased and thymus weights increased. The investigators suggested that these alterations were secondary effects brought on by the nasal lesions. Exposures for 13 weeks in rats and mice at 0, 3.0, 10, or 30 mg/m^3 caused histopathologic lesions in the larnyx, trachea, lungs, and liver (kidneys only in mice) and most notably in the nasal epithelium.[3] Lesions in the nasal olfactory epithelium consisted of pigment accumulation, necrotizing inflammation, metaplasia, and epithelial regeneration. Although increases in lung burdens of iron were found, there were no exposure-related changes in respiratory function, lung biochemistry, bronchoalveolar lavage cytology, total lung collagen, clinical chemistry, or hematology parameters.

Dogs receiving daily oral doses of 300 mg/kg had a reversible drop in hemoglobin, packed cell volume, and erythrocyte count during the first 4 weeks of treatment.[4] The 300 mg/kg/day eventually (time not specified) resulted in hepatic cirrhosis. The dicyclopentadienyl iron-dosed animals had high (up to 30–40 times those of controls) liver iron levels that remained elevated after the agent was discontinued. Twenty-six months after the end of dosing, the treated dogs had liver iron levels that were roughly 30 times higher than those of controls. Testicular hypoplasia was evident in males treated for 6 months.

Of 20 mice given 28 weekly subcutaneous injections of 5 mg of dicyclopentadienyl iron, 17 survived 9 months and there were no tumors.[5]

The compound was not mutagenic in bacterial assays or genotoxic in sister chromatid exchange assays but was immunotoxic, decreasing the rate of lymphocyte proliferation *in vitro*.[6]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for dicyclopentadienyl iron is 10 mg/m^3.

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DIELDRIN
CAS: 60-57-1

$C_{12}H_8Cl_6O$

Synonyms: Compound 497; Octalox; HEOD

Physical Form. Light tan to brown powder

Uses. Insecticide

Exposure. Skin absorption; inhalation; ingestion

Toxicology. Dieldrin primarily effects the central nervous system; high exposures can cause convulsions.

A number of poisonings, including a few fatalities, have occurred among workers involved in spraying or manufacture of dieldrin. Early symptoms of intoxication may include headache, dizziness, nausea, vomiting, malaise, sweating, and myoclonic jerks of the limbs; clonic and tonic convulsions and sometimes coma follow and may occur without the premonitory symptoms.[1–3] In some patients after convulsions, agitation, hyperactivity, and temporary personality changes, including weeping, mania, and inappropriate behavior, have occurred. Recovery is generally prompt over several weeks and complete, although a few patients have been described with persistent symptoms for several months, and recurrent convulsions have rarely occurred.[1] The half-life of dieldrin in humans is reportedly as long as 0.73 years. Dieldrin is well absorbed dermally, which may be the primary route of occupational exposure.[1]

Electroencephalogram changes, including bilateral spikes, spike and wave complexes, and slow theta waves, occur in sufficiently exposed workers. Electroencephalograms have been used successfully in monitoring workers and justifying removal from exposure, but this test has been supplanted by measurement of blood levels. In a study of five aldrin/dieldrin workers who had suffered one or more convulsive seizures and/or myoclonic limb movements, the probable concentration of dieldrin in the blood during intoxication ranged from 16 to 62 µg/100 g of blood; in healthy workers the concentrations of dieldrin ranged up to 22 µg/100 g of blood.[4]

The hepatocarcinogenicity of dieldrin in mice has been confirmed in several experiments, and in some cases, the liver cell tumors metastasized.[5] No excess of tumors has been observed in a number of bioassays in rats and one bioassay in Syrian golden hamsters.[5,6]

Epidemiological studies examining cancer mortality in workers exposed to dieldrin showed no conclusive evidence of carcinogenicity in humans.[7] A study of 870 men employed in the manufacture of aldrin, dieldrin, and endrin found no increase in mortality from all cancers; there were apparent increases in mortality from cancers of the esophagus, rectum, and liver based on very small numbers.[8] In another report, follow-up of 232 workers with similar exposures revealed 9 cancer deaths with 12 expected.[9] Updated epidemiological studies of manufacturing workers have confirmed the earlier findings. A cohort

mortality study of 2384 persons employed sometime between 1952 and 1982 at a Colorado pesticide manufacturing facility found no excess mortality rates attributable to occupational exposure.[10] Similarly, a 23-year follow-up of 570 dieldrin- and aldrin-exposed workers found no increase in overall mortality rates or mortality from liver cancer.[11]

Dieldrin is genotoxic in some assays, but it does not appear to act directly on the DNA molecule.[7]

Accumulating evidence suggests that dieldrin is "not a likely human carcinogen" and that it acts as a species-specific hepatocarcinogen in mice through nongenotoxic mechanisms.[12]

Developmental effects have been noted in animals after a single very large dose in midgestation. A dose of 30 mg/kg administered orally to pregnant golden hamsters during the period of fetal organogenesis caused a high incidence of fetal deaths, congenital anomalies, and growth retardation.[13] No information was available on the health of the maternal animals, but it should be noted that this dosage approaches reported LD_{50} values.[7] No developmental effects were observed in rats exposed to concentrations as high as 6 mg/kg/day on days 7–15 of gestation or in mice exposed up to 4 mg/kg/day on days 6–14 of gestation.[7] Decreased fertility has been reported in some reproductive studies, and decreased postnatal survival after in utero exposure has also been observed.[7]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for dieldrin is 0.25 mg/m^3 with a notation for skin absorption.

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DIEPOXYBUTANE
CAS: 1464-53-5

$C_4H_6O_2$

Synonyms: 2,2′-bioxirane; 1,1′-bi(ethylene oxide); butadiene diepoxide; butadiene dioxide; 2,4-diepoxybutane; dioxybutadiene

Physical Form. Colorless liquid

Uses. Curing of polymers; cross-linking of textile fibers; prevention of microbial spoilage

Exposure. Inhalation; skin absorption

Toxicology. Diepoxybutane is a mucous membrane irritant. Certain stereoisomers of diepoxybutane have been shown to cause cancer in laboratory animals.

In humans, minor, accidental exposure to diepoxybutane caused eyelid swelling, painful eye irritation, and upper respiratory tract irritation within 6 hours.[1] On contact with the skin it is expected to produce burns and blisters.

The oral LD_{50} of diepoxybutane in rats is 78 mg/kg body weight, whereas the inhalation LC_{50} is 371 mg/m^3 for a 4-hour exposure. Rats exposed via inhalation experienced lacrimation, clouding of the cornea, labored breathing, and lung congestion.[1] Leukopenia and lymphopenia were produced in rabbits after six intramuscular injections of 25 mg/kg.[1]

Both D,L- and *meso*-1,2:3,4-diepoxybutane induced skin papillomas and carcinomas in mice after dermal application.[1] Lung tumors were produced in mice after intraperitoneal administration of 27, 108, or 192 mg/kg (total dose). The tumor incidences at these doses were 55%, 64%, and 78%, respectively, compared with 31% in control mice.[1]

Rats exposed by inhalation to 2.5 or 5.0 ppm 1,2:3,4-diepoxybutane 6 hours/day, 5 days/week for 6 weeks and held for 18 months had a dose-dependent increase in neoplasms of the nasal mucosa.[3] Mice similarly exposed showed a trend toward an increase in total neoplastic lesions (including reproductive organs, lymph nodes, bone, liver, harderian gland, pancreas, and lung) as a function of dose.[3] The only significant increase in a single organ neoplasm was the harderian gland.

1,2:3,4-Diepoxybutane is a potent bifunctional alkylating agent. *In vivo*, it induced

DNA adducts, dominant lethal mutations, and gene mutations in mice; chromosomal aberrations and sister chromatid exchanges in Chinese hamsters and mice; and micronuclei in splenocytes and spermatids of rats and mice.[4] *In vitro*, it induced gene mutations, chromosomal aberrations, and sister chromatid exchanges.

1,2:3,4-Diepoxybutane is the purportedly carcinogenic metabolite of 1,3-butadiene.[4]

The IARC has determined that there is sufficient evidence in experimental animals for the carcinogenicity of diepoxybutane.[4]

The ACGIH has not established a threshold limit value (TLV) for diepoxybutane.

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DIETHANOLAMINE
CAS: 111-42-2

$HO(CH_2)_2NH(CH_2)_2OH$

Synonyms: DEA; 2,2-iminodiethanol; dihydroxydiethylamine

Physical Form. Exists either as a colorless liquid or crystals at ambient temperatures.

Uses. Reacts with long-chain fatty acids to form ethanolamine soaps, which are used extensively as emulsifiers, thickeners, wetting agents, and detergents in cosmetic formulations; also used as a dispersing agent in agricultural chemicals; as a chemical intermediate; as a corrosion inhibitor

Exposure. Inhalation

Toxicology. In animal studies, target organs of diethanolamine (DEA) toxicity have included bone marrow, kidney, testis, skin, and central nervous system.

Limited reports of DEA toxicity are available in humans. Clinical skin testing of cosmetic products containing DEA showed mild skin irritation to concentrations above 5%.[1]

The oral LD_{50} in rats has ranged from 0.71 ml/kg to 2.83 g/kg.[2,3] The effects of intraperitoneal administration to rats of doses of 100 or 500 mg/kg were assessed at 4 and 24 hours after dosing.[4] In the liver and kidneys, there was cytoplasmic vacuolization. The high doses caused renal tubular degeneration. In rats fed 0.17 g/kg for 90 days, effects included cloudy swelling and degeneration of kidney tubules and fatty degeneration of the liver.[3,5]

Rats exposed to doses of DEA ranging from 160 to 5000 ppm in drinking water for 13 weeks exhibited dose-dependent hematologic changes, tubular necrosis of the kidney with decreased renal function, demyelination of the brain and spinal cord, and degeneration of the seminiferous tubules.[6] Hematologic changes consisted of a moderate, poorly regenerative anemia that did not appear to involve hemolysis but rather decreased hematopoiesis. Renal tubular epithelial necrosis was more pronounced in female rats than males. Demyelination in the brain was not associated with apparent neurological signs, but long-term effects of this lesion are unknown. Degeneration of the seminiferous tubule epithelium was associated with dose-related decreases in testis and epididymis weights with reduced sperm motility and sperm count in the cauda epididymidis.

In the same study, topical application of DEA doses ranging from 32 to 500 mg/kg for 13 weeks caused skin lesions characterized by ulceration, inflammation, hyperkeratosis, and acanthosis. Other target organs in the skin application study were similar, but less severe, than those observed in the drinking water study. Differences in dose-response relationships between the two studies were attributed to the limited dermal absorption of DEA in rats.

In a follow-up study in mice, exposure to DEA, via drinking water or by topical application, caused dose-dependent toxic effects in the liver (hepatocellular cytological alterations and necrosis), kidney (nephropathy and tubular epithelial necrosis in males), heart (cardiac myocyte degeneration), and skin (site of application: ulceration, inflammation, hyperkeratosis, and acanthosis).[7] Doses ranged from 630 to 10,000 ppm in the drinking water and from 80 to 1250 mg/kg in the topical application study.

In 2-year dermal studies there was no evidence of carcinogenicity in rats but there was clear evidence of carcinogenicity in mice based on increased incidences of liver neoplasms in males and females and increased incidences of renal tubule neoplasms in males.[8] It has also been noted that in the presence of *N*-nitrosating agents, DEA may give rise to *N*N-nitrosodiethanolamine, a known animal carcinogen.[1] The IARC has determined that there is limited evidence for the carcinogenicity of diethanolamine in experimental animals and inadequate evidence in humans.[9]

DEA was not mutagenic in bacterial assays, nor did it induce significant sister chromatid exchanges or chromosomal aberrations in cultured cells.[8]

The mechanism of DEA toxicity is unknown but may be related to its high tissue accumulation and effects on phospholipid metabolism, resulting in alterations in membrane structure and function.[7]

The liquid applied to the skin of rabbits under semiocclusion for 24 hours on 10 consecutive days caused only minor irritation.[1] With long contact time, DEA is irritating to rabbit eyes at concentrations of 50% and above.[1] Toxicity resulting from direct contact may be in part due to irritation associated with the alkalinity of this chemical.[7]

When DEA was administered cutaneously to pregnant rats and rabbits during organogenesis, developmental toxicity (skeletal variations) was observed only in the rat and only at doses causing significant maternal toxicity.[10]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 3 ppm (13 mg/m^3).

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DIETHYLAMINE
CAS: 109-89-7

$(C_2H_5)_2NH$

Synonyms: Diethamine; *N*-ethyl-ethanamine

Physical Form. Colorless liquid

Uses. In the rubber and petroleum industry; in flotation agents; in resins, dyes, pharmaceuticals

Exposure. Inhalation

Toxicology. Diethylamine is an irritant of eyes, mucous membranes, and skin.

Volunteers exposed to concentrations increasing from 0 to 12 ppm for 60 minutes (average concentration 10 ppm) reported distinct nasal and eye irritation and moderate to strong odor detection.[1] Acute nasal reactions, as determined by acoustic rhinometry and rhinomanometry, were not observed with exposure to 25 ppm for 15 minutes.

Exposure to high vapor concentrations may cause severe cough and chest pain; heavy, repeated, or prolonged exposure could result in pulmonary edema.[2,3] Contact of the liquid with eyes causes corneal damage. In one reported case, the liquid splashed into the eye caused intense pain.[4] Despite emergency irrigation and treatment, the cornea became swollen and cloudy; some permanent visual impairment resulted. Prolonged or repeated contact of the eyes with the vapor at concentrations slightly below the irritant level often results in corneal edema with consequent foggy vision and the appearance of haloes around lights.[1] Dermal

contact with the liquid causes vesiculation and necrosis of the skin.[3]

In rats, exposure to the saturated vapor is lethal in 5 minutes and the 4-hour inhalation LC_{50} is 4000 ppm.[5]

Rabbits repeatedly exposed to 50 ppm for 7 hours/day, 5 days/week for 6 weeks showed corneal damage, pulmonary irritation, moderate peribronchitis, and slight thickening of the vascular walls; at 100 ppm, for the same exposure period, there was striking parenchymatous degeneration of the heart muscle in all exposed animals.[6]

Sneezing, tearing, reddened nose, and lesions of the nasal mucosa were observed in rats exposed at 200 ppm for 6.5 hours/day, 5 days/week for 24 weeks.[7] Histopathologic examinations showed squamous metaplasia, suppurative rhinitis, and lymphoid hyperplasia of the respiratory epithelium.

No evidence of mutagenicity was seen in Ames bacterial assays.[8] Diethylamine has an ammonia-like odor that is detectable at 0.13 ppm.[9]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for diethylamine is 5 ppm (15 mg/m^3) with a short-term excursion limit of 15 ppm (45 mg/m^3) and an A4-not classifiable as a human carcinogen designation; there is a notation for skin absorption.

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2-DIETHYLAMINOETHANOL

CAS: 100-37-8

$(C_2H_5)_2NCH_2CH_2OH$

Synonyms: Diethyl ethanolamine; DEAE; *N*,*N*-diethylethanolamine

Physical Form. Colorless liquid

Uses. Anticorrosive agent; chemical intermediate for the production of emulsifiers, detergents, solubilizers, cosmetics, drugs, and textile finishing agents

Exposure. Inhalation; skin absorption

Toxicology. 2-Diethylaminoethanol (DEAE) is an irritant of the eyes, mucous membranes, and skin in animals.

An attempt by a laboratory worker to remove animals from an inhalation chamber containing approximately 100 ppm resulted in nausea and vomiting within 5 minutes after a fleeting exposure; no irritation of the eyes or throat was noted during this brief exposure.[1] Other persons in the same room also complained of a nauseating odor but showed no ill effects.

Through a leak in the steam heating system, DEAE was released into the air of a large office building, and irritative symptoms of

the respiratory tract were experienced by most of the 2500 employees.[2] In addition, 14 workers developed asthma for the first time within 3 months of exposure. Bronchial hyperreactivity may have resulted from significant airway irritation by the amine.

Rats exposed to 500 ppm 6 hours daily for 5 days exhibited marked eye and nasal irritation, and a number of animals had corneal opacity by the end of the third day; the mortality rate was 20%, and at autopsy, findings were acute purulent bronchiolitis and bronchopneumonia.[1] Exposure to 25 ppm for 14 days caused respiratory tract epithelial hyperplasia, squamous metaplasia, and clinical rales.[3]

Whole-body exposure of timed-pregnant Sprague-Dawley rats during organogenesis resulted in maternal toxicity at 66 ppm (suppression of body weight gain) and 100 ppm (dry rales and reduced weight gain).[4] There was no evidence of embryonic or fetal toxicity, including teratogenicity at doses that were maternally toxic.

The liquid is a severe skin irritant; in the guinea pig it is a skin sensitizer.[5] It is also a severe eye irritant and may produce permanent eye injury.

DEAE was not mutagenic or clastogenic in a variety of *in vitro* and *in vivo* assays.[4]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 2-diethylaminoethanol is 2 ppm (9.6 mg/m^3) with a notation for skin absorption.

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DIETHYLENE TRIAMINE
CAS: 111-40-0

$(NH_2CH_2CH_2)_2NH$

Synonyms: 2,2-Diaminodiethylamine; DETA

Physical Form. Yellow viscous liquid

Uses. Hardener and stabilizer for epoxy resins; solvent for dyes, acid gases, and sulfur

Exposure. Inhalation; skin contact

Toxicology. Diethylene triamine (DETA) is a skin, eye, and respiratory irritant; it also causes skin and pulmonary sensitization. On the skin, DETA is a potent primary irritant causing edema and sometimes necrosis.[1] Repeated contact with the liquid may lead to skin sensitization, and an asthmatic-type response may result from repeated inhalation of the vapors.[2,3]

In rats, oral LD_{50} values of 1 and 2 g/kg have been reported; there were no deaths after an 8-hour exposure to saturated vapors at room temperature.[2] Administration of up to 15,000 ppm in the feed of rats for 90 days caused decreases in food consumption but no treatment-related clinical signs or histopathologic findings.[4]

The dermal LD_{50} in rabbits was 1.09 ml/kg.[2] A 10% solution applied to the skin of mice produced dermal ulceration.

In a lifetime study, 25-µl aliquots of a 5% solution applied three times a week to the skin of male mice caused a low incidence of dermatitis, hyperkeratosis, and necrosis.[5] There

were no treatment-related skin tumors, nor was there any evidence of an increased incidence of internal tumors. Systemic effects were also absent, indicating limited absorption of the compound.

In the eye, solutions of 15% or more caused lasting corneal damage but a 5% solution only caused minor injury.[2] The injury caused by single applications appears to be attributable to the highly alkaline character of DETA, rather than to some other innate toxicity.[1]

DETA has a strong ammonia-like odor, but it does not provide adequate warning of hazardous concentrations.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for diethylene triamine is 1 ppm (4.2 mg/m^3) with a notation for skin absorption.

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DIETHYLHEXYL ADIPATE

CAS: 103-23-1

$C_{22}H_{42}O_4$

Synonyms: DEHA; bis(2-ethylhexyl) adipate; octyl adipate

Physical Form. Colorless or very pale amber liquid

Uses. Plasticizer in polyvinyl chloride films, sheeting, extrusions, and plastisols; solvent and emollient in cosmetics

Exposure. Inhalation; skin contact

Toxicology. Diethylhexyl adipate (DEHA) is of low acute toxicity but is carcinogenic in mice by the oral route.

There are no reports of effects in humans from specific exposure to DEHA, but fumes generated at high temperatures may cause throat and eye irritation.[1]

DEHA has a low acute toxicity as indicated by the relatively high oral LD_{50} in rats of 9.1 g/kg.[2] Skin absorption is expected to be low because the dermal LD_{50} in rabbits is 15 g/kg.

In an NTP carcinogenicity study, rats and mice of both sexes were fed DEHA at 12,000 and 25,000 ppm in the diet for 103 weeks.[3] DEHA was noncarcinogenic in rats but caused hepatocellular carcinomas in female mice in both dose groups and hepatocellular adenomas in males at the higher dose. The species difference in carcinogenicity is consistent with a greater extent of peroxisome proliferation in liver of mice as compared to rats.[4]

The IARC has determined that there is limited evidence of carcinogenicity of DEHA in experimental animals and that it is not classifiable as to its carcinogenicity to humans.[4]

DEHA was not mutagenic or genotoxic in a variety of assays, nor did it covalently bind to DNA *in vivo*.[4]

Exposure of rats to DEHA during organogenesis caused an increased frequency of variations and retardations in the fetuses at doses below the maternally toxic range.[4]

The liquid in contact with the skin of rabbits under occlusion for 24 hours produced mild skin irritation.[5] In the eye, examination after 24 hours revealed no irritation from DEHA.

The ACGIH has not established a threshold limit value (TLV) for diethylhexyl adipate.

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DI(2-ETHYLHEXYL) PHTHALATE
CAS: 117-81-7

$C_{24}H_{38}O_4$

Synonyms: DEHP; bis(2-ethylhexyl)phthalate; diethylhexyl phthalate; di-*sec*-octyl phthalate

Physical Form. Clear to slightly colored oily liquid

Uses. Commonly used plasticizing agent for PVCs, which as such is a component of blood bank bags, surgical tubing, and other products including food wrappers and children's toys

Exposure. Inhalation

Toxicology. The acute toxicity of di(2-ethylhexyl) phthalate (DEHP) is low; chronic exposure has been associated with liver damage, testicular injury, and teratogenic and carcinogenic effects in experimental animals.

Two male volunteers developed mild gastric disturbance after swallowing 5 or 10 g.[1] Dermally applied, it was judged to be moderately irritating and, at most, only slightly sensitizing to human skin.

The oral LD_{50} for rats is 26 g/kg, and for rabbits it is 34 g/kg.[1] A single oral dose of 2 g/kg of DEHP to dogs caused no toxicity. The lethal effects appear to be cumulative because the chronic LD_{50} value for intraperitoneal administration to mice 5 times/week for 10 weeks was 1.36 g/kg, in comparison to a single-dose value of 37.8 g/kg.[2] DEHP is poorly absorbed through the skin, but two of six rabbits died several days after dermal exposure to 19.7 g/kg.[3]

Acute, intermediate, and chronic oral exposure to DEHP has been found to have significant effects on rodent liver.[4] Effects may include hyperplasia, within 24 hours of exposure, accompanied by an increase in relative liver weight; proliferation of hepatic peroxisomes; altered enzyme functions; changes in the morphology of the bile ducts; and eventually the appearance of precancerous altered cell foci and tumors.[4] The amount of damage in the rodent liver is influenced by dose and duration of exposure, diet, age, and exposure to other chemicals.[4] There are also distinct species differences in the toxicity of DEHP to the liver. For example, monkeys exposed to DEHP showed either no increase or a nonsignificant increase in liver weight with doses of 10–2000 mg/kg/day for 14–25 days.

In 2-year chronic studies, DEHP caused a significant increase in hepatocellular carcinomas in female rats fed diets containing 12,000 ppm, in male mice ingesting 6000 ppm, and in female mice ingesting 3000 or 6000 ppm.[5] Hepatocellular tumors were confirmed in a number of other oral assays in rats and mice.[3]

DEHP was not mutagenic in a wide variety of microbial and mammalian genotoxic assays.[4]

Investigators have suggested that the production of hepatic tumors with DEHP in

rodents occurs by a nongenotoxic mechanism involving peroxisome proliferation.[3] The central element in developing liver cancer in rodents is the activation of a nuclear receptor in rodent liver, peroxisome proliferator-activated receptor (PPARα), which leads to increased activity of peroxisomal enzymes and is accompanied by increased cell replication.[6] Humans have low liver expression of PPARα and are refractory to peroxisome proliferators.[4] Therefore, the mechanism by which DEHP increases tumors in rats and mice is not considered relevant to humans.[3] The IARC determined that there is sufficient evidence for the carcinogenicity of DEHP in mice and rats and inadequate evidence in humans.[3]

Embryolethal and teratogenic effects have been reported in animal studies. DEHP administration in the diet of mice throughout gestation resulted in an increased incidence of exophthalmia, exencephaly, tail defects, major vessel malformations, and skeletal defects at doses (0.10% and 0.15%) that produced maternal toxicity and at a dose (0.05%) that did not produce significant maternal toxicity.[7] There were also increased resorptions and late fetal deaths, a decreased number of live fetuses, and reduced fetal weights at the two higher dose levels. In contrast, DEHP was not teratogenic in rats at the doses tested but did produce maternal and some embryofetal toxicity at 1.0%, 1.5%, and 2.0% of the diet. Inhalation exposure of up to 0.3 mg/l, 6 hours/day during gestation failed to produce developmental toxicity in rats.[8]

Mice given diets containing 0.1% and 0.3% DEHP for 7 days before and during a 98-day cohabitation period had dose-dependent decreases in male and female fertility and in the number of pups born alive.[9]

DEHP-induced testicular injury has been reported in a number of studies.[4,10] Administration of 20,000 mg/kg in the diet of rats produced seminiferous tubular degeneration and testicular atrophy within 7 days, 12,500 mg/kg produced similar effects within 90 days, and 6000 ppm was effective by the end of 2 years of exposure. Testicular damage has been found to be more severe in young rats than in older rats, and damage appears to be reversible if DEHP is withdrawn from the diet before sexual maturity is reached.

There are no reported reproductive or developmental effects in humans.[4]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for DEHP is 5 mg/m^3 with an A3-confirmed animal carcinogen with unknown relevance to humans notation.

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DIETHYL KETONE

CAS: 96-22-0

$C_2H_5COC_2H_5$

Synonyms: 3-Pentanone, DEK, dimethylacetone, methacetone, propione

Physical Form. Colorless liquid

Uses. In organic synthesis

Exposure. Inhalation

Toxicology. Diethyl ketone is expected to be an irritant and central nervous system depressant at high concentrations.

Limited toxicological information is available for diethyl ketone. Based on analogy with other methyl ketones, high vapor concentrations are expected to irritate the conjunctiva of the eyes and mucous membranes of the nose and throat.[1] Excessive inhalation may produce dizziness, headache, nausea, vomiting, and ataxia.

In rats a 4-hour exposure at 8000 ppm was fatal to four of six animals.[2] There were no neurotoxic effects in rats given repeated oral doses.[3]

The liquid applied to rabbit skin caused mild irritation, and 50 mg instilled in the eye produced moderate irritation. Repeated skin contact would be expected to cause dermatitis by defatting.[1]

A distinct acetone-like odor is detectable at 2 ppm.[4]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for diethyl ketone is 200 ppm (705 mg/m^3) with a TLV-short-term excursion limit (TLV-STEL) of 300 ppm (1057 mg/m^3).

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DIETHYL PHTHALATE

CAS: 84-66-2

$C_6H_4(COOC_2H_5)_2$

Synonyms: 1,2-benzenedicarboxylic acid diethyl ester; DEP

Physical Form. Colorless liquid

Uses. Plasticizer for cellulose ester plastic films and sheets; in molded plastics; manufacturing varnishes; cosmetics

Exposure. Inhalation

Toxicology. Diethyl phthalate (DEP) is of low toxicity.

Exposure to the heated vapor may produce some transient irritation of the nose and throat.[1] Although skin sensitization to DEP is extremely rare, it has been reported.[2] No sys-

temic effects are known pertaining to its occupational use.

The lowest lethal doses in rabbits and guinea pigs were determined to be 4.0 and 5.0 g/kg, respectively, when administered by gavage.[3] There were no adverse effects in rats fed 1.25 g/kg/day or in dogs fed 2.5 g/kg/day for 6 weeks or more.[4]

Male rats dermally administered 300 µl, 5 days/week for 4 weeks had increased relative liver and kidney weights.[5] There was no evidence of carcinogenic activity in male or female rats receiving up to 300 µl/day, 5 days/week for 2 years.[5] Equivocal evidence of carcinogenicity was seen in mice receiving up to 30 µl/day for 103 weeks based on increased incidences of hepatocellular neoplasms.[5]

Diethyl phthalate administered in the diet to rats during major organogenesis increased the incidence of fetal lumbar ribs only at 3200 mg/kg/day, a maternally toxic dose.[6] In another report, there also was an increased incidence of supernumerary ribs, but no other embryo/fetal effects, in the offspring of rats fed 5% DEP on gestational days 6–15; maternal toxicity was evident as reduced body weight gain.[7]

No effects on the male reproductive system have been found in rats in a number of investigations.[3]

DEP was not mutagenic in bacterial assays, nor did it induce chromosomal aberrations in Chinese hamster ovary (CHO) cells; with metabolic activation it did cause sister chromatid exchanges in CHO cells.[5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for diethyl phthalate is 5 mg/m^3.

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DIETHYL SULFATE
CAS: 64-67-5

$C_4H_{10}O_4S$

Synonyms: Diethyl monosulfate; ethyl sulfate; sulfuric acid diethyl ester; diethyl tetraoxosulfate

Physical Form. Colorless, oily liquid

Uses. As an ethylating agent; as an accelerator in the sulfation of ethylene; intermediate in the production by one method of ethyl alcohol from ethylene and sulfuric acid

Exposure. Ingestion; inhalation; skin absorption

Toxicology. Diethyl sulfate is highly toxic by inhalation, ingestion, or skin or eye contact and is carcinogenic in experimental animals.

There is no information on acute toxicity in humans. However, diethyl sulfate is less

volatile and considered less acutely toxic than dimethyl sulfate, which has been shown to produce severe irritation to mucous membranes and the respiratory tract.[1,2]

Animal experiments demonstrated an oral LD_{50} of 350 mg/kg in the rat and 647 mg/kg in the mouse. The lowest dose by inhalation that resulted in death in the rat was 250 ppm for a 4-hour exposure.[2]

An historical cohort study of 743 workers at a plant manufacturing isopropyl alcohol and ethanol showed excess mortality (standardized mortality ratio of 504) from upper respiratory (laryngeal) cancers, based on four cases. These employees had spent most of their time working in the strong acid-ethanol plant, which produced high concentrations of diethyl sulfate.[3] A subsequent case-control study nested in an expanded cohort at this plant indicated that the increased risk was related to exposure to sulfuric acid.[3] An association between estimated exposure to diethyl sulfate and risk for brain tumor (gliomas) was suggested in a study of workers at a petrochemical plant. The IARC has noted that there has been no measurement of exposure to diethyl sulfate in these studies and that concomitant exposure to mists and vapors from strong inorganic acids, primarily sulfuric acid, may play a role in increasing these risks.[3]

Local tumors were produced in rats after subcutaneous administration for 49 weeks. A small group of rats receiving 25 or 50 mg/kg diethyl sulfate by gavage had a low incidence of squamous cell carcinomas of the forestomach, whereas 6 of 24 animals had benign papillomas of the forestomach. In another experiment, a single subcutaneous dose of diethyl sulfate (85 mg/kg) was administered to three pregnant rats on day 15 of gestation. Malignant tumors of the nervous system were observed in 2 of 30 offspring on days 285 and 541. No tumors of this type had been observed in controls.

The IARC has determined that there is sufficient evidence for the carcinogenicity of diethyl sulfate in experimental animals and inadequate evidence of carcinogenicity in humans; overall, it should be regarded as probably carcinogenic to humans.[4]

Diethyl sulfate is a potent direct-acting alkylating agent.[4] It induced unscheduled DNA synthesis in human cells *in vitro*. It induced chromatid breaks in mouse embryos treated transplacentally and dominant lethal mutations in mice, as well as a variety of mutagenic and clastogenic effects in rodent cells in vitro.[3]

A threshold limit value (TLV) has not been established for diethyl sulfate.

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DIFLUORODIBROMOMETHANE
CAS: 75-61-6

CF_2Br_2

Synonyms: Halon 1202; Freon 12-B2

Physical Form. Colorless liquid or gas

Uses. Fire-extinguishing agent

Exposure. Inhalation

Toxicology. Difluorodibromomethane causes respiratory irritation and narcosis in

animals, and severe exposure is expected to produce the same effects in humans.

No effects have been reported from industrial exposures.

Rats exposed to 4000 ppm for 15 minutes showed pulmonary edema, whereas 2300 ppm daily for 6 weeks resulted in the death of more than half of the animals.[1] At 2300 ppm dogs showed rapid and progressive signs of intoxication after a few days of exposure, with weakness and loss of balance followed by convulsions. At autopsy, these dogs had pulmonary congestion, centrilobular necrosis of the liver, and evidence of central nervous system damage. Other dogs tolerated daily exposures of 350 ppm for 7 months without signs of intoxication.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for difluorodibromomethane is 100 ppm (858 mg/m^3).

REFERENCES

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DIGLYCIDYL ETHER

CAS: 2238-07-5

$C_6H_{10}O_3$

Synonyms: Bis(2,3-epoxy propyl)ether; DGE; di(2,3-epoxypropyl) ether

Physical Form. Colorless liquid

Uses. Diluent for epoxy resins; stabilizer of chlorinated organic compounds

Exposure. Inhalation; skin absorption

Toxicology. Diglycidyl ether (DGE), causes severe irritation of the eyes, respiratory tract, and skin; hematopoietic effects have been observed in animals.

Because of its toxicity, DGE generally is not used outside experimental laboratories.[1] No systemic effects have been reported in humans.

The LC_{50} for mice was 30 ppm for 4 hours, but exposure at 200 ppm for 8 hours was not lethal to rats.[2] Rabbits exposed to 24 ppm for 24 hours had leukocytosis at autopsy. There were acute changes in the lungs and kidneys as well as atrophied testes.[3] At 12 ppm, there was thrombocytopenia and at 6 ppm, basophilia.

In rats, three or four exposures at 20 ppm for 4 hours produced intense cytoplasmic basophilia, grossly distorted lymphocytic nuclei with indistinct cellular membranes, and lowered leukocyte and marrow cell counts.[3] Repeated exposure of rats to 3 ppm caused increased mortality, decreased body weight, and leukopenia. Exposures to 0.3 ppm did not cause significant changes. Cutaneous applications greater than 100 mg/kg also caused leukopenia, weight loss, and death.

The oral LD_{50} was 0.17 g/kg in mice and 0.45 g/kg in rats; following intragastric administration, effects were incoordination, ataxia, depressed motor activity, and coma.[2]

Diglycidyl ether is extremely damaging to skin, producing ecchymoses and necrosis. In one long-term study, skin painting three times per week for 1 year caused hyperkeratosis, epithelial hyperplasia, and skin papillomas.[4]

Instilled in rabbit eyes, DGE is a severe irritant. Exposure to vapor at 3 ppm for 24 hours produced erythema and edema of the conjuctiva in rabbits, and at 24 ppm, corneal opacity was produced.[3]

DGE was mutagenic in bacterial test systems.[5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for diglycidyl ether is 0.1 ppm (0.53 mg/m^3).

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DIISOBUTYL KETONE

CAS: 108-83-8

$[(CH_3)_2CHCH_2]_2CO$

Synonyms: Diisopropyl acetone; isovalerone; 2,6-dimethyl-4-heptanone; DBK

Physical Form. Colorless liquid

Uses. Solvent; dispersant for resins; intermediate in the synthesis of pharmaceuticals and insecticides

Exposure. Inhalation

Toxicology. Diisobutyl ketone vapor is an irritant of the eyes and mucous membranes; at high concentrations it causes narcosis in animals, and it is expected that severe exposure will produce the same effect in humans.[1]

Human subjects exposed to 100 ppm for 3 hours noted slight lacrimation and throat irritation, and slight headache and dizziness on returning to fresh air.[2] In another study, the majority of subjects experienced eye irritation above 25 ppm, and nose and throat irritation above 50 ppm within 15 minutes.[3]

The liquid is a defatting agent, and prolonged or repeated skin contact may cause dermatitis.

Although diisobutyl ketone may be more toxic and irritative than lower-molecular-weight ketones at equivalent concentration, it poses less of an inhalation hazard because of its relatively low volatility.[1]

Exposure of female rats to 2000 ppm for 8 hours caused narcosis, and 7 of 12 rats died; however, male rats survived the same treatment, as did both sexes of one other strain of rats.[2] Damage to the lungs, liver, and kidneys was observed at autopsy. Repeated exposures to rats over 30 days resulted in increased liver and kidney weights at 920 and 530 ppm, but there were no effects at 125 ppm.[2] Renal hyalin droplet nephrosis was seen in male rats exposed to 905 and 300 ppm 6 hours/day for 9 days; the significance of this effect to humans is questionable.[4]

There was no evidence of genotoxcity in a number of *in vitro* assay systems.[5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for diisobutyl ketone is 25 ppm (145 mg/m^3).

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DIISOPROPYLAMINE
CAS: 108-18-9

$(CH_3)_2CHNHCH(CH_3)_2$

Synonyms: *N*-(1-methylethyl)-2-propanamine

Physical Form. Colorless liquid

Uses. Chemical intermediate; used to adjust the pH of cosmetic formulations

Exposure. Inhalation; skin absorption

Toxicology. Diisopropylamine is an eye irritant in humans; it is a pulmonary irritant in animals, and severe exposure is expected to produce the same effect in humans.

Workers exposed to concentrations between 25 and 50 ppm complained of disturbances of vision described as "haziness."[1] In two instances, there were also complaints of nausea and headache. Prolonged skin contact with an irritant of this nature is likely to cause dermatitis.

Exposure of several species of animals to 2207 ppm for 3 hours was fatal; effects were lacrimation, corneal clouding, and severe irritation of the upper respiratory tract; at autopsy findings included pulmonary edema and hemorrhage. Repeated exposure to 600 ppm, 7 hours/day for 40 days caused deaths in all rabbits and some guinea pigs; cats and rats survived but had cloudiness of the cornea with loss of vision. It was determined that the ocular effects of diisopropylamine are due to direct contact with the vapor, as no corneal effects occurred from subcutaneous injection in guinea pigs.

In guinea pigs, 5% diisopropylamine caused dermal irritation with repeated exposures, but it was not a sensitizer.[2] The irritative properties of diisopropylamine have been attributed to its alkaline pH, which is neutralized in some formulations.

Conflicting results have been reported in bacterial mutagen assays; diisopropylamine was not genotoxic in DNA repair assays *in vitro*.[2]

Diisopropylamine has a strong odor of ammonia.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for diisopropylamine is 5 ppm (21 mg/m^3) with a notation for skin absorption.

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DIMETHOXYETHYL PHTHALATE
CAS: 117-82-8

$C_6H_4[COOCH_2CH_2OCH_3]_2$

Synonyms: DMEP; 1,2-benzenedicarboxylic acid bis(2-methyoxy-ethyl)ester; bis (methoxyethyl) phthalate; dimethyl cellosolve phthalate

Physical Form. Light colored, clear liquid

Uses. Plasticizer; solvent

Exposure. Inhalation

Toxicology. Dimethoxyethyl phthalate (DMEP) causes teratogenic, reproductive, and fetotoxic effects in animals.

Acute lethality data indicate that DMEP exhibits slight to moderate toxicity. The oral LD_{50} in rats ranged from 3.2 to 6.4 g/kg.[1] Exposure of rats to 1595 ppm for 6 hours caused deaths of all animals, whereas 770 ppm for 6 hours was not lethal.[2] The dermal LD_{50} in guinea pigs was greater than 10 ml/kg, suggesting very little absorption.

Fetotoxic and teratogenic effects were observed in rats administered 0.374 ml/kg of DMEP via intraperitoneal injection on days 5, 10, and 15 of gestation.[3] Resorptions occurred at an incidence of 27.6%, and teratogenic effects included skeletal and gross abnormalities. Pregnant rats given a single intraperitoneal injection of 0.6 ml/kg on day 10, 11, 12, 13, or 14 of gestation had offspring with skeletal malformations.[4] A single intraperitoneal injection of 2.38 ml/kg in mice resulted in a marked reduction in the incidence of pregnancies and litter size per pregnancy.[5] In another study, DMEP administered intraperitoneally to rats on day 12 of gestation produced hydronephrosis, short limbs and tails, and rare heart defects, including dilated ductus arteriosus and aortic arch and ventral polydactyly.[6]

It has been hypothesized that DMEP acts by in vivo hydrolysis to 2-methoxyethanol, also a known teratogen, which in turn is metabolized to methoxyacetic acid, the proximate teratogen.[6,7]

Oral administration of 1000 mg/kg by gavage to male rats for a total of 12 treatments over 16 days caused reduced testes weight and increases in abnormal sperm heads.[8]

DMEP did not cause dermal sensitization in guinea pigs.[2] In the eyes of rabbits, it was not irritating.

A threshold limit value (TLV) for dimethoxyethyl phthalate has not been established by the ACGIH.

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DIMETHYLACETAMIDE
CAS: 127-19-5

$CH_3CON(CH_3)_2$

Synonyms: Acetyldimethylamine; *N*,*N*-dimethyl acetamide; DMAC

Physical Form. Colorless liquid

Uses. Commercial solvent especially for textile fibers

Exposure. Inhalation; skin absorption

Toxicology. Dimethylacetamide (DMAC) causes liver damage.

Workers repeatedly exposed to 20–25 ppm developed jaundice; appreciable skin absorption was thought to have occurred.[1] Nine patients with neoplastic disease were given daily doses of 400 mg/kg by an unspecified

route for 3 or more days as a therapeutic trial; they experienced depression, lethargy, confusion, and disorientation; on the last (fourth or fifth) day of therapy or within 24 hours thereafter, the patients had visual and auditory hallucinations, perceptual distortions, and at times delusions; after 24 hours these effects gradually subsided.[2]

The median lethal concentration was 2475 ppm in rats, and repeated exposures caused liver injury.[3] Male mice exposed to 480 ppm 6 hours/day for 10 exposures showed no signs of clinical toxicity, but mild degeneration and atrophy of the seminiferous tubules was observed at necropsy.[4] No pathologic changes were seen in adult rats similarly exposed. Prepubescent mice were more sensitive to DMAC; 10 exposures at 490 ppm caused 20% mortality, labored breathing, lethargy, and tremors. Histologic lesions included testicular seminiferous tubule hypertrophy, hepatocellular necrosis and hypertrophy, lymphoid organ atrophy, bone marrow hypoplasia, and adrenal cortical necrosis. In another study repeated exposure of rats to a concentration of 195 ppm for 6 months resulted in focal necrosis of the liver; exposure to 40 ppm for the same period of time caused no adverse effects.[5]

Dimethylacetamide was not oncogenic in either mice or rats exposed to 25, 100, or 350 ppm 6 hours/day, 5 days/week for 18 months (mice) or 2 years (rats).[6] Compound-related morphologic changes were found in the liver of both species at the highest doses.

Rabbits receiving dermal exposures of 2000 mg/kg showed anorexia and weakness followed in many instances by cyanosis and death.[3]

The approximate lethal dose for skin absorption in pregnant rats and rabbits was 7.5 and 5.0 g/kg, respectively.[7] Cutaneous application of DMAC resulted in a marked incidence of embryo mortality at doses that did not affect maternal body weight or produce any signs of maternal toxicity. Teratogenic effects (three fetuses from one dam with encephalocele; one of eight with diffuse subcutaneous edema) were found in rats only when DMAC was applied on gestation days 10 and 11 at a total dose of 2400 mg/kg.[7] In another study, DMAC administered by gavage to rats caused treatment-related malformations of the fetal heart, major vessels, and oral cavity but only at levels (400 mg/kg/day) that also produced significant maternal toxicity and other indicators of fetal toxicity including increased postimplantation loss and skeletal variation.[8] Pregnant rats exposed 6 hours/day on days 6–15 of gestation to 30, 100, or 300 ppm had maternal toxicity at the highest dose but no significant increase in the incidence of external, visceral, or skeletal malformations.[9]

In practice, the dermal absorption factor is considered to be so significant that no air concentration, however low, will provide protection if skin contact with the liquid is permitted.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for dimethylacetamide is 10 ppm (36 mg/m^3) with a notation for skin absorption.

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DIMETHYLAMINE
CAS: 124-40-3

$(CH_3)_2NH$

Synonyms: *N*-methylmethanamine; DMA

Physical Form. Gas, liquefying at 7°C

Uses. Manufacture of pharmaceuticals; stabilizer in gasoline; in production of insecticides and fungicides; in manufacture of soaps and surfactants

Exposure. Inhalation; skin contact

Toxicology. Dimethylamine is an irritant of the skin and respiratory tract.

Dermatitis and conjunctivitis are occasionally observed in chemical workers after prolonged exposure.[1] No systemic effects from industrial exposure have been reported.

The LC_{50} for rats exposed 6 hours to dimethylamine and observed for 48 hours after exposure was 4540 ppm.[2] Clinical observations were characterized by signs of eye irritation immediately after onset of exposure, followed by gasping, secretion of bloody mucus from the nose, salivation, and lacrimation within 1 hour of exposure. Corneal opacity was generally observed after 3 hours of exposure. Death was often preceded by convulsions. Rats exposed to nonlethal concentrations (600–2500 ppm for 6 hours) showed signs of eye irritation, moderate gasping, and slight bloody nasal discharge. At autopsy findings included severe congestion, ulcerative rhinitis, and necrosis of the nasal turbinates. At concentrations above 2500 ppm, peripheral emphysema, bronchopneumonia, hepatic necrosis, and corneal ulceration were noted.

At lower concentrations, 175–500 ppm, less damage to the lower respiratory tract occurred, but inflammation, ulcerative rhinitis, and early squamous metaplasia were observed in the respiratory nasal mucosa.[3] Various species survived 5 ppm of continuous exposure for 90 days without signs of toxicity, but at autopsy, some showed mild inflammatory changes in the lungs.[4]

Chronic exposure for 6 hours/day, 5 days/week for 1 year to concentrations ranging from 10 to 175 ppm caused concentration-related lesions in the nasal passages in rats and mice.[5] The respiratory epithelium in the anterior nasal passages and the olfactory epithelium were primarily affected. Hyperplasia of basophilic cells adjacent to the basement membrane was present in the high-dose rats only. At 10 ppm there was minimal loss of olfactory sensory cells in a few mice and rats. In a subsequent report, male rats were exposed to 175 ppm of DMA 6 hours/day for 1, 2, 4, or 9 days or 2 years.[6] Severe tissue destruction occurred in the anterior nose after a single 6-hour exposure; however, there was little evidence of progression of the lesions even after 2 years. The findings indicated a possible regional susceptibility to DMA toxicity or a degree of adaptation by the rat to continued exposure. Despite damage to the nasal epithelium the mucociliary apparatus continued to function in the exposed rats, and this clearance system responded to alterations of nasal structure by modification of mucus flow patterns.[6]

Intraperitoneal injection of 2.5 or 5 mmol/kg/day into pregnant CD-1 mice on days 1–17 of gestation did not cause any obvious maternal or fetal effects.[7] Added to mouse embryo cultures, dimethylamine inhibited embryo development.[7]

Skin contact with the liquid causes necrosis, and a drop in the eye may result in severe corneal injury or permanent corneal opacity.

A "fish" odor is detectable at 0.5 ppm, which may provide warning of overexposure.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for

dimethylamine is 5 ppm (9.2 mg/m^3) with a short-term excursion limit of 15 ppm (27.6 mg/m^3).

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4-DIMETHYLAMINOAZOBENZENE

CAS: 60-11-7

$C_6H_5N_2C_6H_4N(CH_3)_2$

Synonyms: *p*-Dimethylaminoazobenzene; butter yellow; DAB

Physical Form. Yellow solid

Uses. Formerly used as a coloring agent in foods, drugs, and cosmetics

Exposure. Inhalation

Toxicology. 4-Dimethylaminoazobenzene (DAB) is a potent carcinogen in animals.

In humans, contact dermatitis was observed in 90% of factory workers handling DAB.[1] There have been no reports of an increased cancer incidence among exposed persons.[2]

Two of 10 dogs survived ingestion of 20 mg/kg/day for 38 months of continuous treatment followed by 48 months of intermittent treatment; both developed bladder papillomas.[3] Oral administration of 1, 3, 10, 20, or 30 mg/day produced liver tumors in rats; the induction time was inversely proportional to the daily dose, ranging between 34 days for the 30 mg/day dose and 700 days for the 1 mg/day dose.[4] In rats fed 5 mg DAB/day for 40–200 days and then kept for their life span on a normal diet, there was a 20–81% incidence of liver carcinoma.[5]

Cutaneous application of 1 ml of a 2% solution of DAB in acetone two times/week for 90 weeks caused skin tumors in all six male rats treated. Squamous cell, basal cell, and anaplastic carcinomas were observed; there were no tumors in controls given acetone alone.[6]

DAB was genotoxic in the comet assay inducing DNA damage in the stomach, colon liver, bladder, lung, and bone marrow.[7] It is also mutagenic to *Salmonella* in the Ames test. Because of its demonstrated carcinogenicity in animals, human exposure to DAB by any route should be avoided. In recent years, this compound has been used only in laboratories as a model of tumorigenic activity in animals.[8] It is not produced commercially in the United States and is of little occupational health importance.

The ACGIH has not established a threshold limit value (TLV) for 4-dimethylaminoazobenzene.

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N,N-DIMETHYLANILINE

CAS: 121-69-7

$C_6H_5N(CH_3)_2$

Synonyms: Dimethylphenylamine; aminodimethylbenzene (Note: also known as dimethylaniline, which is a synonym for xylidine)

Physical Form. Yellow to brown oily liquid

Uses. Intermediate in the manufacture of dyes; solvent; rubber vulcanizing agent and stabilizer

Exposure. Inhalation; skin absorption

Toxicology. N,N-Dimethylaniline absorption causes anoxia due to the formation of methemoglobin.

Few reports of industrial experience are available from which to form an accurate appraisal of its health hazards; it is said to be less potent than aniline as a cause of methemoglobin, but more of a central nervous system depressant. The effects of methemoglobinemia are cyanosis (especially of the lips, nose, and earlobes), weakness, dizziness, and severe headache.[1]

In dogs, the repeated subcutaneous injection of 1.5 g caused vomiting, weakness, cyanosis, methemoglobinemia, and hyperglobulinemia.[2] Rats survived an 8-hour exposure to concentrated vapor.[3] The single-dose oral LD_{50} for rats was 1.41 ml/kg, and the single-dose dermal LD_{50} for rabbits was 1.77 ml/kg.

Continuous exposure of rats by inhalation to 0.0055 and 0.3 mg/m^3 for 100 days resulted in methemoglobinemia, lowered erythrocyte hemoglobin, leukopenia and reticulocytosis, and reduced muscle chronaxie.[4] Doses up to 500 mg/kg administered by gavage to rats and mice for 13 weeks caused cyanosis and decreased motor activity, as well as hemosiderosis in the spleen liver, kidney, and testes.[5] Bone marrow hyperplasia was observed in rats, and mice had increased hematopoiesis in the liver. In general, all toxic effects could be attributed to chronic methemoglobinemia, erythrocyte destruction, and erythrophagocytosis.

Mice and rats administered up to 30 mg/kg by gavage, 5 days/week for 103 weeks had an increased incidence of forestomach papillomas (female mice) and an increase in splenic sarcomas (male rats) that exceeded normal historical controls.[6]

IARC has determined that there is inadequate evidence in humans for the carcinogenicity of N,N-dimethylaniline and limited evidence in animals.[4] Overall, N,N-dimethylaniline is not classifiable as to its carcinogenicity in humans.

N,N-Dimethylaniline induced gene mutation, sister chromatid exchange, and chromosomal aberrations in cultured mammalian cells. It was not mutagenic in *Salmonella typhimurium*.[4]

The liquid was slightly irritating to the clipped skin of rabbits within 24 hours of a

0.01-ml application, and 0.005 ml caused severe burns when instilled in rabbit eyes.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for N,N-dimethylaniline is 5 ppm (25 mg/m^3) with a short term excursion level of 10 ppm (50 mg/m^3) and a notation for skin absorption.

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DIMETHYL CARBAMOYL CHLORIDE

CAS: 79-44-7

$(CH_3)_2NCOCl$

Synonyms: Dimethylcarbamic chloride; (dimethylamino)carbonyl chloride; dimethyl carbamyl chloride; DMCC

Physical Form. Liquid

Uses. As a chemical intermediate in the manufacture of carbamate drugs and pesticides

Exposure. Inhalation

Toxicology. Dimethyl carbamoyl chloride is a skin, eye, and respiratory irritant; it is carcinogenic in experimental animals by skin application and by subcutaneous or intraperitoneal injection.

One case of eye irritation and one of impaired liver function have been observed in workers exposed to dimethyl carbamoyl chloride.[1]

When rats were exposed to saturated vapors five of six or six of six died after 1 or 2 hours, respectively. Dimethyl carbamoyl chloride damaged the mucous membranes of the nose, throat, and lungs and caused difficulty in breathing, sometimes several days after exposure.[1] Rats tolerated an 8-minute exposure to the saturated vapors and survived 14 days after exposure. Fifty-one of 100 rats exposed 6 hours/day for 15 days at 10 ppm succumbed.

Applied to the skin of rats and rabbits, the undiluted liquid produced skin irritation, with subsequent degeneration of the epidermis; skin sensitization tests in guinea pigs were negative.

In long-term animal studies, dimethyl carbamoyl chloride produced local tumors by each of three routes of administration.[2] Two milligrams applied to the skin of mice three times/week for 492 days caused skin papillomas in 40 of 50 animals; of these, 30 progressed to skin carcinomas. After weekly subcutaneous injections of 5 mg for 26 weeks, 36 of 50 female

mice developed local sarcomas and 3 had local squamous cell carcinomas. Weekly intraperitoneal injections of 1 mg of the chemical for up to 450 days resulted in papillary tumors of the lung in 14 of 30 treated mice, compared with 10 of 30 mice given the vehicle alone. Eight treated mice and one control developed local sarcomas, and one treated mouse developed a squamous cell carcinoma of the skin.

In another study, exposure of rats and male hamsters by inhalation induced a high incidence of nasal tract carcinomas.[3]

No cancer deaths or X ray indications of lung cancer were found in an investigation of 39 dimethyl carbamoyl chloride production workers, 26 processing workers, and 42 ex-workers, aged 17–65, exposed for periods ranging from 6 months to 12 years.[1]

The IARC has determined that there is sufficient evidence in experimental animals for the carcinogenicity of dimethyl carbamoyl chloride and inadequate evidence in humans; in its overall evaluation the IARC considers dimethyl carbamoyl chloride as probably carcinogenic to humans.[4]

Dimethyl carbamoyl chloride is a direct-acting alkylating agent with a wide spectrum of genotoxic activity.[4] ACGIH has classified dimethyl carbamoyl as A2-a suspected human carcinogen with no threshold limit value (TLV).

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DIMETHYLFORMAMIDE
CAS: 68-12-2

$(CH_3)_2NCHO$

Synonyms: DMF; DMFA; *N*,*N*-dimethylformamide

Physical Form. Colorless liquid

Uses. Solvent

Exposure. Inhalation; skin absorption

Toxicology. Dimethylformamide (DMF) is toxic to the liver.

Subjective complaints of exposed workers have included nausea, vomiting, and anorexia.[1] Air concentration measurements may not define the total exposure experience because DMF is readily absorbed through the skin as well as the lungs. A worker who was splashed with the liquid over 20% of the body surface initially suffered only dermal irritation and hyperemia. Abdominal pain began 62 hours after the exposure and became progressively more severe, with vomiting, and the blood pressure was elevated to 190/100. The effects gradually subsided and were entirely abated by the 7th day after the exposure.[2] Some workers have noted flushing of the face after inhalation of the vapor, especially with coincident ingestion of alcohol.[2]

Hepatomegaly, jaundice, and altered liver function tests have been reported in accidental poisonings with DMF. An outbreak of toxic liver disease was associated with DMF exposure at a fabric coating factory.[3] Thirty-six of 58 workers had elevations of either aspartate aminotransferase or alanine aminotransferase. Serological tests excluded known infectious causes of hepatitis in all but two cases. After modification of work practices and removal of the most severely affected from exposure, improvement in liver enzyme abnormalities and symptoms occurred in most patients. Medical surveillance of the working population for 14 months revealed no further cases of toxic liver

disease, indicating that DMF was the causative agent of the outbreak.[4]

Case reports of testicular cancer in leather tannery workers and aircraft mechanics have suggested an association with DMF, but further epidemiological studies have not confirmed the relationship.[5–8]

A case control study of four plants where DMF was produced or used showed no statistically significant association between ever having been exposed to DMF and subsequent development of cancers of the buccal cavity and pharynx, liver, prostate, and testes and malignant melanoma.[9] Although prostate cancer was significantly elevated at one plant when examined by plant site, it did not appear to be related to exposure level or duration.

The IARC has determined that there is inadequate evidence for the carcinogenicity of dimethylformamide in humans.[7]

In both mice and rats exposed 6 hours/day 5 days/week for 12 weeks, the no-effect dose was below 150 ppm and the maximum tolerated dose was below 600 ppm. At doses of up to 1200 ppm there were few signs of overt toxicity, and at necropsy the only treatment related lesions occurred in the liver.[10] Subchronic studies in monkeys showed no exposure-related adverse health effects or reproductive effects after exposure 6 hour/day, 5 days/week for 13 weeks to concentrations of up to 500 ppm.[11]

Chronic inhalation studies in rodents found no increase in tumors.[7] The IARC has determined that there is evidence suggesting lack of carcinogenicity of DMF in animals. Metabolic studies of DMF show quantitative differences in human and rodent pathways, suggesting that rodent studies may not be indicative of human results.[12]

Inhalation and epicutaneous exposures of DMF by rats have produced no teratogenic effects and only slight evidence of embryotoxicity at levels producing some maternal toxicity.[13,14]

In a number of short-term assays, DMF was not mutagenic or genotoxic.[15] Inconsistent results have been reported in human *in vivo* studies for sister chromatid exchange and chromosomal aberration frequencies.[8]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for dimethylformamide is 10 ppm (30 mg/m^3) with a notation for skin absorption.

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1,1-DIMETHYLHYDRAZINE

CAS: 57-14-7

$C_2H_8N_2$

Synonyms: asym-Dimethylhydrazine; unsymmetrical dimethylhydrazine; dimazine; UDMH

Physical Form. Colorless liquid

Uses. Base in rocket fuel formulations; intermediate in organic synthesis

Exposure. Inhalation; skin absorption

Toxicology. 1,1-Dimethylhydrazine is a respiratory irritant and convulsant; it is carcinogenic in experimental animals.

Accidental human exposures have resulted in eye irritation, choking sensation, chest pain, dyspnea, lethargy, nausea, and skin irritation.[1] On the basis of the results of exposure in dogs, the effects expected in humans from exposure for 60 minutes are: 100 ppm, irritation of eyes and mucous membranes; 200 ppm, marked central nervous system stimulation and perhaps death; 900 ppm, convulsions and death.[2] Impairment of liver function (elevated SGPT levels) has been reported in 47 of 1193 workers exposed to 1,1-dimethylhydrazine under variable conditions; in a few of these cases fatty infiltration of the liver was also demonstrated by liver biopsy, although alcohol intake may have been a factor in some cases.[3]

Exposure of dogs to 111 ppm for 3 hours caused vomiting, convulsions, and death; at autopsy, pulmonary edema and hemorrhage were present but were believed to be a secondary manifestation of the convulsive seizures rather than a primary effect of the agent.[4] Dogs repeatedly exposed to 25 ppm developed vomiting, diarrhea, ataxia, convulsions, and hemolytic anemia.[4] At 5 ppm for 26 weeks dogs had slightly decreased body weight, hemolytic anemia, and hemosiderosis of the spleen.[5]

Applied to the shaved skin of dogs the liquid was mildly irritating and rapidly absorbed; the dermal LD_{50} was between 1.2 and 1.7 g/kg.[6] In the eye, it caused mild conjunctivitis.[7]

Administration of 0.1% in the drinking water of 50 male and 50 female Swiss mice resulted in a high incidence of angiosarcomas in various organs (79%); tumors of the lungs (71%), kidneys (10%), and liver (7%) were also observed.[8] In another study, mice given daily gavage doses of 0.5 mg, 5 days/week for 40 weeks showed inconclusive evidence of lung tumor induction.[7] Chronic inhalation of 1,1-dimethylhydrazine by rats produced benign tumors of the lung and pituitary.[9] A broad distribution of tumors occurred in mice after inhalation, with the respiratory system and liver most severely affected. Lesions of the respiratory system included inflammation and other indications of chronic insult including a variety of rare, but benign, tumors of the upper respiratory system and the more common lung adenoma; liver lesions included a variety of benign and malignant tumors. These lesions were seen sporadically at 0.05 ppm.

The carcinogenic risk to humans has not been determined, but 1,1-dimethylhydrazine is classified as a suspected human carcinogen based on animal results. The National Institute for Occupational Safety and Health (NIOSH) has also noted that the role of nitrosodimethylamine, a contaminant of 1,1-dimethylhydrazine, must be considered in evaluating the tumorigenicity of 1,1-

dimethylhydrazine.[7] In one follow-up report, using pure 1,1-dimethylhydrazine, investigators were able to demonstrate that previous oncogenic findings and findings of their study could not be explained by the contaminant.[9]

In a report on embryotoxicity, intraperitoneal administration of 10, 30, or 60 mg/kg/day in rats on days 6–15 of pregnancy caused a dose-dependent reduction in maternal weight gain and slight embryotoxicity in the form of reduced 20-day fetal weights in the high-dose group.[10]

1,1-Dimethylhydrazine was genotoxic in a wide variety of assays.[11]

The ammonical or fishy odor has variously been reported as detectable between 6 and 14 ppm and below 0.3 ppm.[7]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 1,1-dimethylhydrazine is 0.01 ppm (0.025 mg/m^3) with an A3 confirmed animal carcinogen with unknown relevance to humans designation and a notation for skin absorption.

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DIMETHYL HYDROGEN PHOSPHITE

CAS: 868-85-9

$(CH_3O)_2POH$

Synonyms: DMHP; dimethoxyphosphine oxide; dimethyl phosphite; methyl phosphonate

Physical Form. Colorless liquid with a mild odor

Uses. As a flame retardant on Nylon 6 fibers; intermediate in the production of pesticides and herbicides; as a stabilizer in oil and plaster; an additive to lubricants

Exposure. Inhalation

Toxicology. Dimethyl hydrogen phosphite (DMHP) is an irritant of the eyes, mucous membranes, and skin; it causes neurological impairment and reversible cataracts in animals; it is carcinogenic in rats and causes testicular atrophy in mice.

No human cases of intoxication have been reported.[1]

The acute oral LD_{50} values for dimethyl hydrogen phosphite were 3300 and 3000 mg/kg body weight (bw) for male and female Fischer 344/N rats, respectively, and 2800 mg/kg bw for male B6C3F1 mice.[1]

Rats exposed to airborne levels of 934 ppm, 6 hours/day for 3 days died.[2] Effects observed included irritation of the skin, eyes, and mucous membranes, neuromuscular impairment, and lung congestion. Rats exposed to 431 ppm, 6 hours/day for 5 days survived but exhibited the same irritant effects as seen at 934 ppm.

In a month-long study, rats were exposed to 12, 35, 119, or 198 ppm for 6 hours/day, 5 days/week.[3,4] In the high-dose group, 27 of 40 animals were dead by day 27; in the 119 ppm group, 2 animals died on days 14 and 23. There was neurological impairment at 198 ppm and 119 ppm that usually reversed by the following morning. Necrosis and purulent inflammation of the skin were thought to be the only lesions that may have caused death. Although there was treatment-related irritation of the eyes and nares, there was no treatment-related irritation of the trachea or lungs. Lenticular opacities occurred at 35 ppm and above, which progressed to cataracts in the 119 and 198 ppm groups. In rats killed 2 weeks after treatment, the process of cataract formation had stopped; at 4 weeks the formation of normal lens fibers was evident.

Rats treated with 200 mg/kg/day by gavage for 4, 5, or 6 weeks showed early treatment-related changes in the lungs (significant increases in serum angiotensin) and possible preneoplastic changes in the forestomach, characterized by epithelial hyperplasia, hyperkeratosis, subepithelial and submucosal inflammation, and edema.[5]

In a carcinogenic study, male and female rats were given DMHP by gavage 5 days/week for 103 weeks.[6] At 200 mg/kg, there were increases in alveolar/bronchiolar carcinomas, squamous cell carcinomas of the lung, and carcinomas of the stomach in male rats. Neoplastic lesions did not occur in mice after similar treatments. Species-dependent differences in the metabolism of DMPH were limited to more rapid metabolism and elimination by mice compared with rats. Therefore, the species variations in carcinogenicity are most likely attributable to other factors, with metabolism playing only a minor role.[7] The IARC determined that there is limited evidence for the carcinogenicity of dimethyl hydrogen phosphite in experimental animals and that it is not classifiable as to its carcinogenicity to humans.[8]

Limited data indicate that DMHP may have testicular effects; calcification and atrophy of the testes were observed in mice in the course of chronic and subchronic oral studies at 200 mg/kg for 103 weeks and 375 and 750 mg/kg for 13 weeks, respectively.[6]

Dimethyl hydrogen phosphite was not mutagenic to several strains of *Salmonella typhimurium*, but it did cause sister chromatid exchanges and chromosomal aberrations in the Chinese hamster CHO line.[1]

An ACGIH threshold limit value (TLV) has not been established for dimethyl hydrogen phosphite.

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DIMETHYL METHYLPHOSPHONATE

CAS: 756-79-6

$C_3H_9O_3P$

Synonyms: Phosphonic acid, methyl-, dimethyl ester; DMMP

Physical Form. Solid

Uses. As a flame retardant, a preignition additive for gasoline, an antifoam agent, a plasticizer and stabilizer, a textile conditioner, and an antistatic agent; used experimentally to mimic the physical and spectroscopic (but not biological) properties of anticholinesterase agents

Exposure. Inhalation

Toxicology. Dimethyl methylphosphonate (DMMP) administered to male rats is a reproductive toxicant and carcinogen. Effects in humans are unknown.

The acute oral LD_{50} is estimated to be greater than 3000 mg/kg for rats and greater than 6000 mg/kg for mice.[1] Clinical signs reported in rats and mice after doses of up to 6810 mg/kg included inactivity, unsteady gait, and prostration. In 15-day studies, compound-related deaths occurred at 5000 mg/kg/day and above in rats and at 10,000 mg/kg/day in mice; the only compound-related lesions observed were stomach lesions in the mice.

DMMP administered to male Fischer rats by gavage 5 days/week for 90 days at dosages of 250, 500, 1000, and 2000 mg/kg caused a dose-related decrease in sperm count, sperm motility, and the male fertility index.[2] When mated, treated males sired fewer litters with fewer pups per litter, and untreated dams had more resorptions. The percentage of resorptions was 6.1% in the control group and increased to 14.9%, 37.8%, and 79.1% in the 250, 500, and 1000 mg/kg groups, respectively. Histologic abnormalities of the testis were only observed in the high-dose group and were characterized by lack of spermatogenesis or by degeneration, vacuolization, and necrosis of cells in the spermatogenic tubules. Microscopic changes of the prostate were also observed in some of the high-dose animals, whereas abnormalities of the kidney (tubular cell regeneration, hyalin droplet degeneration, and cellular infiltrate) were seen in some animals from each of the dosed groups.

Further study of the reproductive lesions in male rats showed morphologic alterations in Sertoli cells and elongating spermatids, as well as functional defects in spermatozoa after administration of 1750 mg/kg for up to 12 weeks.[3]

In chronic studies, DMMP was administered by gavage in corn oil for up to 2 years at doses of 500 or 1000 mg/kg/day to rats and at doses of 1000 or 2000 mg/kg/day to mice.[1,4] Survival in dosed male rats was reduced, due in part to renal toxicity. Lesions of the kidney included increased severity of spontaneous age-related nephropathy including calcification, hyperplasia of the tubular and transitional epithelium, tubular cell adenocarcinomas, and transitional cell papillomas and carcinomas. Similar lesions were not seen in female rats or in mice of either sex, although reduced survival in male mice prevented adequate analysis. The

authors noted that the spectrum of lesions observed in male rats after DMMP treatment is similar to that seen after chronic administration of a variety of other chemicals, including unleaded gasoline, hydrocarbon solvents, and 1,4-dichlorobenzene, suggesting that a common mechanism may be responsible for the lesions. It cannot be determined whether the kidney tumors seen in male rats after DMMP administration are predictive of carcinogenicity to humans. It has been suggested that certain compounds including DMMP that give a positive result in animal carcinogenicity studies through mechanisms involving secondary carcinogenesis are of questionable significance to humans.[5]

DMMP was not mutagenic in *Salmonella* assays.[6] An ACGIH threshold limit value (TLV) has not been established for dimethyl methylphosphonate.

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2,4-DIMETHYLPHENOL

CAS: 105-67-9

$C_6H_3(CH_3)_2OH$

Synonyms: *m*-xylenol; 1-hydroxy-2,4-dimethylbenzene; 2,4-xylenol; Lysol Brand Disinfectant, soluble concentrate (1.5% solution)

Physical Form. Solid

Uses. Disinfectant; manufacture of pharmaceuticals, plastics, insecticides, fungicides, rubber chemicals, wetting agents, dyestuffs

Exposure. Inhalation; skin absorption

Toxicology. 2,4-Dimethylphenol is expected to be an irritant of the eyes, mucous membranes, and skin, by analogy to other phenols.

The oral LD_{50} for rats was 3.2 g/kg; the dermal LD_{50} in mice was 1.04 g/kg.[1]

Gavage administration of 1200 mg/kg for 10 days was lethal to male and female rats; at 600 mg/kg for the same time period, there was a significant increase in relative liver weight in females and alterations in hematologic and clinical chemistries in males.[2] Hyperkeratosis and epithelial hyperplasia of the forestomach were observed in rats after administration of 180 or 540 mg/kg for 90 days.[2] The higher dose also caused reduced body weights and some deaths in treated animals. In mice, gavage administration of 250 mg/kg/day for 90 days caused squinting, lethargy, prostration and ataxia; significant hematologic changes also occurred in females.[3]

In a dermal carcinogenicity study in mice, twice-weekly application of 20% 2,4-dimethylphenol in benzene (after a single pretreatment with 0.3% dimethylbenzanthracene in benzene as an initiator) produced papillomas in 50% and carcinomas in 11% of animals at 15 weeks; by 23 weeks, 18% had developed carcinomas.[4] When 10% 2,4-dimethylphenol in benzene was applied twice weekly in the absence of an initiator, 31% had papillomas at

20 weeks and no carcinomas were observed. By 24 weeks, 12% had carcinomas.

2,4-Dimethylphenol was tested for mutagenicity in the *Salmonella* microsome preincubation assay using the standard protocol of the National Toxicology Program and five strains of *Salmonella*; results were negative.[5]

The ACGIH has not established a threshold limit value (TLV) for 2,4-dimethylphenol.

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DIMETHYL PHTHALATE

CAS: 131-11-3

$C_{10}H_{10}O_4$

Synonyms: 1,2-benzenedicarboxylic acid dimethyl ester; phthalic acid dimethyl ester; methyl phthalate

Physical Form. Oily liquid

Uses. Plasticizer; insect repellent for application to the skin

Exposure. Inhalation (of spray or mist); skin absorption

Toxicology. Dimethyl phthalate (DMP) is of low-order acute toxicity.[1]

A solution, including 2% DMP in petrolatum, was nonirritating to humans after 48-hour patch tests.[2]

Rats fed 4.0% and 8.0% in the diet showed slight, but significant, changes in growth; chronic nephritis was seen at the higher dose, but mortality rates were the same as controls.[3] Applied to 10% of the body surface of rabbits for 90 days, 4.0 ml/kg caused some deaths with pulmonary edema and slight renal damage; no skin irritation was observed.[4] The undiluted liquid instilled into rabbit eyes produced no grossly observable irritation for up to 48 hours.[5]

Intraperitoneal injection of pregnant rats with 10%, 33%, or 50% of the LD_{50} (3.4 ml/kg) on days 5, 10, and 15 of gestation resulted in litters with a higher number of skeletal abnormalities.[6] These results were not confirmed in a more recent study in which mice were administered up to 5% DMP in the drinking water during gestation.[7] Although treatment with 5% DMP resulted in increased relative maternal liver weight and reduced body weight gain, there was no effect on any parameter of embryo/fetal development. Adult males exposed perinatally to 750 mg/kg by gavage from gestational day 14 through postnatal day 3 showed no effects of the testis, epididymis, or reproductive organs; by contrast, testicular alterations have consistently been found in male rats exposed to phthalate esters with adjacent 4- to 6-carbon primary side chains.[8]

In genotoxic assays DMP was determined to be a weak bacterial mutagen.[9]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for dimethyl phthalate is 5 mg/m^3.

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DIMETHYL SULFATE

CAS: 77-78-1

$(CH_3)_2SO_4$

Synonyms: Sulfuric acid dimethyl ester; DMS

Physical Form. Colorless, oily liquid

Uses. Methylating agent in the manufacture of many organic chemicals

Exposure. Inhalation; skin absorption

Toxicology. Dimethyl sulfate (DMS) is highly toxic; it is a severe irritant of the eyes, mucous membranes, and skin; it is carcinogenic in experimental animals.

When DMS comes into contact with a moist mucosal surface it is slowly hydrolyzed into sulfuric acid, methanol, and methyl hydrogen sulfate.[1] The methanol can be absorbed into the circulation, leading to neurotoxic effects, whereas the sulfuric acid and methyl hydrogen sulfate induce severe irritative and erosive actions to the mucosa.

Several human deaths have occurred from occupational exposure, and it has been estimated that inhalation of 100 ppm for 10 minutes would be fatal.[2,3] A major cause of mortality in DMS intoxication is respiratory failure, a consequence of mucosal inflammation and edema of major airways and of noncardiogenic pulmonary edema. Often, exposure of humans produces no immediate effects other than occasional slight eye and nose irritation; after a latent period of up to 10 hours or more, there is onset of headache and giddiness with intense conjunctival irritation, photophobia, and angioneurotic edema, followed by inflammation of the pharyngolaryngeal mucosa, dysphonia, aphonia, dysphagia, productive cough, oppression in the chest, dyspnea, and cyanosis.[2,4] Vomiting and diarrhea may intervene.[2,4] Dysuria may occur for 3–4 days; there may be persistence of laryngeal edema for up to 2 weeks and of photophobia for several months. Other effects include delirium, fever, convulsions, and coma as well as damage to heart, liver, and kidneys.[2,5] The long-term sequelae of acute DMS poisonings has been examined in 62 patients followed for 2–12 years.[1] Hoarseness remained in 33% of the moderately to severely intoxicated patients. Mild ventilatory disturbances were demonstrated in five cases, and mild to moderate pulmonary function abnormalities were observed in three patients. No abnormalities were found in ECG and routine blood examinations. No evidence of pulmonary neoplasms was found on follow-up chest X rays. In another case there was persistent cough and mucopurulent sputum 10 months after exposure, with repeated infective episodes, probably secondary to mucosal damage by DMS.[6] It was not known whether more extensive fibrosis would develop with time.

Contact of the liquid with the eyes or skin will cause very severe burns because of its pow-

erful vesicant action.[2] In an incident of moderate skin contact with the liquid, generalized intoxication occurred even though there was prompt treatment of the skin; vapor inhalation was for a few minutes at the most.[5]

In mice and rats, inhalation at 0.1–4.0 ppm throughout pregnancy caused preimplantation losses and embryotoxic effects including anomalies of the cardiovascular system.[3] In another study, no significant fetal effects were detected in rats exposed to 1.5 ppm 6 hours/day during days 7 through 16 of gestation. At this dose maternal toxicity was evidenced by reduced food consumption and body weight gain.[7]

Dimethyl sulfate is carcinogenic to animals after its inhalation or subcutaneous injection, producing mainly local tumors, and after prenatal exposure, producing tumors of the nervous system.[8] Of 15 rats surviving exposure to 10 ppm 1 hour/day for 19 weeks, 3 developed squamous cell carcinoma of the nasal cavity, 1 developed a glioma of the cerebellum, and another developed lymphosarcoma of the thorax with metastases in the lungs. Several early deaths from inflammation of the nasal cavity and pneumonia were also reported.[8] A statistically significant increase in lung adenomas was observed in a group of 90 mice exposed at 4 ppm for 4 hours/day, 5 days/week. A single intravenous dose of 20 mg/kg given to 8 pregnant rats on day 15 of gestation induced malignant tumors, including 3 tumors of the nervous system, in 7 of 59 offspring that were observed for over 1 year.[9]

Despite anecdotal case reports of cancer in exposed individuals, no significant increase in mortality or deaths from lung cancer was found in a group of workers exposed for various periods between 1932 and 1972.[3,8]

The IARC has determined that there is sufficient evidence for the carcinogenicity of dimethyl sulfate to experimental animals and inadequate evidence in humans; overall, it should be regarded as probably carcinogenic to humans.[8]

Dimethyl sulfate is a potent genotoxic chemical and can directly alkylate DNA both *in vivo* and *in vitro*.[3,8] The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for dimethyl sulfate is 0.1 ppm (0.5 mg/m^3) with a notation for skin absorption and an A2-suspected human carcinogen designation.

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DINITROBENZENE (all isomers)
CAS: 25154-54-5

1,2-Dinitrobenzene: CAS 528-29-0
1,3-Dinitrobenzene: CAS 99-65-0
1,4-Dinitrobenzene: CAS 100-25-4

$C_6H_4(NO_2)_2$

Synonyms: Dinitrobenzol; DNB; 1,2-DNB; 1,3-DNB; 1,4-DNB; *ortho*-dinitrobenzene; *meta*-dinitrobenzene; *para*-dinitrobenzene

Physical Form. Colorless or yellowish needles or plates

Uses. Synthesis of dyestuffs, explosives, celluloid production

Exposure. Inhalation; skin absorption

Toxicology. All isomers of dinitrobenzene (DNB) cause anoxia due to the formation of methemoglobin; moderate exposure causes respiratory tract irritation, and chronic exposure results in anemia. Testicular toxicity has been reported in laboratory animals after ingestion of *m*-DNB.

Exposed workers have complained of a burning sensation in the mouth, dry throat, and thirst; somnolence, staggering gait, and coma have been observed with more intense exposures.[1] Most signs and symptoms of overexposure are due to the loss of oxygen-carrying capacity of the blood.

The onset of symptoms of methemoglobinemia is insidious and may be delayed for up to 4 hours; headache is commonly the first symptom and may become quite intense as the severity of methemoglobinemia progresses.[2] Cyanosis occurs when the methemoglobin concentration is 15% or more; blueness in the lips, the nose, and the earlobes is usually recognized by fellow workers.[2]

The subject usually feels well, has no complaints, and is insistent that nothing is wrong until the methemoglobin concentration approaches approximately 40%.[2] At methemoglobin concentrations of over 40%, there is usually weakness and dizziness; at up to 70% concentration, there may be ataxia, dyspnea on mild exertion, tachycardia, nausea, vomiting, and drowsiness.[2] Coma may ensue with methemoglobin levels of about 70%, and the lethal level is estimated to be 85–90%.[3]

Five workers at an Ohio rubber plant became ill with symptoms, including yellow discoloration of the hands, blue discoloration of the lips and nail beds, headache, nausea, chest pain, dizziness, confusion, and difficulty in concentrating; one worker suffered a seizure.[4] Medical examinations showed that blood methemoglobin levels ranged from 3.8% to 41.2%. Effects were attributed to dermal exposure to an adhesive containing 1% by weight *p*-DNB. After replacement of the adhesive, symptoms disappeared and methemoglobin levels were within normal limits.

In another report of acute intoxication by *m*-DNB dust, six workers developed cyanosis followed by slight to moderate anemia.[5] Prolonged recovery from the anemia (approximately 1 month) was characteristic of the cases, but no adverse health effects were attributable to the exposure in a 10-year follow-up.

The ingestion of alcohol aggravates the toxic effects of dinitrobenzene. In general, higher ambient temperatures increase susceptibility to cyanosis from exposure to methemoglobin-forming agents. Chronic exposure of workers causes anemia; there are scattered reports of liver injury. Visual impairment has occurred in the form of reduced visual acuity and central scotomas, particularly for red and green colors; yellow discoloration of the conjunctiva and sclera is common.[1,6] Yellow-brown discoloration of the hair and exposed skin of workers has also been observed.[1]

A number of animal studies have shown that *m*-DNB is a potent testicular toxicant. Subchronic ingestion of 20 mg/l in drinking water caused testicular atrophy in rats.[7] At higher levels of 200 mg/l, more than 50% of the seminiferous tubules were collapsed, with neither germinal cells nor Sertoli cells present. Male rats gavaged 5 days/week with 3.0 mg/kg/day did not sire litters when bred with females during treatment week 10.[8] Dimin-

ished sperm production, decreased cauda epididymal sperm reserves, nonmotile spermatozoa, atypical sperm motility, decreased weights of the testes and epididymis, and seminiferous tubular atrophy were also observed. Sperm production was also decreased in males dosed at 1.5 mg/kg/day. Single acute exposure of rats to 48 mg/kg caused alterations in testis weight and sperm motility; histologic changes included maturation depletion of mid- and late spermatids and immature germ cells in the epididymis.[9] Fertilizing ability was lost by 5–6 weeks after treatment, and some animals failed to recover within 5 months. Susceptibility to the reproductive effects of *m*-DNB varied with the age of the animals in this study. Increases in plasma lactate dehydrogenase isozyme C4 (LDH-C4) were found to precede noticeable histologic findings of testicular damage in rats.[10] LDH-C4 may be used as a biochemical marker of acute testicular damage.

Marked differences in species susceptibility to *m*-DNB have also been observed.[11] Hamsters showed no testicular lesions at dose levels up to 50 mg/kg, whereas damage to rat testicular tubules was readily apparent at 25 mg/kg. Similarly, *m*-DNB induced substantially less methemoglobin in the hamster than in the rat (15% vs. 80% at 25 mg/kg dose).

Follow-up studies have demonstrated that *m*-DNB exerts a direct effect on the germinal epithelium and not through alterations in hypothalamic and pituitary control of gonadal function.[12] No reproductive effects have been reported in humans.

In vitro studies show that *m*-DNB is mutagenic in *Salmonella typhimurium*.[13]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for all isomers of dinitrobenzene is 0.15 ppm (1.0 mg/m^3) with a notation for skin absorption.

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DINITRO-*o*-CRESOL
CAS: 534-52-1

$CH_3C_6H_2OH(NO_2)_2$

Synonyms: DNOC; 2-methyl-4,6-dinitrophenol; dinitrol

Physical Form. Yellow, crystalline solid

Uses. Herbicide; insecticide; intermediate in the synthesis of fungicides; polymerization inhibitor for vinyl aromatic compounds

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Dinitro-*o*-cresol (DNOC) causes an increase in metabolic rate that results in hyperpyrexia. Severe exposure may cause coma and death. Exposure also causes a yellow pigmentation of the skin, hair, sclera, and conjunctivae.

DNOC is an uncoupler of mitochondrial oxidative phosphorylation resulting in increased cellular respiration (increased oxygen consumption) and the release of energy in the form of heat because energy is no longer captured by adenosine diphosphate (ADP) to form adenosine triphosphate (ATP).[1] The shortage of ATP in critical organs such as the heart and respiratory muscles may lead to the blocking of their vital functions.[1] Symptoms associated with DNOC toxicity are restlessness, flushed skin, sweating, thirst, deep and rapid respiration, tachycardia, severe increase of body temperature, cyanosis, coma, and death.[1]

In a report of eight fatalities among agricultural sprayers, symptoms of intoxication included fatigue, profuse sweating, excessive thirst, and weight loss, which were incorrectly attributed to heat strain.[2] There was rapid decline with hyperpnea, tachycardia, and fever; death occurred within 48 hours of exposure.

The risk of serious intoxication increases during hot weather.[1] A nonfatal case of intoxication resulting from exposure to 4.7 mg/m^3 resulted in fever, tachycardia, hyperpnea, profuse sweating, cough, shortness of breath, and a marked increase in basal metabolic rate.[3] The clinical picture resembled that of thyroid crisis.

Lethal doses may be absorbed through the skin; local irritation is usually slight. Skin application of 50 g of a 25% dinitro-*o*-cresol ointment to a 4-year-old boy caused vomiting, headache, yellow stained skin and sclera, elevated pulse and respiratory rate, unconsciousness, and death within 3.5 hours.[3] Autopsy showed diffuse petechial hemorrhages in the intestinal mucosa and brain, as well as pulmonary edema.

In human volunteers given 75 mg/day orally for 5 days, the earliest symptom was an exaggerated sense of well-being at blood levels of dinitro-*o*-cresol of approximately 20 µg/g.[4] At a level near 40 µg/g of blood, symptoms were headache, lassitude, and malaise; yellow coloration of the sclera appeared on the fourth day of exposure and persisted for 5 days; urinary excretion of unchanged dinitro-*o*-cresol was so slow that blood levels of 1–1.5 µg/g were still detectable 40 days after the last dose was administered.[4] Blood levels appear to correlate with the severity of intoxication.[3] Individuals with concentrations of 40 µg/g of whole blood or greater will most likely develop toxic effects. Those with ranges between 20 and 40 µg/g may or may not show adverse effects, and most with blood levels below 20 µg/g are not affected.[3]

The development of bilateral cataracts has been reported in chronic intoxication due to the repeated ingestion of dinitro-*o*-cresol for ill-advised therapeutic purposes; cataracts have not been observed after industrial or agricultural exposure.[3] Contact with the eyes or absorption of DNOC by any route can cause a characteristic yellow staining of the conjunctiva and sclera of the eye.[5] DNOC stains human skin yellow on contact. Although the yellow staining of the skin and sclera may be unsightly, such cosmetic effects are not regarded as adverse.[5]

In reproductive studies, DNOC did not affect either sperm counts or testicular weights in mice given single doses in the range of

3–12 mg/kg/day for 5 days.[6] Intermediate-duration feeding and gavage studies have suggested that the ovaries and uterus may be target organs of DNOC.[5] In addition, male rats fed DNOC for 90 days had aspermatogenesis. However, these results have not been confirmed in other studies using similar dosing protocols.[5] DNOC did not induce teratogenic effects in rats receiving oral doses up to 25 mg/kg body weight/day from gestation day 6 to 15.

In one chronic feeding study in rats DNOC did not cause an increased incidence of any type of tumor.[1] DNOC was clastogenic, increasing the frequency of chromosomal aberrations both *in vivo* and *in vitro*.[5] Conflicting results for mutagenicity have been obtained in bacterial assays.[5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for dinitro-*o*-cresol is 0.2 mg/m^3 with a notation for skin absorption.

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2,4-DINITROPHENOL

CAS: 51-28-5

$C_6H_4N_2O_5$

Synonyms: 2,4-DNP; Aldifen; Chemox PE; Dinofan; Fenoxyl Carbon N; Maroxol 50; Caswell No. 392; Sulfo Black B; Nitro Kleenup

Physical Form. Yellow solid

Uses. In manufacture of dyes, other organic chemicals, wood preservatives, photographic developer, and explosives

Exposure. Inhalation

Toxicology. 2,4-Dinitrophenol (2,4-DNP) uncouples oxidative phosphorylation from electron transport, resulting in diminished production of ATP, with the energy dissipated as heat, which can lead to fatal hyperthermia.[1]

Fatal cases of 2,4-DNP poisoning were reported among workers in the munitions industry in France.[2] Workers were exposed to airborne vapor and dust of 2,4-DNP and had direct dermal contact with the solid material, although duration and levels of exposure were not reported. Deaths were preceded by sudden onset of extreme fatigue, elevation of body temperature to 40°C or more, profuse sweating, thirst, and labored respiration. No characteristic lesions were found at autopsy.

Two workers exposed to mists and dust of 2,4-DNP in a US chemical plant for a few months developed fever, profuse sweating, and restlessness.[3] After treatment and rest they returned to work, collapsed, and died. Workroom air levels, measured after the deaths, were found to be at least 40 mg/m^3, and significant dermal exposure may also have occurred.

During the 1930s, 2,4-DNP was used extensively as a weight loss agent.[4] Cataracts developed in a small percentage of patients who took the agent, with at least 164 cases in the published literature.[5] Representative case reports that provided doses indicate that cataracts developed in the patients at doses

ranging from 1.86 to 3.6 mg/kg/day, but no correlation with duration of exposure could be established. Individual susceptibility to 2,4-DNP induced cataractogenesis appears to vary widely. Development of agranulocytosis, peripheral neuritis, and dermal effects such as rash, pruritus, urticaria, and maculopapular skin lesions were also observed.[6,7]

No teratogenic effects have been reported in limited developmental toxicity studies in rodents. Decreased fetal body weight and crown-rump length were noted in rats and mice after parenteral administration.[5]

2,4-DNP was not genotoxic in most in vivo and *in vitro* studies.[5]

An ACGIH threshold limit value (TLV) has not been established for 2,4-DNP.

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DINITROTOLUENE (all isomers)
CAS: 25321-14-6

$CH_3C_6H_3(NO_2)_2$

Synonyms: DNT, dinitroluol

Physical Form. Yellow crystals

Uses. In the production of toluene diisocyanate, which is, in turn, used to produce polyurethane foams; explosives; dyes

Exposure. Inhalation; skin absorption

Toxicology. Dinitrotoluene (DNT) exposure causes anoxia owing to the formation of methemoglobin; in animal studies, chronic exposure to the 2,6-DNT isomer has been associated with hepatocellular carcinomas.

There are six isomers of DNT, with technical or commercial DNT composed primarily of 2,4-DNT (80%) and 2,6-DNT (20%). The lethal doses of the various DNT isomers range from 309 mg/kg for 3,5-DNT to 1102 mg/kg for 2,3-DNT in male rats; in male mice the 3,5-isomer has an LD_{50} of 611 mg/kg, whereas the 2,4-isomer has an LD_{50} of 1924 mg/kg.[1] The individual isomers were generally less toxic in mice than rats, and the lethal dose for cats was much lower than for rodents (27 mg/kg for the 2,4-isomer).

In humans, very early reports found pallor, cyanosis, and anemia as common symptoms in workers exposed to presumably high concentrations of technical DNT.

Hematologic effects have been observed in a variety of animal studies. The most common findings are methemoglobinemia, anemia, reticulocytosis, and an increase in Heinz bodies. Cyanosis was observed in rats administered 60 mg/kg/day of 2,4-DNT for 5 days.[2] Severe anemia occurred in dogs administered 25 mg/kg/day and rats administered 206 mg/kg/day for 13 weeks; mild anemia was seen in mice given 441 mg/kg/day for the same duration.[3] In chronic studies, hematologic effects have been observed, but the animals

often exhibited "compensated anemia," an adaptive response to the DNT exposure.

Neurological signs were noted in one dog receiving 10 mg/kg/day of 2,4-DNT for 8 weeks and consisted of tremors followed by extensor rigidity; minimal signs in other animals consisted of incoordination and stiffness, particularly in the hind legs.[1]

A chronic study in rats showed isomer-specific hepatocarcinogenesis in F344 rats. Administration of 7 or 14 mg/kg/day of 2,6-DNT for 1 year produced hepatocellular carcinomas in 85% and 100% of the animals, respectively.[4] The majority of the tumors had a trabecular pattern, and pulmonary metastases were present. In contrast, a diet of 27 mg/kg/day of 2,4-DNT for 1 year caused no tumors. Treatment with 35 mg/kg/day of technical-grade DNT, containing 76% 2,4-DNT and 18% 2,6-DNT, resulted in a 47% incidence of hepatocellular tumors. The results demonstrated that the 2,6-isomer is a potent and complete hepatocarcinogen, under the test conditions, whereas the 2,4-isomer is nonhepatocarcinogenic. The results also explain the inconsistent results that had been reported in previous bioassays: In an initial study by the National Cancer Institute (NCI) 2,4-DNT was found to be nonhepatogenic, whereas a CIIT study produced a 100% incidence in the same strain with a technical-grade DNT.[5,6] In the NCI bioassay 2,6-DNT comprised less than 5% of the DNT, whereas in the CIIT study it was over 18% of the mixture. Chronic studies are not available on the other isomers.

In an attempt to determine whether the carcinogenicity observed in animal studies was predictive for humans, the mortality experience of ammunitions workers with opportunity for substantial DNT exposure was examined. No evidence of carcinogenic effect was found, but an unsuspected excess of ischemic heart disease was noted. Additional analyses showed evidence of a 15-year latency period and suggested a relationship with duration and intensity of exposure.[7]

A study of nearly 5000 DNT-exposed workers found an excess of liver and biliary cancer among those employed at least 5 months at the study facility between 1949 and 1980 and with at least 1 day on a job with probable DNT exposure.[8] The six observed cases were statistically significant based on comparison with an internal referent group of unexposed workers. The authors noted the limitations of a small number of workers with long duration of exposure and the lack of quantitative information on exposure levels to DNT and other chemicals. A retrospective cohort study of this same population did not find increased mortality from ischemic heart disease.[9]

The IARC has determined that there is sufficient evidence in experimental animals for the carcinogenicity of 2,4 DNT and 2,6-DNT; there is inadequate evidence in humans for the carcinogenicity of 2,4-, 2,6-, and 3,5-DNT.[10]

Animal studies have shown that oral exposure to DNT can result in adverse effects on reproduction. Observed effects have included decreased sperm production, testicular atrophy, changes in Sertoli cell morphology, degenerated seminiferous tubules, and decreased fertility.[1] It has been suggested that DNT acts on Sertoli cells, resulting in both inhibition of spermatogenesis and changes in testicular-pituitary endocrine activity.[11] A study of 30 workers exposed to DNT and other chemicals found a decrease in sperm counts relative to controls, a slight change in one category of abnormal sperm, and a slight increase in spontaneous abortions for wives.[1] Other studies reported no detectable differences in sperm levels or fertility rates as a result of occupational exposure.[12]

Dinitrotoluene was not found to be teratogenic after oral administration to rats; embryo/fetal toxicity was observed only at a dose that also produced 46.2% maternal mortality.[13]

The DNTs appear to cause mutations in *Salmonella typhimurium* assays after metabolic activation.[12] In vivo 2,4-DNT causes unscheduled DNA synthesis in rat hepatocytes and chromosomal aberrations in human lymphocytes; both 2,4- and 2,6-DNT have induced DNA adducts in rat liver.[12]

All six isomers have been found to be nonirritating in the eye of rabbits. Applied to the skin of rabbits, 2,4-, 2,6-, and 3,5-DNT were

nonirritating whereas 2,3-, 3,4-, and 2,5-DNT were mildly to moderately irritating.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for dinitrotoluene is 0.2 mg/m^3 (0.03 ppm) with an A3-confirmed animal carcinogen with unknown relevance to humans designation and a notation for skin absorption.

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DIOXANE
CAS: 123-91-1

$C_4H_8O_2$

Synonyms: 1,4-Diethylene dioxide; diethylene ether; 1,4-dioxacyclohexane; 1,4-dioxane; *p*-dioxane; dioxyethylene ether

Physical Form. Colorless liquid

Uses. Solvent; stabilizer in chlorinated solvents

Exposure. Inhalation; skin absorption

Toxicology. Dioxane is an irritant of the eyes and mucous membranes; on prolonged exposure it is toxic to the liver and kidneys. It is carcinogenic in experimental animals.

Human volunteers exposed to 50 ppm for 6 hours reported eye irritation throughout the exposure.[1] At 300 ppm for 15 minutes there was transient eye, nose, and throat irritation.[2] Exposure to 1600 ppm for 10 minutes caused immediate burning of the eyes with lacrimation, and at 5500 ppm for 1 minute slight vertigo was also noted.[3]

Five deaths due to heavy exposure for 5

weeks were reported.[4] Signs and symptoms of poisoning included epigastric pain, anorexia, and vomiting, followed by oliguria, anuria, coma, and death. At autopsy, there was liver necrosis, kidney damage, and edema of the lungs and brain. Another fatal case involved a 1-week exposure to levels ranging from 208 to 605 ppm and possibly higher with concurrent skin exposure.[5] Epigastric pain, increased blood pressure, convulsions and unconsciousness preceded death. Studies of workers exposed at levels up to 24 ppm for periods of up to 50 years found no increase in chronic disease, no excess total deaths, no excess cancer deaths, and no common cause of death.[6]

Applied to human skin, dioxane causes dryness without other signs of irritation; hypersensitivity has been reported.[6]

In animal experiments, guinea pigs exposed to 30,000 ppm for 3 hours exhibited narcosis after 87 minutes and died within 2 days.[7] The LC_{50} for rats was 14,000 ppm for 4 hours.[8] Repeated exposure of several animal species to 1000 ppm produced damage to kidneys and liver, and repeated inhalation of 800 ppm over 30 days resulted in fatal kidney injury in some exposed rabbits.[7,9]

The liquid applied to rabbit and guinea pig skin was rapidly absorbed and produced signs of incoordination and narcosis. Repeated applications caused liver and kidney damage.[6] Instilled in a rabbit's eye dioxane produced hyperemia and purulent conjunctivitis.[10]

High doses of dioxane by oral administration produced malignant tumors of the nasal cavity and liver in rats, and tumors of the liver and gallbladder in guinea pigs.[11] Rats administered either 0.5% or 1.0% (vol/vol) in the drinking water had squamous cell carcinomas of the nasal turbinates; hepatocellular adenomas were seen in the dosed females.[12] In another study, inhalation of 111 ppm, 7 hours/day, 5 days/week for 2 years did not result in any increased tumor incidence in rats.[13]

A mortality study of 165 workers who had been exposed to low concentrations of dioxane (since 1954) did not show any increased cancer risk.[14]

Most tests for genotoxic activity including bacterial assays, chromosomal aberration assays, sister chromatid exchange assays, and Chinese hamster ovary (CHO) micronucleus assays have produced negative results; the *in vivo* mouse liver micronucleus assay was positive after oral administration of up to 3000 mg/kg.[15]

The IARC has determined that there is sufficient evidence of carcinogenicity to animals and inadequate evidence in humans and that dioxane is possibly carcinogenic to humans.[11]

Administered to rats by gavage on days 6–15 of gestation, 1.0 ml/kg/day caused slight embryo and maternal toxicity in the form of reduced weights. There were no teratogenic effects.[16]

The warning properties are inadequate to prevent overexposure. Although dioxane has a low odor threshold (3–6 ppm), it is not unpleasant and individuals acclimatize within a few minutes.[6]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for dioxane is 25 ppm (90 mg/m^3) with a notation for skin absorption.

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DIPHENYLAMINE

CAS: 122-39-4

$(C_6H_5)_2NH$

Synonyms: *N*-phenylbenzeneamine; *N*-phenylaniline; *N*,*N*-diphenylamine; *N*-diphenylaniline; DPA

Physical Form. Colorless solid

Uses. Rubber antioxidant and accelerator; fungicide; in veterinary medicine; stabilizer for nitrocellulose explosives and celluloids; manufacture of dyes

Exposure. Inhalation; oral

Toxicology. Diphenylamine causes kidney and liver damage in animals.

A single report of skin sensitization indicates that diphenylamine could be a skin sensitizer in humans. It is slightly irritating to rabbit skin and moderately to severely irritating in rabbit eyes.[1]

In a 2-year feeding study of beagle dogs of both sexes, 0.01%, 0.1%, or 1% diphenylamine was administered in the diet.[2] Decreased weight gain and anemia were noted at the two higher levels. Increases in liver and kidney weights were observed at the highest level. Rats fed diets ranging from 0.5% to 2.5% for 1–2 years had cystic dilation of renal tubules and a reversible anemia.[3] Diphenylamine treatment did not cause an increase in neoplasms in either species.

Cystic lesions of the proximal nephron occurred in newborn offspring of pregnant rats treated with commercial diphenylamine during gestation. No significant cystic tubule changes were identified in pups whose dams were administered chromatographically pure diphenylamine. An impurity present in diphenylamine, *N*,*N*,*N*′-triphenyl-*p*-phenylenediamine, has been identified as inducing polycystic kidney disease.[4]

Diphenylamine was not mutagenic in the Ames *Salmonella typhimurium* test.[5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 10 mg/m^3.

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1,2-DIPHENYLHYDRAZINE

CAS: 122-66-7

$C_{12}H_{12}N_2$

Synonyms: Hydrazobenzene; *N,N'*-diphenylhydrazine; sym-diphenylhydrazine

Physical Form. White, crystalline solid

Uses. Formerly used as a starting material in the production of benzidine for dyes; production of certain drugs.

Exposure. Ingestion; inhalation; skin absorption

Toxicology. 1,2-Diphenylhydrazine is a liver toxin in rodents and appears to be carcinogenic in experimental animals.

No information is available on the toxicity of 1,2-diphenylhydrazine in humans.

In rats and mice given 1,2-diphenylhydrazine in the diet for 4 weeks, the lethal ranges were 54 mg/kg/day and above for rats and 390 mg/kg/day and above for mice.[1] Gross pathologic examinations showed intestinal hemorrhages in mice that died.

Chronic oral administration (78 weeks treatment, followed by observation) of 4 or 15 mg/kg/day in male rats and 2 or 5 mg/kg/day in females caused significantly increased mortality in the high-dose females. In mice mortality was increased for males and females at 52 mg/kg/day. The cause(s) of the mortality in the rats and mice was not indicated. Statistically increased incidences of interstitial inflammation of the lungs were observed in treated male rats and in low-dose females but not in mice. Treatment also produced degenerative alterations in the liver of rats (fatty metamorphosis) and female mice (coagulative necrosis), and in treated male rats there was stomach hyperkeratosis and acanthosis. In these same animal studies, 1,2-diphenylhydrazine caused increased incidences of hepatocellular carcinoma and zymbal gland carcinomas in male rats; neoplastic nodules of the liver and mammary adenocarcinomas were observed in female rats; and in female mice, there was an increased incidence of hepatocellular carcinomas.

Animals did not show histologic alterations in reproductive organs in chronic studies, but reproductive function was not evaluated.[1,2]

1,2-Diphenylhydrazine is a solid with a low vapor pressure at ambient temperature, which makes inhalation exposure of this substance in the vapor state unlikely. Exposure to dusts of 1,2-diphenylhydrazine is conceivable.[2]

Limited information is available on the metabolism of 1,2-diphenylhydrazine.[2] Two of the known metabolites, aniline and benzidine, may contribute to the toxicity and/or carcinogenicity of the substance.

A threshold limit value (TLV) has not been established for 1,2-diphenylhydrazine.

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DIPROPYLENE GLYCOL METHYL ETHER

CAS: 34590-94-8

$CH_3OC_3H_6OC_3H_6OH$

Synonyms: Dipropylene glycol monomethyl ether; DPGME; DPM

Physical Form. Colorless liquid

Uses. Solvent for nitrocellulose and synthetic resins

Exposure. Inhalation

Toxicology. Dipropylene glycol methyl ether (DPGME) at very high concentrations causes narcosis in animals, and it is expected that severe exposure will produce the same effect in humans. Because the propylene glycol ethers are metabolized differently from the ethylene glycol ethers, they are not associated with potent teratogenic, spermatotoxic, or hematopoietic effects.[1]

Concentrations expected to be hazardous to humans are disagreeable and not tolerated; in addition, concentrations above 200 ppm (40% saturated atmosphere) are difficult to attain, suggesting that these levels would not normally be encountered in the work environment.[2] Vapor concentrations reported as 300 ppm caused eye and nasal irritation in humans.[3] No evidence of skin irritation or sensitization was observed when the undiluted liquid was applied to the skin of 250 subjects for prolonged periods or after repeated applications.[3]

A single 7-hour exposure of rats to 500 ppm resulted in mild narcosis with rapid recovery.[3] Repeated daily inhalation exposures to 300–400 ppm for over 100 days produced minor histopathologic liver changes in rabbits, monkeys, and guinea pigs; rats initially experienced slight narcosis but developed tolerance to this effect after a few weeks.[3] Daily exposure of rats and rabbits to 200 ppm for 13 weeks caused no effects.[2] Topical administration of 10 mg/kg five times/week for 13 weeks to shaved rabbit skin caused six deaths among seven animals.[3]

The LD_{50} for rats was 5.4 ml/kg; the low oral toxicity indicates that there is practically no likelihood that toxic amounts of these materials would be swallowed in ordinary handling and use.[3]

DPGME was not embryo/fetotoxic or teratogenic in rats or rabbits when administered by inhalation during gestation at the highest concentration (300 ppm) that is practicably attainable at room temperature and pressure.[4]

Direct contact of the eyes with the liquid or with high vapor concentrations may cause transient irritation.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for dipropylene glycol methyl ether is 100 ppm (606 mg/m^3) with a short-term excursion limit of 150 ppm (909 mg/m^3) and a notation for skin absorption.

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DIPROPYL KETONE

CAS: 123-19-3

$(CH_3CH_2CH_2)_2CO$

Synonyms: 4-heptanone; DPK; propyl ketone; butyrone; heptan-4-one

Physical Form. Colorless liquid

Uses. Solvent for nitrocellulose, oils, resins, and polymers and in flavorings

Exposure. Inhalation

Toxicology. Dipropyl ketone causes narcosis in animals, and it is expected that severe exposure in humans will produce the same effect.

The oral LD_{50} in rats was 3.73 g/kg.[1] The LC_{50} for 6-hour exposure was 2690 ppm in the rat; 6 hours at 1600 ppm caused narcosis.[2] Repeated exposure for 6 hours/day to 1200 ppm for 5 days/week for 2 weeks caused marginal liver enlargement.

The liquid on the skin of guinea pigs under occlusive wrap caused slight irritation.[2] In the eye of the rabbit there was also slight irritation.

There are no reports of adverse effects in humans.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for dipropyl ketone is 50 ppm (233 mg/m^3).

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DIQUAT
CAS: 85-00-7

$C_{12}H_{12}Br_2N_2$

Synonym: 1,1-Ethylene-2,2-dipyridylium dibromide

Physical Form. Yellow crystals; available commercially as aqueous solutions (15–25% wt/vol) and as water-soluble granules (2.5%)

Use. Contact herbicide

Exposure. Inhalation; ingestion; skin absorption

Toxicology. Diquat causes gastrointestinal damage, and in animals chronic exposure produces cataracts.

The estimated lethal dose for humans is 6–12 g of diquat.[1] Ingestion may cause severe and extensive mucosal damage to the mouth, stomach, and small intestine.[2] As a consequence, generalized abdominal pain, vomiting, and diarrhea can occur. Paralytic ileus may develop 1–4 days after exposure and is thought to be responsible for the accumulation of large amounts of fluid in the gut, leading to hypovolemic shock.[2] Nephrotoxicity has frequently been reported and may range from transient proteinuria to acute renal failure. Altered liver function as shown by a rise in liver transaminase is usually mild. Ventricular arrhythmias, pulmonary complications, and coma have occurred in fatal cases. Postmortem findings have included diffuse erosions and mucosal necrosis of the esophagus, stomach, and ileum, acute tubular necrosis, and bronchopneumonia.[2] There has been no evidence of proliferative or fibroplastic changes in the lung characteristic of paraquat intoxication.

Skin contact with concentrated solutions may lead to a color change and softening of the fingernails.[1] Shedding of the nail was reported after prolonged contact.[2] Exposure to the dust or mist can cause nosebleeds and throat irritation.

The oral LD_{50} in rats ranged from 230 to 440 mg/kg.[3] Effects included dilated pupils, lethargy, and labored respiration. The primary systemic effect of diquat in animals is gastrointestinal damage resulting in diarrhea with consequent dehydration.[4] When diquat was applied daily to the skin of rabbits at 40 mg/kg, four of six rabbits died after 8–20 applications. Before death, there was weight loss, incoordination, and muscular weakness.[3]

Prolonged exposure to diquat is necessary

to produce cataracts, and a clear dose-response relationship has been established in chronic feeding studies in animals. At a level of 1000 ppm complete opacities occurred in rats within 6 months; at 50 ppm for 12 months only some of the animals exhibited slight opacities.[1] Lens opacities developed within 11 months in dogs fed 15 mg/kg/day and within 17 months at 5 mg/kg/day.[3] Dogs tolerated 1.7 mg/kg/day for 4 years without developing cataracts.

Rats exposed to 1.9 mg/m^3 for 4 hours/day, 6 days/week for 5 months showed inflammatory changes in the peribronchial and perivascular connective tissues.[5] Long-term studies have shown no carcinogenic potential.[3,5] Most mutagenicity data suggest that diquat is not mutagenic.[1]

In a multigeneration study of reproductive effects, levels of 500 or 125 ppm did not effect fertility, litter production, or litter size and did not cause congenital abnormalities.[6] Lens opacities were found in the parents and F_1 and F_2 generation receiving 500 ppm, but not at the 125 ppm level.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for diquat is 0.5 mg/m^3 for total dust and 0.1 mg/m^3 for the respirable fraction of dust; there is a notation for skin absorption.

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DISULFIRAM
CAS: 97-77-8

$C_{10}H_{20}N_2S_4$

Synonyms: Antabuse; bis(diethylthiocarbamoyl) disulfide; TETD; tetraethylthiuram disulfide; Thiuram E

Physical Form. White crystalline solid

Uses. Rubber accelerator and vulcanizer, as an activator of thiazole accelerators, and as a plasticizer in neoprene; pharmaceutical grade used in treatment of alcoholism

Exposure. Inhalation

Toxicology. Disulfiram affects the central nervous system, thyroid, and skin; in combination with alcohol it causes an "Antabuse-alcohol" syndrome.

Small doses of disulfiram reportedly can cause effects on thyroid iodine uptake and thyroid gland hypertrophy.[1] It may also produce dermatitis and acneform rashes.

Most of the human experience with disulfiram has come from its use as an avoidance therapy for alcoholism. Metabolites of disulfiram inhibit aldehyde dehydrogenase, resulting in elevated levels of acetaldehyde after ethanol ingestion. Side effects include flushing of the face, tachycardia, severe headache, apprehension, hyperpnea, hypotension, dizziness, nausea, vomiting, and fainting.[2] Severe reactions may include convulsions, myocardial infarction, and marked respiratory depression.[1]

Disulfiram metabolites include diethyldithiocarbamate and its metabolites, the moieties that irreversibly inhibit aldehyde

dehydrogenase, and carbon disulfide, thought to be responsible for the occasional polyneuritis and psychotic episodes.[3,4] Several episodes of hepatotoxicity have also been reported.[5,6] Type-IV allergic contact dermatitis has been observed in a few individuals.[7]

In a lifetime carcinogenicity bioassay, disulfiram was not carcinogenic in either rats or mice when fed in the diet.[8] The highest doses were 600 ppm in rats and 2000 ppm in mice.

Increased fetal resorptions, but no teratogenic effects, were seen in rats exposed at 100 mg/kg/day from day 3 of gestation.[1] A weak genotoxic response was observed in mice treated in vivo as evidenced by an increase in sister chromatid exchanges in bone marrow and spermatogonial cells.[9]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 2 mg/m^3.

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DISULFOTON

CAS: 298-04-4

$C_8H_{19}O_2PS_3$

Synonyms: *O*,*O*-diethyl-*S*-ethylmercaptoethyldithiophosphate; Di-Syston; Frumin AL; Solvirex; Dithiosystox; Thiodementon

Physical Form. Pure material is a colorless liquid, and technical grade is a dark yellow liquid

Uses. Systemic insecticide and acaracide

Exposure. Inhalation; skin absorption

Toxicology. Disulfoton is an anticholinesterase agent.

Exposure to disulfoton can result in inhibition of cholinesterase activity in blood and at nerve synapses of muscles, secretory organs, and nervous tissue in the brain and spinal cord.[1] Central nervous system signs and symptoms include anxiety, restlessness, depression of respiratory and circulatory centers, ataxia, convulsions, and coma.

Nicotinic signs of intoxication include muscle weakness, tremor and fasciculations, and involuntary twitching. Muscle weakness that affects the respiratory muscles may contribute to dyspnea and cyanosis. Tachycardia may result from stimulation of sympathetic ganglia in cardiac tissue and may mask the bradycardia due to the muscarinic action on the heart. Nicotinic action at the sympathetic ganglion may also result in pallor, high blood pressure, and hyperglycemia.

Muscarinic signs include miosis, increased salivation, sweating, urination and defecation, vomiting and nausea, and increased bronchial secretions.

Severe signs and symptoms of disulfoton intoxication (miosis, salivation, monoplegia) were observed in a man within 2–3 hours of consuming 3–4 tablespoons of disulfoton.[2] Five volunteers received an oral dose of 0.75 mg/day for 30 days without an adverse effect on plasma or erythrocyte cholinesterase.[3]

Oral LD_{50} values between 6.2 and 12.5 mg/kg body weight (bw) for males and between 1.9 and 4.2 mg/kg bw for females have been reported in rats.[3] Inhalation LC_{50} values for rats were 290 mg/m^3 in males and 63 mg/m^3 for females.

Tolerance to repeated or sublethal exposures of disulfoton has been demonstrated.[3]

Typically, the cholinergic symptoms (tremors, fasiculations, excessive salivation) disappear with increasing duration of exposure but the acetylcholinesterase activity remains depressed.

There was no evidence of a carcinogenic response in mice fed 2.08 mg/kg/day for 23 months or in beagle dogs fed up to 0.098 mg/kg/day for 2 years.[3]

Disulfoton was not fetotoxic or teratogenic in the offspring of rabbits administered doses of 1.5 mg/kg/day, which caused clinical signs of maternal toxicity.[3]

Equivocal results have been reported in genotoxic assays, including positive and negative results in bacterial assays and sister chromatid exchange studies. Mutagenic potential was not demonstrated in assays for chromosomal aberrations, nor did disulfoton induce micronuclei in mice exposed *in vivo*.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for disulfoton is 0.1 mg/m^3 with a notation for skin absorption.

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DIVINYL BENZENE

CAS: 1321-74-0

$C_{10}H_{10}$

Synonyms: Diethenylbenzene; DVB; 1,4-divinyl benzene; vinylstyrene

Physical Form. Straw-colored liquid

Uses. Comonomer for preparation of cross-linked polymers in production of ion exchange beads and gel permeation chromatography polystyrene beads; polymerization monomer for synthetic rubber, drying oils, and casting resins

Exposure. Inhalation

Toxicology. Divinyl benzene is an irritant of eyes, nose, and mucous membranes.

Mild respiratory irritation occurred in workers exposed to 0.4–4 ppm divinyl benzene.[1] Mild irritation was also reported from skin and eye contact.

A single 2-hour exposure of five rats to fume generated from polymerizing divinyl benzene at 120°C yielded a level of 27,317 ppm and produced peripheral vasodilation, lethargy, salivation, bilateral corneal opacity, and dyspnea.[2] When the temperature of the polymerizing divinyl benzene was kept at 80°C, yielding a concentration in the chamber of 3312 ppm, effects were ataxia, tachypnea,

ocular irritation, and rhinitis. Exposure of rats for 7 hours to 645 ppm resulted in no observable effects.

Male and female mice exposed at 0, 25, 50, or 75 ppm 6 hours/day, 5 days/week for up 2 weeks had concentration-dependent changes in the olfactory epithelium; hepatocellular necrosis was observed at the highest dose, and some male mice also had transient tubular damage in the kidneys.[3]

Instillation of 0.1 ml into the eyes of rabbits for 30 seconds caused irritation and conjunctivitis, the latter of which was still present 8 days later.[4] On the abdominal skin of rabbits, a mixture of divinyl benzene and ethyl vinyl benzene repeatedly applied and occluded for 2 weeks caused slight erythema, edema, and moderated exfoliation at the application site.

Divinyl benzene was weakly genotoxic *in vivo*, inducing a dose-dependent increase in sister chromatid exchanges and an increase in the frequency of chromosome aberrations in male mice exposed at concentrations of up to 75 ppm for 3 days.[5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for divinyl benzene is 10 ppm (53 mg/m^3).

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ENDOSULFAN
CAS: 115-29-7

$C_9H_6Cl_6O_3S$

Synonyms: Thiodan

Physical Form. Technical endosulfan is a semiwaxy solid containing 90–95% of a 70% : 30% mixture of the α and β stereoisomers

Uses. Insecticide

Exposure. Inhalation

Toxicology. Endosulfan is a convulsant.

Convulsions were reported in nine workers exposed to the endosulfan-containing insecticide Thiodan® during bagging of the product.[1] Other effects noted before the convulsions were malaise, nausea, vomiting, dizziness, confusion, and weakness. Level and duration of exposure were not indicated. Similar symptoms (tonic and clonic convulsions, vomiting, confusion, and muscular twitchings) were reported in 18 cases of endosulfan overexposure during spraying operations.[2]

Accidental or intentional ingestion of endosulfan has resulted in death in humans. In two cases of suicide, the dose was up to 100 ml of Thiodan®, and in three other poisonings the doses were not specified.[3] Initial signs of poisoning included gagging, vomiting, diarrhea, agitation, writhing, cyanosis, dyspnea, and coma.

Signs of acute endosulfan intoxication in animals are similar to those seen in humans and include hyperexcitability, dyspnea, decreased respiration, fine tremor, and tonic-clonic convulsions. Oral LD_{50} values range from 7.4 mg/kg in male mice to 40–125 mg/kg for

male rats.[4–6] Female rats were 4–5 times more sensitive to acute effects than male rats.[5]

In a 2-year carcinogenicity study rats and mice were fed endosulfan in the diet for the first 80% of their life span and then observed for the remaining 20%.[7] In rats there was a high incidence of toxic nephropathy in both sexes and testicular atrophy in males. In both species high early morality was observed in the male groups, and no conclusions could be drawn regarding carcinogenicity. There was no evidence of carcinogenicity in the female mice or rats. In another study dietary concentrations of 75 ppm for rats and 18 ppm for mice caused increased incidence of enlarged kidneys and progressive glomerulonephrosis in rats but no increased tumor incidence.[8]

Equivocal results have been found in genotoxic assays, but endosulfan was mutagenic and clastogenic and induced effects on cell cycle kinetics in various *in vivo* and *in vitro* tests.[6]

In reproductive studies, male rats treated at 3.0 mg/kg from day 15 to 21 of gestation had reduced sperm production in adulthood.[9]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 0.1 mg/m^3 with a notation for skin absorption.

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ENDRIN
CAS: 72-20-8

$C_{12}H_8Cl_6O$

Synonyms: 2,7:3,Dimethanonaphth(2,3-*b*)oxirene; Compound 269; Experimental Insecticide 269

Physical Form. White, crystalline solid

Uses. All uses of endrin in the United States were canceled by the manufacturer in 1986; formerly used as an insecticide, avicide, and rodenticide

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Endrin is an insecticide with high acute toxicity that primarily affects the central nervous system.

In humans, the first effect of endrin intoxication is frequently a sudden epileptiform convulsion that may occur from 30 minutes to up to 10 hours after overexposure; it lasts for several minutes and is usually followed by a stuporous state for 15 minutes to 1 hour.[1,2] Severe poisoning results in repeated violent convul-

sions and, in some cases, status epilepticus.[3] The electroencephalogram (EEG) may show dysrhythmic changes that frequently precede convulsions; withdrawal from exposure usually results in a normal EEG within 1–6 months.[2] In most cases, recovery is rapid, but headache, dizziness, lethargy, weakness, and anorexia may persist for 2–4 weeks.[2] In less severe cases of endrin intoxication, the complaints are headache, dizziness, leg weakness, abdominal discomfort, nausea, vomiting, insomnia, agitation, and, occasionally, slight mental confusion.[1,3]

Poisonings resulting in convulsions have occurred in manufacturing workers. Recovery after occupational exposures is usually complete within 24 hours. Unlike dieldrin, which persists in the body, endrin is rapidly eliminated from the body and apparently does not accumulate, even in fatty tissue.[3,4] However, endrin is the most acutely toxic of the cyclodiene compounds, which also include chlordane, heptachlor, dieldrin, and aldrin.[4]

Ingestion of endrin has resulted in numerous fatalities.[2,4] In one nonfatal incident, ingestion of bread made with endrin-contaminated flour caused sudden convulsions in three people; in one person the serum endrin level was 0.053 ppm 30 minutes after the convulsion and 0.038 ppm after 20 hours; in the other two cases, no endrin was detected in the blood at 8.5 or 19 hours, respectively, after convulsions. The oral dose that causes death has been estimated to be approximately 10 mg/kg body weight; the single oral dose that causes convulsions was estimated to be 0.25–1.0 mg/kg body weight.[5]

In animal studies repeated dermal application of endrin has caused convulsions and death without irritation to the skin.[5]

Single doses of 2.5 mg/kg of endrin administered orally to pregnant golden hamsters during the period of fetal organogenesis caused a high incidence of fetal death, congenital anomalies, growth retardation, and maternal toxicity.[6] Administered over three generations to rats, endrin did not induce reproductive effects.[5]

Rats fed a diet of 50 or 100 ppm endrin for 2 years developed degenerative changes in the liver.[1] The IARC has concluded that animal bioassays in mice and rats have been inadequate to evaluate the carcinogenicity of endrin.[7] Limited studies of endrin-exposed workers have not detected increased mortality due to cancer.[8] Tumor-promoting effects were not demonstrated when endrin was tested in combination with subminimal quantities of chemicals known to be carcinogenic to animals.[5]

Endrin was not mutagenic in several in vitro microbial or mammalian cell assays.[5,8]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for endrin is 0.1 mg/m^3 with a notation for skin absorption.

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ENFLURANE
CAS: 13838-16-9

CHF_2OCF_2CHClF

Synonyms: Ethrane®; 2-chloro-1,1,2-trifluoro ethyl difluoromethyl ether

Physical Form. Liquid

Uses. Anesthetic in clinical anesthesia

Exposure. Inhalation

Toxicology. Enflurane is a general anesthetic used for inducing clinical anesthesia.

Exposure of humans at 15,000–20,000 ppm causes anesthesia.[1] At levels of 4200–5300 ppm for 30 minutes, cognitive tests indicated a performance decrement for remembering word pairs.[2]

No signs of liver, kidney, or testicular damage was observed in mice administered 5000 ppm 4 hours/day, 5 days/week for 12 weeks.[3] Chronic administration of enflurane at 3000 ppm for up to 78 weeks did not lead to an increased incidence of neoplasia in Swiss/ICR mice.[4] Similarly, no carcinogenic effect was observed in another study in which treatment started in utero.[5]

The IARC has determined that there is inadequate evidence for the carcinogenicity of enflurane in animals and that it is not classifiable as to its carcinogenicity to humans.[6]

Minor developmental abnormalities including increased incidence of cleft palate, minor skeletal and visceral abnormalities, and developmental variants were seen in the offspring of mice exposed at 10,000 ppm 4 hours/day on days 6–15 of gestation.[7] There were no teratological effects in the offspring of rats exposed for 6 hours/day for 3 days during pregnancy at 16,500 ppm.[8]

Enflurane caused single-strand breaks in DNA in human lymphocytes tested in vitro.[9] Damage was dose dependent, but large individual variations in DNA repair were noted.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for enflurane is 75 ppm (566 mg/m^3).

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EPICHLOROHYDRIN
CAS: 106-89-8

C_3H_5OCl

Synonyms: 1-Chloro-2,3-epoxypropane; 3-chloro-1,2-epoxypropane; (chloromethyl)-ethyleneoxide; chloromethyloxirane; 3-chloro-1,2-propylene oxide; α-epichlorohydrine

Physical Form. Colorless liquid

Uses. In the manufacture of epoxy and phenoxy resins

Exposure. Inhalation; skin absorption

Toxicology. Epichlorohydrin is a severe irritant of skin, eye, and respiratory tract. Repeated or prolonged exposure can cause lung liver and kidney damage. It is a direct-acting mutagen and is carcinogenic in experimental animals.

According to one industrial report, exposure at 20 ppm for 1 hour caused temporary burning of the eye and nasal passages.[1] At 40 ppm irritation was more persistent, lasting 48 hours.[1] Pulmonary edema and renal lesions may result from exposure to concentrations greater than 100 ppm. In one worker acutely exposed to unspecified but probably very high concentrations, immediate effects were nausea, vomiting, headache, and dyspnea with conjunctival and upper respiratory irritation. During the 2 years following the incident, bronchitis, liver damage, and hypertension were observed.[1]

Exposed workers had a marked increase in percentage of lymphocytes with chromatid breaks, chromosome breaks, severely damaged cells, and abnormal cells.[2]

Skin contact causes itching, erythema, and severe burns that appear after a latent period ranging from several minutes to days, depending on the intensity of exposure. One worker who failed to remove contaminated shoes for 6 hours developed severe skin damage, with painful enlarged lymph nodes in the groin.[1] Skin sensitization has been reported.[3]

Mice showed signs of irritation, gradual development of cyanosis, and muscular relaxation of the extremities and finally died from depression of the respiratory system after multiple 1-hour exposures to 2370 ppm.[4] Rats repeatedly exposed to 120 ppm 6 hours/day experienced labored breathing, profuse nasal discharge, weight loss, leukocytosis, and increased urinary protein excretion. At autopsy, there was lung, liver, and kidney damage.[5] Respiratory distress was observed at 56 ppm during multiple exposures, whereas 17 ppm for 19 days produced no effects. Function of the liver and kidney was altered in rats receiving 5.2 or 1.8 ppm for 4 hours.[1]

Male rats administered five oral doses of 20 mg/kg had a temporary fertility loss, whereas a single 100 mg/kg dose caused spermatocele formation and probable permanent sterility.[6] Fifty inhalation exposures at 50 ppm for 6 hours each caused transient infertility in male rats; no changes were observed in reproductive parameters of female rats; rabbits remained fertile.[7] There was no evidence of teratogenicity in rat fetuses at doses that caused death in some of the treated dams.[8]

No detrimental effect on fertility has been found in occupationally exposed workers where exposure levels are estimated to be less than 1 ppm.[9]

A number of studies indicate that epichlorohydrin induces tumors of localization dependent on the mode of application. A high incidence (100% for females, 81% for males vs. none in controls) of squamous cell carcinomas of the forestomach occurred in rats administered 10 mg/kg 5 times/week for up to 2 years by gastric intubation.[10] Administered in the drinking water, epichlorohydrin also caused squamous cell carcinomas of the forestomach in rats.[11] Exposure to 100 ppm, 6 hours/day for 30 days produced a high incidence of malignant tumors of the nasal cavity in rats.[12] An increase in local sarcomas occurred in mice given weekly subcutaneous injections.[13]

A variety of epidemiological studies have not found increased cancer mortality among exposed workers.[14–16] Initial reports associating

epichlorohydrin exposure with lung cancer and also heart disease mortality have not been confirmed.[17] In a recent mortality study update of 863 employees with exposure to epichlorohydrin there were no excess deaths from heart disease, lung cancer, or nonmalignant respiratory disease for employees with 20 or more years after first exposure.[18]

The carcinogenic risk to humans cannot be fully assessed, however, because of mixed exposures, limited number of deaths, and indeterminate levels and duration of exposure. The IARC has determined that there is sufficient evidence of carcinogenicity in animals and inadequate evidence in humans and that epichlorohydrin is probably carcinogenic to humans.[19]

Epichlorohydrin is a direct-acting mutagen by virtue of its activity as an alkylating agent.[20] It causes genetic damage in most bacterial and mammalian test systems in vivo and in vitro.[19,20]

The proposed 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for epichlorohydrin is 0.1 ppm (0.38 mg/m^3) with an A2-suspected human carcinogen designation and a notation for skin absorption.

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EPN
CAS: 2104-64-5

$C_{14}H_{14}NO_4PS$

Synonyms: *O*-ethyl *O*-*p*-nitrophenyl phenylphosphonothioate; EPN-300

Physical Form. Light yellow to brown solid

Uses. Acaricide; insecticide

Exposure. Inhalation; skin absorption; ingestion

Toxicology. EPN is an anticholinesterase agent.

A few deaths have been reported after poisoning by EPN, most resulting from suicidal ingestion, but at least one death has been associated with EPN spraying. It is moderately to highly toxic in animals, but less potent than parathion.[1]

Signs and symptoms of overexposure are caused by the inactivation of the enzyme cholinesterase, which results in the accumulation of acetylcholine at synapses in the nervous system, skeletal and smooth muscle, and secretory glands.[1–3] The sequence of the development of systemic effects varies with the route of entry. The onset of signs and symptoms is usually prompt but may be delayed up to 12 hours. After inhalation, respiratory and ocular effects are the first to appear, often within a few minutes of exposure. Respiratory effects include tightness in the chest and wheezing owing to bronchoconstriction and excessive bronchial secretion; laryngeal spasm and excessive salivation may add to the respiratory distress; cyanosis may also occur. Ocular effects include miosis, blurring of distant vision, tearing, rhinorrhea, and frontal headache.

After ingestion, gastrointestinal effects, such as anorexia, nausea, vomiting, abdominal cramps, and diarrhea, appear within 15 minutes to 2 hours. After skin absorption, localized sweating and muscular fasciculations in the immediate area usually occur within 15 minutes to 4 hours; skin absorption is somewhat greater at higher ambient temperatures and is increased by the presence of dermatitis.[2,3]

With severe intoxication by all routes, an excess of acetylcholine at the neuromuscular junctions of skeletal muscle causes weakness aggravated by exertion, involuntary twitchings, fasciculations, and eventually paralysis. The most serious consequence is paralysis of the respiratory muscles. Effects on the central nervous system include giddiness, confusion, ataxia, slurred speech, Cheyne–Stokes respiration, convulsions, coma, and loss of reflexes. The blood pressure may fall to low levels, and cardiac irregularities, including complete heart block, may occur.[1–3]

Complete symptomatic recovery usually occurs within a week; increased susceptibility to the effects of anticholinesterase agents persists for up to several weeks after exposure. Daily exposure to concentrations that are insufficient to produce symptoms after a single exposure may result in the onset of symptoms. Continued daily exposure may be followed by increasingly severe effects.

No significant effects on plasma or red blood cell cholinesterase activity occurred in volunteers given 6 mg of EPN for up to 47 days; 9 mg appears to be the threshold for toxicity.[4]

Delayed neuropathy characterized by distal axonal degeneration is a systemic health effect caused by some organophosphate pesticides and is not due to anticholinesterase inhibition. EPN is neurotoxic to atropine-protected hens, producing polyneuropathy progressing to paralysis and some deaths after ingestion of 5–10 mg/kg/day. There are no reports, however, of neurotoxicity from EPN in humans.[1]

EPN was not teratogenic or fetotoxic to mice at maternally nontoxic doses.[5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for EPN

is 0.5 mg/m^3 with a notation for skin absorption.

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1,2-EPOXYBUTANE
CAS: 106-88-7

C_4H_8O

Synonyms: 1,2-Butene oxide; butylene oxide; 1,2-butylene epoxide; ethyl ethylene oxide; ethyl oxirane

Physical Form. Colorless liquid with pungent odor

Uses. Primarily used as a stabilizer for chlorinated hydrocarbon solvents; also used as a chemical intermediate in the production of butylene glycols

Exposure. Inhalation

Toxicology. 1,2-Epoxybutane exposure causes body weight effects and nasal lesions in experimental animals; chronic exposure is carcinogenic to rats but not to mice.

No adverse effects from 1,2-epoxybutane exposure have been reported in humans.

All rats exposed to 6550 ppm died during the 4-hour exposure period; at 2050 ppm ocular discharge and dyspnea were observed, and eye irritation occurred at the 1400 ppm level.[1] In mice, 2050 ppm was lethal to all and 1420 ppm was lethal to four of five mice of each sex. In 14-day studies, mortality was seen at 3200 ppm in male rats and at 1600 ppm in female rats and mice of both sexes. Compound-related lesions included pulmonary hemorrhage and rhinitis in rats at 1600 ppm and nephrosis in mice at 800 ppm; final body weights of surviving animals were significantly reduced compared with the controls in these exposure groups.

No deaths were observed in rats at concentrations up to 800 ppm or in mice up to 400 ppm in an NTP study lasting 13 weeks (6 hours/day, 5 days/week). Nasal cavity lesions and reduced body weight were seen in rats exposed at 800 ppm. In mice, renal tubular necrosis was found at 800 ppm, a dose that was lethal. Inflammation of the nasal turbinates was observed in female mice at 100 ppm and above and in male mice at 200 ppm and above. In an earlier study, slight growth retardation was observed in rats and mice exposed at 600 ppm for 13 weeks; inflammatory and degenerative changes in the nasal mucosa were observed in both species. Myeloid hyperplasia in bone marrow occurred in male rats only.[2] No effects were noted at 75 or 150 ppm.

Rats exposed for 2 years to 400 ppm had increased incidence of papillary adenomas of the nasal cavity; the incidences of alveolar/bronchiolar adenomas or carcinomas (combined) were also increased in the male rats, but not in the females.[1] Nonneoplastic lesions of the nasal cavity included inflammation, epithelial hyperplasia, and squamous metaplasia of the nasal epithelium, as well as atrophy of the olfactory sensory epithelium. Mice exposed at 50 or 100 ppm for 2 years had no significant increases in the incidence of neoplastic lesions

of the nasal cavity. Treatment-related nonneoplastic nasal changes were similar to those seen in rats.

In a combined-exposure experiment oral administration of trichloroethylene containing 1,2-epoxybutane induced squamous cell carcinomas of the forestomach in mice, whereas administration of the trichloroethylene alone did not.[3]

A 10% solution applied to the shaved skin of mice three times per week for 77 weeks caused no visible skin reaction and no tumors.[4]

The IARC has determined that there is limited evidence for the carcinogenicity of 1,2-epoxybutane in experimental animals and that it is possibly carcinogenic to humans.[5]

Exposure to 1000 ppm before and during gestation did not cause any teratogenic effects in rats; fetal growth and viability were not affected despite depressed maternal body weight gain.[6] Rabbits exposed at 250 or 1000 ppm 7 hours/day during gestational days 0 to 24 had maternal deaths at both exposure concentrations. No teratogenic effects were observed, although the pregnancy rate was reduced in the high-dose group. 1,2-Epoxybutane is a direct-acting alkylating agent, and it is genotoxic in a wide range of assays.[5]

Instilled in the eyes of rabbits, 1,2-epoxybutane caused corneal injury.[7]

A threshold limit value (TLV) has not been established for 1,2-epoxybutane, although US manufacturers have recommended a voluntary time-weighted average-threshold limit value of 40 ppm.

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EPOXY RESINS
CAS: 61788-97-4

Synonyms: Epoxies; Epon resins

Physical Form. Uncured resins are long-chained prepolymers that are viscous liquids or solids; the cured resins are strong, solid polymers

Uses. Molding compounds; surface coatings; adhesives; laminating or reinforcing plastics

Exposure. Inhalation; skin contact

Introduction. Epoxy resins are polymers containing more than one epoxide group (a three-membered ring containing two carbon atoms and one oxygen atom).[1] An epoxy resin system is composed of two primary components: 1) the uncured resin and 2) the curing agent (also referred to as the hardener, catalyst, accelerator, activator, or cross-linking agent).

Uncured resins are oligomers of relatively low molecular weight that may be a liquid or a solid. Before epoxy resins can become useful products, they must be cured, with the addition of a curing agent. Curing involves the cross-linkage by polymerization of the reactive epoxy groups into a three-dimensional matrix.

In addition to the two primary components, several other components may be included: diluents/solvents, fillers, and pigments. Diluents, which may represent 10–15% of resin volume, are added primarily to reduce viscosity. There are two types of diluents: reactive and nonreactive. Reactive diluents, primarily the glycidyl ethers, contain epoxy groups, which will take part in the curing process. Nonreactive diluents include a variety of organic solvents. Some uncured resins (liquids) are primary skin irritants or sensitizers or both. Toxicity generally decreases with increase in molecular weight and epoxy number. The resins with the greatest potential for sensitization are those with molecular weights under 500.[2] None of the uncured resins possesses significant volatility; thus inhalation poses little hazard.[1] The vast majority of epoxy resins are manufactured by the reaction between epichlorohydrin and bisphenol A, producing DGEBA (diglycidyl ether of bisphenol A) resins. After the initial manufacture of uncured resin, epichlorohydrin is probably not present during the subsequent mixing and polymerization steps.

Toxicology. The toxicity of epoxy resin systems results from the toxicity of the various components, each of which must be considered.

Curing agents account for much of the potential hazard associated with use of epoxy resins.[1,2] There are several major types of curing agents: aliphatic amines, aromatic amines, cycloaliphatic amines, acid anhydrides, polyamides, and catalytic curing agents. The latter two types are true catalysts, in that they do not participate in the curing process.

The aliphatic amines, including triethylene tetramine (TETA) and diethylene triamine (DETA), are highly alkaline (pH 13–14), caustic, and volatile and may cause severe burns.[3] They can cause skin irritation and sensitization and respiratory tract irritation. Eye irritation with conjunctivitis and corneal edema (resulting in "halos" around lights) may occur. Asthmatic symptoms suggesting respiratory tract sensitization have been described.[1] In ski manufacturing workers using epoxy resins, 3-(dimethylamino) propylamine has been shown to cause declines in FEV_1 and flow rates and work-related respiratory symptoms (e.g., cough, chest tightness).[4]

Aromatic amines are generally solids and less irritating than aliphatic amines. 4,4′-Methylene dianiline (MDA) has caused outbreaks of reversible toxic hepatitis, apparently after skin absorption. Severe symptoms, including elevated AST, alkaline phosphatase, and bilirubin and liver enlargement, have been observed in some workers using it as a curing agent with epoxy resins.[5] *m*-Phenylenediamine is a strong irritant and allergic sensitizer; like MDA, it stains the skin and nails yellow.[2] 4,4′-Diaminodiphenyl sulfone (DDS) is tumorigenic in experiments animals.[1]

Acid anhydrides can cause severe eye and skin irritation and burns, depending on the concentration and duration of contact.[1] Inhalation of high concentrations can cause significant respiratory tract irritation. Phthalic anhydride (PA), tetrachlorophthalic anhydride (TCPA), and trimellitic anhydride can induce asthma in epoxy resin workers; frequently a dual (immediate and late) asthmatic response has been documented. Specific IgE antibodies on RAST testing have been demonstrated in patients with TCPA asthma.[6] One worker developed asthma on grinding epoxy resin cured with phthalic anhydride, presumably due to release of some unreacted residual phthalic anhydride during grinding of a cured moulding.[7]

Polyamides, reaction products of aliphatic amines and fatty acids, are considerably less toxic than the aliphatic amines but are moderately irritating to the skin and extremely irritating to the eyes.[1,2]

Isophorone diamine, a cycloaliphatic amine, has been reported to cause skin sensitization.[7]

Glycidyl ethers, reactive diluents in epoxy

resin systems, are characterized by the presence of the 2,3-epoxypropyl group and an ether linkage to another organic group. Virtually all of these substances are liquids with low vapor pressures at room temperature. Dermal contact is the major route of exposure. Vapor pressures become more appreciable at higher temperatures, which may occur during the curing process. Some glycidyl ethers commonly used in epoxy resin systems are allyl glycidyl ether (AGE), *n*-butyl glycidyl ether (BGE), *o*-cresyl glycidyl ether (CGE), isopropyl glycidyl ether (IGE), phenyl glycidyl ether (PGE), resorcinol diglycidyl ether, and 1,4-butanediol diglycidyl ether.[1,8] In humans exposed to glycidyl ethers, adverse effects have generally been limited to irritation and sensitization.[8] PGE and BGE have produced severe skin irritation in humans, causing burns and blistering. AGE has produced skin and eye irritation in humans. Skin sensitivity to AGE, BGE, and PGE has been documented in some humans occupationally exposed to epoxy resins.[1,8] In animals, glycidyl ethers have produced central nervous system (CNS) effects, including muscular incoordination, reduced motor activity, agitation and excitement, deep depression, narcotic sleep, and coma. PGE has produced CNS depression with dermal administration; BGE and AGE have produced depression after inhalation exposure.[8] Experimental inhalation of glycidyl ethers has resulted in pulmonary irritation and inflammation, including pneumonitis and peribronchiolitis. For example, rats exposed to PGE at 10 ppm for 7 hours/day, 5 days/week for 10 weeks had peribronchial and perivascular inflammatory infiltrates. Exposure to some glycidyl ethers, usually by injection, has been demonstrated to produce testicular abnormalities, alteration of leukocyte counts, atrophy of lymphoid tissue, and bone marrow cytotoxicity.[8]

Solvents used as nonreactive diluents include acetone, cellosolve, methyl ethyl ketone, methyl isobutyl ketone, methylene chloride, 1,1,1-trichloroethane, toluene, and xylene. Skin and eye irritation and, in higher concentrations, CNS depression and respiratory irritation may result from exposure to these solvents as diluents for epoxy resin systems. These solvents may dehydrate and defat the skin, which may render the skin more vulnerable to the irritating and sensitizing components of epoxy resin formulations.[1,2]

Fillers used in epoxy resins are normally inert, finely divided powders. Common fillers include calcium carbonate, clay (bentonite), talc, silica, diatomaceous earth, and asbestos. Workers exposed to excessive amounts of some of these dusts may experience lung damage.[1]

The curing process renders the resin essentially inert and nontoxic. At room temperature, full curing may take several days; incompletely cured resins may cause skin irritation and sensitization.[1] Respiratory symptoms may result from inhalation of cured epoxy dusts during grinding, presumably due to release of residual curing agent.[1,7] Skin irritation and sensitization have been associated with epoxy resin exposure.

Dermatitis from epoxy resin components usually develops first on the hands, particularly between the fingers, in the finger webs, on the dorsum of the hands, and on the wrists. It may vary in severity from erythema to a marked bullous eruption.[2] When sensitization occurs, the eruption is typically pruritic, with small vesicles on the fingers and hands resembling dyshidrotic eczema. The eruption may spread to other areas of the body that accidentally contact resin components, such as the face and neck. In highly sensitized individuals, vapors from the curing agent or reactive diluents may cause recurrence of itching and redness in the absence of direct skin contact.[2]

Prevention of epoxy dermatitis requires meticulous attention to avoiding skin contact during mixing and application, use of protective clothing such as PVC gloves, good housekeeping, regular hand washing before eating and breaks, and prohibition of eating and smoking in the work area. In some cases, sensitized workers may need to be completely removed from the work area and further exposure.[2]

There are no reports of carcinogenic, mutagenic, teratogenic, or reproductive effects to humans from uncured resins, curing agents, or glycidyl ethers, but there are some positive

animal studies.[1,8] Animal experiments using DGEBA resins have generally indicated no carcinogenic activity but are inconclusive.[1] Diglycidyl resorcinol ether administered by gavage to rats and mice for 2 years caused an increased incidence of forestomach tumors.[9] Mutagenicity tests using various liquid and solid epoxy resins have yielded some positive and some negative results.[1]

Of the aromatic amine curing agents, diaminodiphenyl sulfone is tumorigenic in animal experiments, whereas 4,4′-methylenedianiline is a suspect animal carcinogen.[1] Many of the glycidyl ethers produce a mutagenic response in the Ames assay and in some other short-term tests.[8] Glycidyl ethers are rapidly metabolized to less cytotoxic substances and rapidly conjugate with skin proteins on dermal contact. Their low volatility decreases the possibility of significant systemic absorption via inhalation. Together, these factors reduce the likelihood of conjugation with nuclear macromolecules in somatic or germ cells, which otherwise might result in carcinogenic or teratogenic effects.[8]

A threshold limit value (TLV) is not established for epoxy resins.

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ETHANE
CAS: 74-84-0

CH_3CH_3

Synonyms: Bimethyl; dimethyl; methylmethane; ethyl hydride

Physical Form. Colorless gas

Uses. In the production of ethylene, vinyl chloride, and chlorinated hydrocarbons; as a component of bottled fuel gas

Exposure. Inhalation

Toxicology. Ethane is considered to be toxicologically inert and is classified as a simple asphyxiant gas.

At extremely high concentrations, ethane displaces oxygen from the air and blood.[1] Humans are asymptomatic while breathing air containing 16.5–21% oxygen by volume. The first symptoms of oxygen deprivation (at concentrations of 12–16%) are rapid respirations and air hunger, followed by diminished mental alertness and impaired muscular coordination.[2] Emotional instability may ensue, and fatigue occurs rapidly. In severe cases (concentrations less than 10%), there may be nausea and vomiting, prostration, loss of consciousness, and, finally, convulsions, coma, and death.[2] Atmospheres deficient in oxygen do not provide ade-

quate warning of hazardous concentrations, and ethane itself is odorless.[1]

The ACGIH has not assigned a numerical threshold limit value (TLV) for occupational exposure to ethane because the limiting factor is the available oxygen, the minimal content which should be 18% by volume under normal atmospheric pressure; at concentrations below those required to produce severe oxygen deprivation, ethane presents an explosive hazard.[1]

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ETHANOLAMINE

CAS: 141-43-5

$NH_2CH_2CH_2OH$

Synonyms: 2-Aminoethanol; 2-hydroxyethylamine; ethylolamine; colamine; monoethanolamine

Physical Form. Colorless liquid

Uses. As a chemical intermediate; corrosion inhibitor; in the production of cosmetics, detergents, paints, and polishes

Exposure. Inhalation; skin absorption

Toxicology. Ethanolamine is an eye and respiratory tract irritant.

No systemic effects from industrial exposure have been reported. The liquid applied to the human skin for 1.5 hours caused marked erythema.[1]

Dogs and cats exposed to 990 ppm for 4 days survived, but four of six guinea pigs died from exposure to 233 ppm for 1 hour; pathologic changes were chiefly those of pulmonary irritation, with some nonspecific changes in the liver and kidneys.[1] In animals exposed repeatedly to 66–100 ppm there was some mortality during the 24–30 days of exposure, and all animals were lethargic.[2] No mortality or pathology resulted from 90-day continuous exposure of dogs to 26 ppm, of rats to 12 ppm, or of guinea pigs to 15 ppm.[2] The liquid produced moderate irritation on the skin of rabbits and severe irritation in the eyes of rabbits.[1]

In one study ethanolamine administered by gavage to pregnant rats on days 6–15 of gestation at levels of 50, 300, or 500 mg/kg/day caused dose-dependent increases in intrauterine deaths, malformations, and intrauterine growth retardation.[3] Sex of the pups and intrauterine position with respect to contiguous rat siblings were important factors in the degree of development exhibited. Contrary to these findings, no signs of developmental toxicity or increased incidences of malformations were observed in another study in rat fetuses or pups gavaged at doses of up to 450 mg/kg/day on days 6–15 of gestation.[4] At this dose maternal toxicity was evidenced by decreases in feed consumption and body weight gains. Ethanolamine was not developmentally toxic after dermal application during gestation at exposure levels up to 225 mg/kg/day for rats and 75 mg/kg/day for rabbits.[5] Maternal effects were observed in both species at these doses and consisted of significant increases in the incidence of skin irritation/lesions and maternal body weight effects.

The odor is described as ammonia-like or musty at 25 ppm but is detected by means of a sensation at 3 ppm.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for ethanolamine is 3 ppm (7.5 mg/m^3) with a short-term excursion level (STEL) of 6 ppm (15 mg/m^3).

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2-ETHOXYETHANOL
CAS: 110-80-5

$C_2H_5OCH_2CH_2OH$

Synonyms: Ethylene glycol monoethyl ether; cellosolve; EGEE; 2-EE

Physical Form. Colorless liquid

Uses. Used in semiconductor industry as a photoresist; solvent for nitrocellulose lacquers and alkyd resins; in dyeing textiles and leather; in cleaners and varnish removers

Exposure. Inhalation; skin absorption

Toxicology. 2-Ethoxyethanol (EE) is of low acute toxicity, but repeated or chronic exposures have caused hematotoxic, fetotoxic, teratogenic, and testicular effects in experimental animals.

In mice, the LC_{50} for 7 hours was 1820 ppm; death was attributed to pulmonary edema and kidney injury.[1] Dogs repeatedly exposed to 840 ppm for 12 weeks developed a slight decrease in red blood cells and hemoglobin and an increase in immature white blood cells. In female rats exposed to 125 ppm for 4 hours there was an increase in erythrocyte osmotic fragility, an effect that has been noted from other glycol ethers and in other species as well.[2]

Teratology studies in rats and rabbits have demonstrated both embryo/fetotoxicity and congenital malformations after exposure by oral, inhalation, or dermal routes. Exposures of pregnant rabbits at 160 ppm resulted in significant increases in cardiovascular, renal, and ventral body wall defects, minor skeletal changes, and fetal resorptions, with minimal maternal toxicity. Similarly, exposure of pregnant rats at 200 ppm resulted in fetal growth suppression and an increase in cardiovascular defects and wavy ribs, in the absence of significant maternal toxicity.[3] Dermal exposure of pregnant rats led to increased fetal resorptions, cardiovascular malformations, and skeletal variation.[3] A no-effect level of 10–50 ppm for reproductive effects in animals has been observed.[3]

In the drinking water of mice continuously housed as breeding pairs, 0.5% had no effect on fertility, but 1% significantly reduced the numbers of litters produced.[4] Cross-breeding studies showed that the fertility of each sex was severely reduced at 2% and substantially reduced at 1%.

In rats, a single 3-hour exposure to 4500 ppm caused testicular atrophy, as did 500 ppm for 11 days, whereas 250 ppm had no testicular effect.[5,6] Oral doses of 300 mg/kg/day for 6 weeks reduced testicular weight and spermatid counts, and some effects were detected at doses of 150 mg/kg/day in mated rats.[7]

Reproductive and testicular effects have also been reported in humans with exposure to EE, but the significance of these studies cannot be evaluated because of concomitant exposures,

population bias, and uncertainty of exposure levels. An evaluation of 73 painters exposed to 9.9 mg/m^3 EE (range of 0–80.5 mg/m^3) found an increased prevalence of oligospermia and azoospermia and an increased odds ratio for lower sperm count.[8] In another report of workers exposed to EE (0–24 ppm) in a metal castings process, no effect was found on semen volume or sperm viability, motility, velocity, or morphology; some differences in the proportion of abnormal sperm shapes was observed.[9] In a case-control study, ethoxyacetic acid, the primary metabolite of EE and its acetate, was detected in 39 of 1019 infertile men vs. 6 of 475 normal fertile controls (odds ratio 3.11).[10] The presence of ethoxyacetic acid in the urine was strongly associated with exposure to solvents, especially paint products.

The liquid instilled in the eyes of animals caused immediate discomfort, some conjunctival irritation, and a slight transitory irritation of the cornea, which was readily reversible.[11] Repeated and prolonged contact of the liquid with the skin of rabbits caused only a mild irritation, but toxic amounts were readily absorbed through the skin.

Because EE is well absorbed through the skin, ambient monitoring of environmental exposure level is not considered to be an accurate method of determining absorbed dose. Biological monitoring of the ethoxyethanol metabolite 2-ethoxyacetic acid in urine has been shown to be an effective indicator of absorbed dose in workers.[12]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 2-ethoxyethanol is 5 ppm (18 mg/m^3) with a notation for skin absorption.

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2-ETHOXYETHYL ACETATE

CAS: 111-15-9

$C_2H_5OCH_2CH_2OOCCH_3$

Synonyms: Cellosolve acetate; ethylene glycol monoethyl ether acetate; EGEEA; 2-ethoxy ethanol acetate; 2-EEA; EEA; EEAc; ethyl glycol acetate

Physical Form. Colorless liquid

Uses. In the coatings industry, especially in the semiconductor industry; solvent for nitrocellulose and some resins

Exposure. Inhalation; skin absorption

Toxicology. 2-Ethyoxyethyl acetate (EEA) is irritating to the eyes, nose, and throat, and at high concentrations it causes central nervous system depression; in chronic studies it is myelotoxic, spermatoxic, and teratogenic.

Guinea pigs survived exposure to saturated vapor concentrations (4000 ppm), but two such exposures of cats for 4–6 hours caused narcosis, kidney damage, and death.[1] Exposure for 8 hours to 1500 ppm was fatal to two of six rats. Mice, guinea pigs, and a rabbit survived 12 8-hour exposures to 450 ppm, but another rabbit and two cats died before the end of the exposure period; kidney damage was observed at autopsy.[2] Dogs survived 120 daily exposures to 600 ppm with slight eye and nose irritation but without apparent systemic injury as determined by histopathology and hematologic tests.[3]

A number of developmental toxicity studies have been conducted on EEA.[4–7] In rabbits, inhalation exposure to 100–300 ppm resulted in maternal toxicity, including clinical signs and alterations in hematology (reduced hemoglobin).[4] Developmental toxicity was seen as an increased incidence of totally resorbed litters above 200 ppm and an increase in nonviable fetuses at 300 ppm; fetal ossification was observed above 100 ppm, and the incidence of total malformations was 100% at 300 ppm. Similar effects were observed in rats, with maternal and developmental toxicity at 100–300 ppm and teratogenic effects at 200–300 ppm.

In another experiment, exposure of rats to 600 ppm on days 7–15 of gestation caused 100% fetal resorptions, 390 ppm caused skeletal and cardiovascular defects, and one cardiac malformation occurred at 130 ppm.[5]

Mice given oral doses of 500 mg/kg/day for 5 weeks had testicular atrophy; both red and white blood cell formation were also affected at this level.[6]

The information on toxic effects in humans is limited, but it is expected that adverse effects would be consistent with those seen in animals.[8] In one recent survey of shipyard painters, the high-EEA-exposure group had significantly lower mean white blood cells than the control group and a significant proportion of all exposed painters were leukopenic.[9]

Because EEA is well absorbed through the skin, ambient monitoring of environmental exposure levels is not considered to be an accurate method of determining absorbed dose. Biological monitoring of the EEA metabolite 2-ethoxyacetic acid in urine has been shown to be an effective indicator of absorbed dose in workers.[10] Cytogenic examination of persons exposed to EEA did not show an increase in sister chromatid exchanges or in micronuclei.[10]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 2-ethoxyethyl acetate is 5 ppm (27 mg/m^3) with a notation for skin absorption.

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ETHYL ACETATE
CAS: 141-78-6

$CH_3COOC_2H_5$

Synonyms: Acetic ether; ethyl acetic ester; ethyl ethanoate

Physical Form. Colorless liquid

Uses. Lacquer solvent; artificial fruit essences

Exposure. Inhalation

Toxicology. Ethyl acetate causes respiratory tract irritation; at very high concentrations it produces narcosis in animals, and it is expected that severe exposure will cause the same effect in humans.

Unacclimated human subjects exposed to 400 ppm for 3–5 minutes experienced nose and throat irritation.[1] However, no adverse symptoms were observed in workmen exposed at 375–1500 ppm for several months.[2] In rare instances, exposure may cause sensitization resulting in inflammation of the mucous membranes and in eczematous eruptions.[3]

Cats exposed to 9000 ppm for 8 hours suffered irritation and labored breathing; 20,000 ppm for 45 minutes caused deep narcosis, and 43,000 ppm for 14–16 minutes was fatal; at autopsy, findings were pulmonary edema with hemorrhage and hyperemia of the respiratory tract.[3] Repeated exposure of rabbits to 4450 ppm resulted in secondary anemia with leukocytosis, hyperemia, and damage to the liver.[3]

In mice ethyl acetate at 2000 ppm for 20 minutes produced acute neurobehavioral effects including changes in posture, decreased arousal, increased tonic/clonic movements, disturbances in gait, and delayed righting reflexes. Some handling-induced convulsions and slight lacrimation were also observed.[4]

Ethyl acetate was not mutagenic in bacterial assays; it was not genotoxic in a number of in vivo assays but did cause chromosomal damage in hamster cells *in vitro*.[5]

Ethyl acetate has a fruity odor detectable at 10 ppm.[6]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for ethyl acetate is 400 pm (1440 mg/m^3).

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ETHYL ACRYLATE
CAS: 140-88-5

$C_5H_8O_2$

Synonyms: Ethyl 2-propenoate; 2-propenoic acid ethyl ester; acrylic acid ethyl ester

Physical Form. Colorless liquid

Uses. A monomer widely used in the production of polymers and copolymers for manufacturing textiles, latex paints, paper coatings, dirt release agents, and specialty plastics

Exposure. Inhalation

Toxicology. Ethyl acrylate is an irritant of the skin, eyes, respiratory tract, and mucous membranes of the gastrointestinal tract; it has a history of dermal sensitization. It is carcinogenic in experimental animals.

The vapor is moderately irritating at 4 ppm, and it is believed that workers would not tolerate 25 ppm for any length of time.[1] However, in another report, prolonged exposure to 50–75 ppm supposedly produced drowsiness, headache, and nausea.[2] Skin sensitization has occurred from industrial exposure; a 4% concentration in petrolatum produced sensitization reactions in 10 of 24 volunteers.[3]

In rats, 2000 ppm for 4 hours was fatal, with death attributed to severe pulmonary irritation; 1000 ppm for 4 hours was not fatal but caused irritation of the skin.[4] Repeated exposure to 500 ppm was fatal to rats, and 275 ppm was lethal to rabbits and guinea pigs.[5] Irritation of the eyes, nose, and mouth as well as lethargy, dyspnea, and convulsive movements preceded death. At autopsy, there was pulmonary edema and degenerative changes in liver, kidneys, and heart muscle. The epidermis and dermis are the primary target tissues when the liquid is applied to the skin.

Gavage administration of a single dose causes profound gastric toxicity that includes concentration- and time-dependent mucosal and submucosal edema and vacuolization of the forestomach.[6] These studies suggest that ethyl acrylate is an acutely irritating chemical causing lesions in tissues directly exposed to it.[7]

Chronic exposure of mice and rats to 25, 75, or 225 ppm caused concentration-dependent lesions within the nasal cavity.[8] There was no indication of an oncogenic response in any organ or tissue.[8]

Ethyl acrylate applied to the skin of mice three times per week for life caused dermatitis, dermal fibrosis, epidermal necrosis, and hyperkeratosis; neoplastic changes were not observed.[9]

Ethyl acrylate was carcinogenic in rats and mice when administered by gavage in corn oil, producing squamous cell carcinomas of the forestomach.[10] There were also dose-related increases in the incidences of nonneoplastic lesions including hyperkeratosis, hyperplasia, and inflammation. In a follow-up to this study, rats administered 200 mg/kg/day by gavage for 6 months had an increase in forestomach epithelial hyperplasia, which was reversible.[11] In contrast, animals treated for 12 months on the same dosing regime developed forestomach squamous cell carcinomas and papillomas. The authors conclude that ethyl acrylate carcinogenesis is a consequence of promotion of spontaneously initiated cells.

In a cohort study, an excess mortality from cancer of the colon and rectum was observed in a group of men employed extensively in the early 1940s in jobs entailing the highest exposures to vapor-phase ethyl acrylate and methyl methacrylate.[12] The excess mortality appeared in those with the equivalent of 3 years' exposure and after a latency period of 20 years. Two cohorts with later dates of hire did not show excess mortality. The authors acknowledge the possibility of confounding exposures in the first cohort and further suggest that the role of ethyl acrylate in inducing tumors is not supported by any known biological mechanisms. Specifically, there is no evidence that ethyl acrylate can cause carcinogenesis at distant sites.

The IARC has determined that there is sufficient evidence for carcinogenicity in experimental animals and that ethyl acrylate is possibly carcinogenic to humans.[2]

Ethyl acrylate was negative in most genotoxic assays.

Exposure of pregnant rats to 150 ppm 6 hours/day during days 6–15 of gestation caused some maternal toxicity and a slight, but not statistically significant, increase in malformed fetuses; at 50 ppm, there was neither maternal toxicity nor an adverse effect on the fetus.[13]

One drop of the liquid instilled in the eye of the rabbit caused corneal necrosis within 24 hours.[4]

The odor is detectable below 1 ppm and should serve as a good warning property.[1,4]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for ethyl acrylate is 5 ppm (21 mg/m^3) with a short-term excursion limit of 15 ppm (61 mg/m^3) and an A2-suspected human carcinogen designation.

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ETHYL ALCOHOL
CAS: 64-17-5

C_2H_5OH

Synonyms: Ethanol; algrain; anhydrol; ethyl hydrate; ethyl hydroxide; grain alcohol

Physical Form. Clear, colorless, mobile, flammable liquid

Uses. Solvent

Exposure. Inhalation; ingestion

Toxicology. Ethyl alcohol is an irritant of the eyes and mucous membranes and causes central nervous system depression; chronic excessive ingestion is associated with developmental effects and various cancers.

Few adverse effects have been reported in humans from dermal or inhalation exposures in

industrial settings.[1] Exposure of humans at 5000–10,000 ppm has caused transient irritation of the eyes and nose, and cough.[1,2] At 15,000 ppm, effects were continuous lacrimation and cough. A level of 20,000 ppm was judged as just tolerable; above this level the atmosphere was described as intolerable and suffocating on even brief exposure.[2]

Chronic exposure to the vapor may result in irritation of mucous membranes, headache, and symptoms of central nervous system depression such as lack of concentration and somnolence.[3] However, in current industrial practice, the vapor is considered to be practically devoid of systemic hazard from inhalation.

Ethanol is not appreciably irritating to skin even with repeated or prolonged exposure.[1] Splashed in the eye, the liquid causes immediate burning and stinging sensation with reflex closure of the lids and tearing.[4]

Intoxication from ingestion is related to the blood alcohol levels: At 0.05–0.15% there is slight impairment of visual acuity, muscular incoordination, and changes in reaction time, mood, and personality; at 0.15–0.30% there is slurred speech, slowed reaction time, and increasing muscular incoordination; at blood levels approaching 0.50% there is severe intoxication with blured or double vision, stupor, nausea, coma, and respiratory depression; death can occur from respiratory or circulatory failure.[1] Ethyl alcohol consumption can also increase the metabolism, and sometimes the toxicity, of other chemicals. Chronic ingestion can cause damage to the liver including fatty infiltration, necrosis, fibrosis, and cirrhosis.

Ethyl alcohol is a developmental toxin in humans. Excessive consumption is associated with fetal alcohol syndrome, which is characterized by joint, limb, and cardiac anomalies and behavioral and cognitive impairment.[1,5]

According to the IARC, sufficient evidence of carcinogenicity for alcoholic beverages has been established in humans.[5] Epidemiological studies clearly indicate that consumption of alcoholic beverages is causally related to cancers of the oral cavity, pharynx, larynx, esophagus, and liver. Since the IARC evaluation, evidence has accumulated for an association between the consumption of alcoholic beverages and an increase in the risk of developing breast cancer and also colorectal tumors.[6]

Ethyl alcohol is not a bacterial or mammalian cell mutagen *in vitro*.[7] Increased frequencies of sister chromatid exchanges and aneuploidies have been observed in the peripheral lymphocytes of alcoholics.[5] Although some degree of genotoxicity may result from excessive alcohol drinking, it is not considered relevant to occupational exposures.[7]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for ethyl alcohol is 1000 ppm (1880 mg/m^3).

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ETHYLAMINE

CAS: 75-04-7

$C_2H_5NH_2$

Synonyms: Monoethylamine; aminoethane; ethanamine

Physical Form. Liquid

Uses. In resin chemistry; stabilizer for rubber latex; intermediate for dyestuffs, pharmaceuticals; in oil refining

Exposure. Inhalation

Toxicology. Ethylamine is an irritant of the eyes, mucous membranes, and skin.

Eye irritation and corneal edema in humans have been reported from industrial exposure.[1]

Exposure of rats to 8000 ppm for 4 hours was fatal to two of six animals within 14 days.[2] Rabbits survived exposures to 50 ppm daily for 6 weeks but showed pulmonary irritation and some myocardial degeneration; corneal damage was observed 2 weeks after exposure.[3] In the rabbit eye, one drop of a 70% solution of ethylamine caused immediate, severe irritation. A 70% solution dropped on the skin of guinea pigs caused prompt skin burns leading to necrosis; when held in contact with guinea pig skin for 24 hours, there was severe skin irritation with extensive necrosis and deep scarring.[1]

Ethylamine was not mutagenic in a variety of bacterial strains.[4]

The odor is like that of ammonia.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for ethylamine is 5 ppm (9.2 mg/m^3) with a short-term excursion limit of 15 ppm (27.6 mg/m^3) and a notation for skin absorption.

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ETHYL AMYL KETONE

CAS: 541-85-5

$C_8H_{16}O$

Synonyms: 5-Methyl-3-heptanone; ethyl *sec*-amyl ketone; EAK

Physical Form. Colorless liquid

Uses. Solvent for resins; organic intermediate

Exposure. Inhalation

Toxicology. Ethyl amyl ketone is an irritant of the eyes and mucous membranes; at very high concentrations it produces central nervous system depression in animals, and it is expected that severe exposure will cause the same effect in humans.

Humans exposed to 25 ppm experienced irritation of the eyes and respiratory tract and detected a strong odor; at 100 ppm, irritation of mucous membranes, headache, and nausea were too severe to tolerate for more than a few minutes.[1] Eye contact with the liquid causes transient corneal injury. Prolonged or repeated cutaneous contact may lead to drying and cracking of the skin. Skin sensitization was not induced in guinea-pigs given repeated treatments with diluted solutions.[2]

Three of six mice and no rats died after a

4-hour exposure to 3000 ppm, whereas exposure to 6000 ppm for 8 hours caused death in all exposed mice and in four of six rats; all animals developed signs of eye and respiratory tract irritation; varying degrees of ataxia, prostration, respiratory distress, and narcosis were observed.[1] Surviving animals recovered with no apparent adverse effects.

The 2003 ACGIH threshold limit value-time weighted average (TLV-TWA) for ethyl amyl ketone is 25 ppm (131 mg/m^3).

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ETHYL BENZENE

CAS: 100-41-4

C_8H_{10}

Synonyms: Ethylbenzol; phenylethane

Physical Form. Colorless liquid

Uses. Primarily used in the production of styrene; also used as an industrial solvent, as a constituent of asphalt and naptha, and as an antiknock agent in aviation and motor fuels

Exposure. Inhalation; skin absorption

Toxicology. Ethyl benzene is an irritant of the skin eyes and mucous membranes; at high concentrations it causes neurological and respiratory depression.

Humans exposed briefly to 1000 ppm experienced eye irritation, but tolerance developed rapidly; 2000 ppm caused lacrimation, nasal irritation, and vertigo; 5000 ppm produced intolerable irritation of the eyes and nose.[1]

When chronic exposures exceeded 100 ppm, complaints included fatigue, sleepiness, headache, and mild irritation of the eyes and respiratory tract.[2]

The rate of absorption of ethyl benzene through the skin of the hand and the forearm in human subjects was 22–33 mg/cm^2/hour, indicating that skin absorption could be a major route of uptake of liquid ethyl benzene.[3,4]

In guinea pigs, exposure to 10,000 ppm caused immediate and intense eye and nose irritation, ataxia, narcosis, and death in 2–3 hours; 5000 ppm was lethal during or after 8 hours of exposure; 2000 ppm produced ataxia in 8 hours, and 1000 ppm caused eye irritation.[1]

Inhalation of ethyl benzene at 600 ppm for 186 days by rats and guinea pigs resulted in slight changes in liver and kidney weights and slight testicular histopathology in rabbits and monkeys.[5] Exposure of rabbits to 230 ppm 4 hour/day for 7 months resulted in changes in blood cholinesterase activity, leukocytosis, reticulocytosis, and dystrophic changes in the liver and kidneys.[6]

Exposure to 782 ppm for 4 weeks caused an increase in platelet counts in male rats and an increase in total leukocyte count in female rats; hematologic parameters did not change for mice or rabbits exposed to the same or higher concentrations.[7] Despite its chemical similarity, ethyl benzene does not appear to cause the same damage to the hematopoietic system as benzene.[8]

In chronic inhalation studies rats and mice were exposed to 0, 75, 250, or 750 ppm 6 hours/day, 5 days/week for 104 weeks.[9] For male rats exposed at 750 ppm survival was decreased, and the incidence of renal tubule neoplasms and testicular adenomas was increased. The findings from an extended evaluation of the kidneys showed a significant increase in the incidences of renal tubule adenoma and hyperplasia in high-dose males and females. In high-dose mice there were increased incidences of alveolar/bronchiolar neoplasms in males, whereas females had

increased incidences of hepatocellular neoplasms. Incidences of hyperplasia of the pituitary gland pars distalis were increased in 250 and 750 ppm females, and thyroid gland follicular cell hyperplasia was increased in both males and females exposed at 750 ppm.

The IARC has determined that there is sufficient evidence for the carcinogenicity of ethyl benzene in animals and inadequate evidence in humans. Overall, it is considered possibly carcinogenic to humans.[10]

Pregnant rats exposed at 100 or 1000 ppm 6 hours/day on days 1–19 of gestation had offspring with significant increase in extra rib formation; at the higher dose, maternal toxicity was indicated by increased liver, kidney, and spleen weights.[11] Rabbits similarly exposed on days 1–24 of gestation had significantly fewer live pups per litter at both exposure levels.[11]

Ethyl benzene is not mutagenic in most test systems, but it has caused a mutagenic effect in mouse lymphoma cells and has induced a marginal yet significant increase in sister chromatid exchanges in human lymphocytes at toxic doses.[4]

Two drops of the liquid in the eyes of a rabbit caused slight conjunctival irritation but no corneal injury.[5] The liquid in contact with the skin of a rabbit caused erythema, exfoliation, and vesiculation.[5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for ethyl benzene is 100 ppm (434 mg/m^3) with a short-term excursion limit (TLV-STEL) of 125 ppm (543 mg/m^3).

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ETHYL BROMIDE
CAS: 74-96-4

C_2H_5Br

Synonyms: Bromoethane; hydrobromic ether; bromic ether

Physical Form. Colorless liquid

Uses. Ethylating agent in synthesis of pharmaceuticals; refrigerant

Exposure. Inhalation

Toxicology. Ethyl bromide is a respiratory irritant and causes hepatic and renal toxicity; at high concentrations, it causes narcosis.

The former use of ethyl bromide as a human anesthetic (at concentrations approaching 100,000 ppm) produced respiratory irritation and caused some fatalities, either immediately, due to respiratory or cardiac arrest, or delayed, due to effects on the liver, kidneys, or heart.[1] At autopsy, findings were pulmonary edema and marked fatty degeneration of the liver, kidneys, and heart. Relatively little experience with this substance in industry has been reported, but exposure of volunteers to 6500 ppm for 5 minutes produced vertigo, slight headache, and mild eye irritation.[1]

Guinea pigs exposed to 50,000 ppm for 98 minutes died within an hour after exposure.[2] Exposure to 24,000 ppm for 30 minutes was fatal within 3 days; at autopsy, findings were pulmonary edema and centrilobular necrosis of the liver; exposure to 3200 ppm for 9 hours produced lung irritation, and death occurred after 1–5 days. The 1-hour LC_{50} was 27,000 ppm for male rats and 16,200 ppm for mice.[3]

In inhalation studies conducted by the National Toxicology Program, acute, subchronic, and chronic effects of ethyl bromide were examined in mice and rats.[4] All mice and three of five female rats died before the end of a 4-hour exposure to 5000 ppm; rats and mice exposed to 2000 ppm 6 hours/day died before the end of 14-day studies. In 14-week studies, 1600 ppm was lethal to some animals and caused compound-related lesions including muscle atrophy and atrophy of the testis and uterus thought to be secondary to body weight loss; rats also had minimal to moderate multifocal mineralization in the cerebellum and minimal-to-severe hemosiderosis of the spleen.

A variety of effects (dependent on species and sex) were seen in the 2-year studies with exposures of 100, 200, or 400 ppm 6 hours/day, 5 days/week.[4] There was some evidence of carcinogenic activity of ethyl bromide for male F344/N rats, as indicated by increased incidences of pheochromocytomas of the adrenal gland (control, 8/40; 100 ppm, 23/45; 200 ppm, 18/46; 400 ppm, 21/46), neoplasms of the brain and lung may also have been related to exposure to ethyl bromide. For female F344/N rats, there was equivocal evidence of carcinogenic activity, as indicated by marginally increased incidences of neoplasms of the brain and lung. In the high-dose rats, alveolar epithelial hyperplasia was increased, as were the incidences of epithelial hyperplasia and squamous metaplasia of the nasal cavity. For male B6C3F1 mice, there was equivocal evidence of carcinogenic activity, based on marginally increased incidences of neoplasms of the lung. There was clear evidence of carcinogenic activity for female B6C3F1 mice, as indicated by neoplasms of the uterus.

The IARC has determined that there is limited evidence in experimental animals for the carcinogenicity of ethyl bromide and that it is not classifiable as to its carcinogenicity to humans.[5]

Ethyl bromide was mutagenic in *Salmonella* assays with and without microsomal activation when tested in an enclosed system; it also induced sister chromatid exchange in Chinese hamster ovary cells.[4]

Applied to the skin of mice, the liquid produced local necrosis.[6] Prolonged or repeated contact of ethyl bromide to the skin may lead to significant absorption of the compound. Instilled in rabbit eyes, it was an irritant.

The etherlike odor of ethyl bromide is detectable only at concentrations well above 200 ppm and, therefore, will not give warning of hazardous concentrations.[6]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for ethyl bromide is 5 ppm (22 mg/m^3) with a notation for skin absorption.

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ETHYL BUTYL KETONE

CAS: 106-35-4

$C_7H_{14}O$

Synonyms: 3-Heptanone; EBK

Physical Form. Colorless liquid

Uses. Solvent and intermediate for organic materials

Exposure. Inhalation

Toxicology. Ethyl butyl ketone (EBK) is mildly irritating to the skin and eyes of animals and causes narcosis at high concentrations.

No adverse effects have been reported in humans.

Rats survived a 4-hour exposure to 2000 ppm, but 4000 ppm for 4 hours was fatal.[1] The oral LD_{50} in rats was 2.76 g/kg, and the LD_{50} for penetration of rabbit skin was greater than 20 ml/kg.[1]

Rats given 1.0% EBK in drinking water for 120 days showed no signs of neurotoxicity.[2] Exposure of rats at 700 ppm 72 hours/week for 24 weeks was also without neurotoxic effect.[3] Extremely large gavage doses, 2 g/kg/day, 5 days/week for 14 weeks, were required to produce signs of neurotoxicity; two of two rats had hindlimb weakness and tail drag.[4] Neuropathology showed central-peripheral-distal axonapathy characterized by giant axonal swelling and neurofilamentous hyperplasia.[4]

Dropped into rabbit eyes or applied to skin the liquid has caused mild irritation.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for ethyl butyl ketone is 50 ppm (234 mg/m^3).

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ETHYL CHLORIDE

CAS: 75-00-3

CH_3CH_2Cl

Synonyms: Chloroethane; monochloroethane; hydrochloric ether

Physical Form. Colorless gas

Uses. Blowing agent in foamed plastics; in the production of tetraethyl lead; formerly used as an inhalation anesthetic agent

Exposure. Inhalation; skin absorption

Toxicology. Ethyl chloride at high concentrations causes central nervous system depression.

In the past, concentrations of 40,000 ppm were used clinically to produce anesthesia.[1] Sudden and unforeseen fatalities from ethyl chloride anesthesia have been reported. Concentrations of 20,000 ppm or above have reportedly caused increased respiratory rate, cardiac depression, dizziness, eye irritation, and abdominal cramps.[1] Exposure to 19,000 ppm resulted in mild analgesia after 12 minutes, and 13,000 ppm caused slight symptoms of inebriation.[2]

Chronic effects from industrial exposure have not been reported, although skin absorption is said to occur. In liquid form this substance may cause frostbite.

Guinea pigs exposed to 40,000 ppm appeared uncoordinated in 3 minutes, had eye irritation, and were unable to stand after 40 minutes; some animals died from exposure for 9 hours, but exposure for 4.5 hours was nonfatal; histopathologic changes in the lungs, liver, and kidneys were observed in euthanized animals of the latter group.[3]

Two-week repeated exposure of rats and dogs to 4000 or 10,000 ppm caused no treatment-related effects except for slight increases in liver-to-body weight ratios in male rats.[4] Similarly, the only observed effect in mice exposed for 11 days, 23 hour/day at up to 5000 ppm was an increase in relative liver weight and a slight increase in hepatocellular vacuolation.[5] Neurobehavioral observation, clinical chemistry, hematology studies, and necropsy failed to show other effects, indicating that ethyl chloride was well tolerated despite the unusually long exposure periods.

Histopathologic examination of reproductive organs showed no evidence of toxicity in rats and dogs exposed at 10,000 ppm for 2 weeks or rats and mice exposed at 19,000 ppm for 13 weeks.[4,6]

Pregnant mice exposed to 5000 ppm, 6 hours/day on days 6–15 of gestation had no overt maternal toxicity; there was slightly delayed ossification of skull bones in the offspring.[1]

In a chronic inhalation study 86% (43/50) of female mice exposed at 15,000 ppm, 6 hours/day for 102 weeks had highly malignant uterine carcinomas vs. none (0/49) in the controls.[6] The incidence of hepatocellular carcinomas was also increased. Male mice had an increase in alveolar and bronchial adenomas, but results were confounded by poor survival. Both male and female rats had marginally significant increases in epithelial tumors and brain astrocytomas, respectively. More recent studies have suggested that the mechanism of uterine tumor induction in mice is species specific, is a high-dose phenomenon, and may be related to glutathione conjugation rather than other metabolic pathways.[7]

The genotoxic potency of ethyl chloride appears to be low. It was negative in *in vivo* micronucleus tests, but it has produced both positive and negative results in bacterial gene mutation assays.[1]

The IARC has determined that there is limited evidence in experimental animals for the carcinogenicity of ethyl chloride and that it is not classifiable as to its carcinogenicity to humans.[8]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for ethyl chloride is 100 ppm (264 mg/m^3) with an A3-animal carcinogen designation and a notation for skin absorption.

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ETHYLENE

CAS: 74-85-1

C_2H_4

Synonyms: Ethene; acetene; bicarburetted hydrogen; olefiant gas

Physical Form. Colorless gas

Uses. Chemical intermediate in the manufacture of polyethylene, ethylene oxide, ethylene dichloride, and ethyl benzene; used as a fruit and vegetable ripening agent

Exposure. Inhalation

Toxicology. Ethylene is of low toxicity and has traditionally been regarded as a simple asphxiant.

Concentrations of less than 2.5% are physiologically inert; at very high concentrations, there may be narcosis, unconsciousness, and asphyxia due to oxygen displacement.[1] Humans exposed to as much as 50% ethylene in air, where the oxygen is decreased to 10%, may experience unconsciousness, and death may occur at 8% oxygen. Exposure to 37% for 15 minutes may result in memory disturbances.[1]

Ethylene inhaled at 11.5 g/m^3 (10,000 ppm) for 4 hours was hepatotoxic in rats pretreated with the polychlorinated biphenyl Arochlor 1254, given orally at a dose of 300 µmol/kg daily for 3 days to induce liver enzymes. It is not toxic without such treatment.[2,3]

Rats exposed to 300, 1000, or 3000 ppm 6 hours/day, 5 days/week for up to 2 years showed no statistically significant evidence of chronic toxicity or oncogenic effects.[4] (A subsequent review of the same data by other investigators found that the incidence of mononuclear cell leukemia was somewhat increased in both sexes at the highest dose level.[5]) Metabolic studies in rats and mice indicate that ethylene may be metabolized to ethylene oxide, an agent with genotoxic and carcinogenic potential.[2,5]

Rats and mice exposed 6 hours/day, 5 days/week for 4 weeks to concentrations of up to 3000 ppm did not have increased frequencies of micronucleus formation in the bone marrow.[6] Ethylene was not genotoxic in *Salmonella typhimurium*.[2]

The IARC has determined that there is inadequate evidence of carcinogenicity of ethylene in humans and experimental animals.[2]

Ethylene is not irritating to the skin and eyes.[1] The gas has a faintly sweet odor that probably does not provide adequate warning of hazardous concentrations. Owing to the highly flammable and explosive characteristics of ethylene, it should be handled cautiously.[1]

The ACGIH regards ethylene as a simple asphyxiant and does not recommend a threshold limit value because the limiting factor is available oxygen. The menimal oxygen cordent should be 18% by volume under normal axmospheric pressure.

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ETHYLENE CHLOROHYDRIN

CAS: 107-07-3

$ClCH_2CH_2OH$

Synonyms: β-Chloroethyl alcohol; glycol chlorohydrin; 2-chloroethanol

Physical Form. Colorless liquid

Uses. Production of ethylene glycol and ethylene oxide; solvent for cellulose acetate, cellulose ethers, and various resins

Exposure. Inhalation; skin absorption

Toxicology. Ethylene chlorohydrin is an irritant of the skin and eyes and is toxic to the liver, kidneys, cardiovascular system, and central nervous system.

Several human fatalities have resulted from inhalation, dermal contact, or ingestion of ethylene chlorohydrin. Typically, neurotoxic symptoms were described, and death was attributed to cardiac and respiratory collapse.[1] One fatality was caused by exposure to an estimated 300 ppm for 2.25 hours.[2] In another fatal case, autopsy showed pulmonary edema and damage to the liver, kidneys, and brain.[2]

Exposure to the vapor has caused irritation of the eyes, nose, and throat; visual disturbances; vertigo, incoordination, and paresthesias; and nausea and vomiting.[2,3] More severe exposure has also caused headache, severe thirst, delirium, low blood pressure, cyanosis, collapse, shock, and coma. In some cases, there have been albumin, casts, and red blood cells in the urine.

Ethylene chlorohydrin is highly irritating to mucous membranes but produces little reaction on contact with rabbit skin.[1] Toxic amounts can be absorbed through the skin without causing dermal irritation; the dermal LD_{50} for rabbits is 68 mg/kg.[4] This value extrapolated to humans suggests that a volume slightly more than a teaspoon could be lethal with prolonged contact.[4]

The liquid instilled in rabbit eyes caused moderately severe injury, but human eyes have recovered from corneal burns within 48 hours.[5]

Inhalation exposures of 15 minutes/day at concentrations of approximately 1000 ppm were fatal to rats within a few days.[6]

In 2-year dermal studies, there was no evidence of carcinogenicity in rats given 50 or 100 mg/kg/day or mice given 7.5 or 15 mg per animal per day.[1] Increased risks for pancreatic cancer and lymphopoietic cancers associated with a chlorohydrin plant that primarily produced ethylene chlorohydrin have been attributed to by-products of the process including ethylene dichloride; ethylene chlorohydrin itself has not been associated with the occurrence of tumors.[7] A more recent study of a different cohort of ethylene and propylene chlorohydrin production workers found no increased risk of pancreatic, lymphopoietic, or hematopoietic cancers.[8]

Significant levels of fetotoxicity and maternal toxicity, but no teratogenicity, were found in rabbits administered 36 mg/kg/day intravenously.[9]

Skin contact is particularly hazardous because the absence of signs of immediate irritation prevents any warning when the skin is wetted by the substance.[3]

The 2003 ACGIH ceiling-threshold limit value (C-TLV) for ethylene chlorohydrin is 1 ppm (3.3 mg/m^3) with a notation for skin absorption.

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ETHYLENEDIAMINE
CAS: 107-15-3

$NH_2CH_2CH_2NH_2$

Synonyms: 1,2-Diaminoethane; EDA

Physical Form. Colorless liquid

Uses. Intermediate in the manufacture of EDTA; catalytic agent in epoxy resins; dyes, solvent stabilizer; neutralizer in rubber products

Exposure. Inhalation

Toxicology. Ethylenediamine is a primary irritant, being corrosive when undiluted, and is also a skin sensitizer.

In human subjects, inhalation of 400 ppm for 5–10 seconds caused intolerable nasal irritation; 200 ppm caused tingling of the face and slight nasal irritation; 100 ppm was inoffensive.[1]

Most of the information regarding the skin sensitization potential of ethylenediamine has come from its use as a stabilizer in pharmaceutical preparations, especially in Mycolog cream, where it has reportedly caused many cases of sensitization.[2,3] Results of skin patch tests, conducted between 1972 and 1974, showed that 6% of the 3216 patients tested exhibited sensitivity to a 1% ethylenediamine-HCl solution.[4] Although ethylenediamine is a potent sensitizer, industrial exposure rarely leads to sensitization and dermatitis because exposure is not prolonged or intimate and normal skin usually is involved.[2] In clinical practice, the ethylenediamine in Mycolog cream is often applied to damaged skin, which is more readily sensitized than the relatively normal skin of most industrial workers.[2] A follow-up study of 16 patients who had exhibited a strong contact allergy to ethylenediamine in 1974 or 1975 showed that in 25% of the cases the sensitivity had disappeared after a period of 10 years in which the allergen had been avoided.[5]

In a case of asthma resulting from ethylenediamine exposure in a 30-year-old man, initial symptoms of sneezing, nasal discharge, and productive cough began 2.5 years after employment and progressed during the following 5 months. An inhalation provocation test with ethylenediamine produced chest tightness, cough, wheezing, and a 26% reduction in FEV_1 4 hours after exposure. The reaction was reproducible on a different day and was specific; a similar reaction was not demonstrated

with other chemicals to which the subject was exposed.[6]

A study of EDA-sensitized workers (as determined by EDA-associated rhinitis, coughing, and wheezing) in an industrial population suggested that smoking may decrease the latency between first exposure to EDA and onset of respiratory symptoms.[7]

Exposure of rats to 4000 ppm for 8 hours was uniformly fatal, whereas 2000 ppm was not lethal.[8] Rats exposed daily for 30 days to 484 ppm did not survive; injury to lungs, liver, and kidneys was observed; at 132 ppm there was no mortality.[1]

In chronic studies nonneoplastic effects on the liver (pleomorphic changes to hepatocytes) have been observed in rats after oral dosing at 45 mg/kg body weight (bw)/day for 2 years, with no effects seen at 9 mg/kg bw/day.[9,10] It was not carcinogenic in lifetime skin painting studies in mice. Ethylenediamine was not genotoxic in a variety of *in vivo* and *in vitro* tests.[11]

No reproductive toxicity was found in rats exposed to 0.50 g/kg/day for two generations.[12] A reduction in body weight gain and changes in liver and kidney weights were observed in the F_0 and F_1 parent rats. A microscopic liver lesion occurred in the F_1 rats, with a greater prevalence and severity in the females. In developmental toxicity studies signs of fetotoxicity and developmental delays occurred only at maternally toxic doses.[10]

In the eye of a rabbit, the liquid caused extreme irritation and corneal damage; partial corneal opacity was produced by a 5% solution.[8] The undiluted liquid applied to the shaved skin of rabbits and left uncovered produced severe irritation and necrosis.[8]

The 2003 ACGIH threshold limit value-time weighted average (TLV-TWA) for ethylenediamine is 10 ppm (25 mg/m^3) with a notation for skin absorption.

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ETHYLENE DIBROMIDE
CAS: 106-93-4

$C_2H_4Br_2$

Synonyms: 1,2-Dibromoethane; EDB

Physical Form. Clear liquid

Uses. A fumigant (now banned for soil and grain use); in gasoline as a lead scavenger; chemical intermediate in the industrial synthesis of other brominated compounds

Exposure. Inhalation; skin absorption

Toxicology. Ethylene dibromide (EDB) is a severe mucous membrane, eye, and skin irritant. It is a testicular toxicant and causes liver and kidney damage; it is carcinogenic in experimental animals.

In an early report, accidental use of ethylene dibromide as a human anesthetic produced general weakness, vomiting, diarrhea, chest pains, coughing, shortness of breath, cardiac insufficiency, and uterine hemorrhaging.[1] Death occurred 44 hours after inhalation. Postmortem examination showed upper respiratory tract irritation, swelling of the pulmonary lymph glands, advanced states of parenchymatous degeneration of the heart, liver, and kidneys, and hemorrhages in the respiratory tract.

Two workers collapsed while inside a tank that was later found to contain a 0.1–0.3% EDB solution.[2] Removed after 20–45 minutes in the tank, one man was intermittently comatose, and the other was delirious and combative. Both experienced vomiting, diarrhea, abdominal pain, and burning of the eyes and throat. Metabolic acidosis and acute renal and hepatic failure ensured. Death occurred 12 and 64 hours later, respectively, despite supportive measures.

Skin contact produces intensive burning pain preceding hyperemia that develops into blisters.[1] Skin sensitization has been reported.[1]

Acute exposure of experimental animals resulted in adverse effects similar to those described for humans. Rats did not survive when exposed to the vapor for longer than 6 minutes at 3000 ppm; minimum lethal concentration for an 8-hour exposure was 200 ppm; these exposures caused hepatic necrosis, pulmonary edema, and cloudy swelling of renal tubules.[3] Depression of the central nervous system (CNS) was observed in rats exposed at higher concentrations, and deaths occurred within 24 hours from respiratory or cardiac failure. At lower concentrations, death due to pneumonia occurred as a result of injury to the lungs and was delayed for up to 12 days after exposure.

Four species of animals tolerated daily inhalation of 25 ppm for 6 months without adverse effects.[3]

Application of a 10% solution or the undiluted liquid to rabbit skin caused marked CNS depression and death within 24 hours.[3] A dermal LD_{50} of 400 mg/kg was estimated.[1]

An increased incidence of skin carcinomas and lung tumors has been found in mice receiving repeated skin applications.[4] Rats and mice chronically exposed to 10 or 40 ppm had increased incidence of an tumors at multiple sites.[5] Animal studies have shown increased toxic and carcinogenic effects when EDB is administered with disulfiram, a widely used drug in alcoholism control programs.[6]

Human epidemiological studies to observe carcinogenic effects are inconclusive because of small cohort size, incomplete exposure data, and insufficient latencies.[7]

EDB is toxic to the male reproductive system in several species.

Testicular atrophy was seen in rats and mice with chronic gavage administration of 41 or 107 mg/kg day, respectively.[8] Abnormal spermatozoa and decreased spermatozoic concentration occurred in bulls fed EDB.[9]

Intraperitoneal injection of 10 mg/kg for 5 days to male rats caused a decrease in average litter size in females mated 3 weeks after exposure and no litters after 4 weeks.[10] Continuous exposure to 32 ppm during gestation caused minor skeletal anomalies in rats and mice.[11]

Adverse reproductive effects have also been reported in humans. Fumigators chronically exposed to EDB showed statistically significant decreases in sperm count and percentages of viable and motile sperm and increases in sperm with specific abnormalities compared with controls.[12] Decrease in sperm velocity and semen volume has been reported in another group of fumigators who were exposed to EDB seasonally.[13] No adverse effects were found on sperm counts of 50 workers exposed to less than 5.0 ppm.[14]

Ethylene dibromide is a potent mutagen, producing a broad spectrum of mutations in a variety of *in vivo* and *in vitro* assays and binds covalently with DNA in vivo.[15,16]

The IARC has determined that there is inadequate evidence in humans but sufficient evidence in experimental animals for the carcinogenicity of ethylene dibromide. An overall evaluation of probably carcinogenic to humans is given.[16] A threshold limit exposure limit has not been assigned by ACGIH.

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ETHYLENE DICHLORIDE
CAS: 107-06-2

$C_2H_4Cl_2$

Synonyms: 1,2-Dichloroethane; dichloroethane; ethylene chloride

Physical Form. Colorless liquid

Uses. Manufacture of vinyl chloride; antiknock agent; fumigant, insecticide; degreaser compounds; rubber cements

Exposure. Inhalation; ingestion

Toxicology. Ethylene dichloride is a central nervous system depressant and causes injury to the liver and kidneys; in chronic gavage studies it is carcinogenic to experimental animals.

In one fatality, exposure to concentrated vapor in a tank for 30 minutes caused drowsiness, nausea, and respiratory distress; coma developed 20 hours after initial exposure.[1] Serum levels of lactate and ammonia were increased, followed by elevation of glutamic transaminases, lactic dehydrogenase, and creatine phosphokinase. Ornithine carbamyl transferase and glutamic oxaloacetic transaminase of mitochondrial origin were remarkably high. Multiple organ failure developed, and the patient died in cardiac arrhythmia on the fifth day. At autopsy, the lungs were severely congested and edematous; diffuse degenerative changes of the myocardium, extensive centrilobular necrosis of the liver, and acute tubular necrosis of the kidneys were noted.

Workers exposed to 10–200 ppm complained of lacrimation, dizziness, insomnia, vomiting, constipation, and anorexia; liver tenderness on palpation, epigastric pain, and elevated urobilinogen were observed.[2] Impairment of the central nervous system and increased morbidity, especially diseases of the liver and bile ducts, were found in workers chronically exposed to ethylene dichloride at concentrations below 40 ppm and averaging 10–15 ppm.[2]

Ingestion of quantities estimated between 8 and 200 ml have been reported to be lethal, with a toxic response similar to that of cases of inhalation.[3,4]

Interactions between ethylene dichloride and other substances have been reported in animal studies. Specifically, a combination treatment with disulfiram caused testicular atrophy (not seen with either agent alone) and lowered the ethylene dichloride dose at which liver effects occurred.[5] Increased hepatotoxicity has also been observed in some animals given phenobarbital along with ethylene dichloride.

Eye contact with either the liquid or high concentrations of vapor causes immediate discomfort with conjunctival hyperemia and slight corneal injury; corneal burns from splashes recover quickly with no scarring. Prolonged skin exposure, as from contact with soaked clothing, produces severe irritation, moderate edema, and necrosis; systemic effects may ensue as the liquid is readily absorbed through the skin.[2]

For intermediate-duration studies, the lethal oral dose depended on the method of administration.[6,7] Administered in the drinking water for 13 weeks, 8000 ppm was relatively nontoxic to two strains of rats, causing elevated liver weights and minimal histologic evidence of kidney damage in female F344/N rats. Gavage administration of 240 mg/kg in male rats and 300 mg/kg in females for 13 weeks was lethal; necrosis of the cerebellum occurred in one-third of the treated animals.

Chronic administration by gavage of 95 or 47 mg/kg/ day for 78 weeks caused a significant increase in hemangiosarcomas of the circulatory system in rats.[8] Squamous cell carcinomas of the forestomach were significantly increased in male rats, and high-dose females had increased incidences of mammary gland adenocarcinomas and fibroadenomas. A variety of tumors have been similarly induced in mice.[8] Intraperitoneal and inhalation studies in animals have not shown a significant carcinogenic response.[9,10]

Pronounced increases were seen for total cancer, lymphatic and hematopoietic cancers, and leukemia in a mortality study of chlorohydrin production workers.[11] The investigators attributed the excesses to ethylene dichloride exposure based on probable exposures of the workers; however, concomitant exposure to other chemicals precludes identifying the etiologic agent(s).

Ethylene dichloride has been shown to alkylate DNA, and it is genotoxic in a variety of *in vivo* and *in vitro* assays.[10] It was not fetotoxic or teratogenic in rats, rabbits, or mice at doses that were not maternally toxic.[10]

The IARC has determined that there is

sufficient evidence for the carcinogenicity of ethylene dichloride in animals and, in the absence of adequate human data, it should be regarded as possibly carcinogenic to humans.[9]

Most subjects could detect ethylene dichloride at a concentration of 6 ppm.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for ethylene dichloride is 10 ppm (40 mg/m^3).

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ETHYLENE GLYCOL
CAS: 107-21-1

CH_2OHCH_2OH

Synonyms: 1,2 Dihydroxyethane; 1,2-ethanediol; ethylene alcohol; ethylene dihydrate

Physical Form. Clear, colorless liquid

Uses. Antifreeze and coolant mixtures for motor vehicles; in hydraulic fluids and heat exchangers; solvent

Exposure. Inhalation; ingestion

Toxicology. Ethylene glycol aerosol causes irritation of the upper respiratory tract; ingestion can cause central nervous system depression, severe metabolic acidosis, liver and kidney damage, and pulmonary edema.

Inhalation is not usually a hazard because the low vapor pressure precludes excessive vapor exposure. Exposure to the vapor from the liquid heated to 100°C has been reported to cause nystagmus and coma of 5- to 10-minutes duration.[1] Human volunteers exposed to an aerosol of 12 ppm for 20–22 hours/day for

4 weeks complained of throat irritation and headache.[2] At 56 ppm, there was more pronounced irritation of the upper respiratory tract, and at 80 ppm of aerosol, the irritation and cough were intolerable.

The chief hazard from ethylene glycol is associated with ingestion of large quantities in a single dose. Several metabolites are responsible for the clinical syndrome, which can be divided into three stages.[3] During the first 12 hours, central nervous system manifestations predominate. If the intoxication is mild, the patient appears to be drunk but without the breath odor of alcohol. In more severe cases, there will be convulsions and coma. Other signs may include nystagmus, ophthalmoplegia, papilledema, depressed reflexes, and tetanic convulsions. The central nervous system manifestations are related to the aldehyde metabolites of ethylene glycol, which reach their maximum concentrations 6–12 hours after ingestion.

In the second stage, cardiopulmonary symptoms become prominent, consisting of mild hypertension, tachypnea, and tachycardia. Widespread capillary damage is assumed to be the primary lesion. If the patient survives the first two stages, renal complications may be expected at 24–72 hours postingestion. Albuminuria and hematuria are common findings, and oxalate crystals are excreted in the urine. Glycoaldehyde, glycolic acid, and glyoxylate are the putative agents for kidney damage.[3]

The most significant laboratory findings in ethylene glycol intoxication are severe metabolic acidosis from the accumulation of glycolate and the presence of high anion gap.[3] Low arterial pH and bicarbonate levels are often observed. Nonspecific findings are leukocytosis and increased amounts of protein in the cerebrospinal fluid. Chelation of calcium oxalate may cause hypocalcemia, which, when severe enough, can lead to tetany and cardiac dysfunction.[3] The minimum lethal dose is on the order of 100 ml in adults, although much higher doses have reportedly been survived.[4]

There is limited information on effects from occupational exposures. In a cross-sectional survey, there was no evidence of effects on kidney function (based on urinary concentrations of albumin, β-*N*-acetyl-glucosaminidase, β_2-microglobulin, and retinol-binding protein) in a small group of aircraft workers (some of whom wore protective breathing equipment) exposed to ethylene glycol vapor or mist during deicing operations.[5]

The effects of the liquid in the eyes of rabbits are immediate signs of moderate discomfort with mild conjunctivitis but no significant corneal damage.[6] In one human incident of a splash in the eye, there was reversible conjunctival inflammation.[7] The liquid produces no significant irritant action on the skin.

In developmental studies, maternal deaths from kidney failure occurred at 2000 mg/kg/day in rabbits and at 3000 mg/kg/ day in mice.[8] Rat dams survived 5000 mg/kg/day.[9] Developmental toxicity including teratogenicity occurred in mice and rats at doses of 500 and 1250 mg/kg/day, respectively. Maternal toxicity was not evident at these levels.[8] Rabbit fetuses did not exhibit developmental toxicity, even at doses that were maternally lethal.[9] No teratogenic effects were observed in rats and mice after inhalation or dermal exposure, suggesting that route of exposure is critical to producing fetal effects.[9] Ethylene glycol was not a selective reproductive toxin in a three-generation study or repeated-dose studies in rodents.[10]

No evidence of a carcinogenic effect was found in mice or rats administered up to 1000 mg/kg/day for 2 years or in female mice fed up to 50,000 ppm or males fed up to 25,000 ppm ethylene glycol in the diets for 2 years.[11,12]

Ethylene glycol was found to be nonmutagenic in the *Salmonella typhimurium* assays; it did not induce sister chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells.[12]

The 2003 ACGIH ceiling threshold limit value (C-TLV) for ethylene glycol as an aerosol is 39 ppm (100 mg/m^3).

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ETHYLENE GLYCOL DINITRATE

CAS: 628-96-6

$CH_2NO_3CH_2NO_3$

Synonyms: EGDN; nitroglycol; 1,2-dinitroethane

Physical Form. Oily liquid

Uses. As an explosive usually mixed with nitroglycerin (NG) in the manufacture of dynamite

Exposure. Inhalation; skin absorption. Data on toxic effects are reported chiefly from industrial exposures to ethylene glycol dinitrate (EGDN)-NG mixed vapors.

Toxicology. EGDN causes vasodilation and cardiac effects.

Intoxication results in a characteristic intense, throbbing headache, presumably due to cerebral vasodilation, often associated with dizziness and nausea and occasionally with vomiting and abdominal pain.[1,2] More severe exposure also causes hypotension, flushing, palpitation, low levels of methemoglobinemia, delirium, and depression of the central nervous system. Aggravation of these symptoms after alcohol ingestion has been observed. On repeated exposure, a tolerance to headache develops but is usually lost after a few days without exposure. At times, persistent tachycardia, diastolic hypertension, and reduced pulse pressure have been observed. On rare occasions, a worker may have an attack of angina pectoris a few days after cessation of repeated exposures, a manifestation of cardiac ischemia. Sudden death due to unheralded cardiac arrest has also been reported under these circumstances.[3]

Volunteers exposed to the vapor of a mixture of EGDN and NG at a combined concentration of 2 mg/m^3 experienced headache and a fall in blood pressure within 3 minutes of exposure; a mean concentration of 0.7 mg/m^3 for 25 minutes also produced lowered blood pressure and slight headache.[4]

A mortality study of 4061 workers, employed in a Scottish explosives factory and followed from 1965 to 1980, revealed an excess of deaths from acute myocardial infarction in the younger group of workers exposed to both NG and EGDN. This excess was not observed in workers considered to have been exposed to NG only.[5]

EGDN is readily absorbed through the intact skin.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for ethylene glycol dinitrate is 0.05 ppm (0.3 mg/m^3) with a notation for skin absorption.

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ETHYLENE GLYCOL MONOBUTYL ETHER
CAS: 111-76-2

$C_4H_9OCH_2CH_2OH$

Synonyms: Butyl cellosolve; 2-butoxy ethanol; EGBE; EGMBE

Physical Form. Colorless liquid

Uses. Widely used solvent and cleaning agent

Exposure. Inhalation; skin absorption

Toxicology. Ethylene glycol monobutyl ether (EGBE) is an irritant of the eyes and mucous membranes, and in animals it is a hemolytic agent.

Exposure of humans to high concentrations (300–600 ppm) of the vapor for several hours would be expected to cause respiratory and eye irritation, narcosis, and damage to the kidney and liver.[1]

Human subjects exposed to 195 ppm for 8 hours had discomfort of the eyes, nose, and throat, although there were no objective signs of injury and no increase in erythrocytic fragility.[2] Similar symptoms occurred at 113 ppm for 4 hours.[2] No clinical signs of adverse effects or subjective complaints occurred among seven male volunteers exposed to 20 ppm for 2 hours.[3]

Statistically significant decreases in hematocrit and increases in mean corpuscular hemoglobin concentration have been reported in men occupationally exposed to 0.46–0.75 ppm EGBE for 1–6 years.[4] It was noted that changes were small, showed no relationship to exposure concentration, and were still within normal biological variability.

Although not relevant to occupational exposure, ingestion of EGBE has resulted in respiratory, cardiovascular, hematologic, hepatic, renal, ocular ,and metabolic effects.[4]

The 4-hour LC_{50} values were 486 ppm for male rats and 450 ppm for female rats; toxic effects included narcosis, respiratory difficulty, and kidney damage.[5] Acute or prompt deaths are likely to be due to the narcotic effects of the substance, whereas delayed deaths are usually attributable to congested lungs and severely damaged kidneys. In a 9-day study, rats exposed to 245 ppm, 6 hours/day had significant depression of red blood cell count and hemoglobin with increases in nucleated erythrocytes, reticulocytes, and lymphocytes.[5] Decreased body weight gains and increased liver weights were also found. Toxic effects showed substantial reversal 14 days after exposure. In a 90-day study, only mild hematologic alterations were observed in rats exposed to 77 ppm 30 hours/week. Repeated gavage administration to rats of 222, 443, or 885 mg/kg/day for 90 days caused a significant dose-dependent decrease in hemoglobin concentration and red blood cell counts.[6] Secondary effects included increased spleen weights, splenic congestion, and increased hemosiderin deposition in the liver and kidneys. EGBE had no adverse effects on

testes, bone marrow, thymus, or white blood cells. The mechanism for EGBE-induced red blood cell depression in rats is unknown, but acid metabolites may be involved.[3,4] There appear to be strikingly different hematologic effects among species; differences in metabolism are probably responsible.[5] It has been suggested that the hematologic effects are of lesser consequence in humans in contrast to rodents because acute exposures of 200 ppm produced no alterations in erythrocyte fragility.[3]

Two-year inhalation studies revealed equivocal evidence of carcinogenic activity in female rats based on the increased combined incidences of benign or malignant pheochromocytoma (mainly benign) of the adrenal medulla and no evidence of carcinogenic activity in male rats exposed to 31.2, 62.5, or 125 ppm; there was some evidence of carcinogenic activity in male mice based on increased incidences of hemangiosarcoma of the liver and in female mice based on increased incidences of forestomach squamous cell papilloma or carcinoma (mainly papilloma).[7] Increased incidences of forestomach neoplasms in male and female mice occurred in groups in which ulceration and hyperplasia were also present. A mild regenerative anemia and effects secondary to the anemia were also noted.

EGBE did not induce sister chromatid exchanges or chromosomal aberrations in mammalian cell assays *in vitro*, and *in vivo* it did not induce micronuclei in bone marrow cells of rodents. It was not mutagenic in bacterial assays with or without metabolic activation.[7]

EGBE appears to be less hazardous than other monoalkyl ethers of ethylene glycol with regard to reproductive effects.[5] Mice treated orally with 1000 mg/kg for 5 weeks had no change in absolute or relative testis weights.[8] Exposure of pregnant rats at 100 ppm or rabbits at 200 ppm during organogenesis resulted in maternal toxicity and embryotoxicity, including decreased number of viable implantations per litter.[9] Slight fetotoxicity in the form of poorly ossified or unossified skeletal elements was also observed in rats. Teratogenic effects were not observed in either species.[9]

In continuous breeding studies in mice EGBE affected reproductive parameters including the number of litters per pair; the number of live pups per litter; the proportion of pups born alive; and adjusted live pup weights only at levels (1% and 2% in drinking water) that resulted in significant mortality of the dams.[10,11] In males, testis and epididymis weights were normal, as were sperm number and motility even at generally toxic doses.[11] At the 0.5% dose level, EGBE did not significantly affect the fertility or reproductive performance of either first- or second-generation mice.[10]

Daily skin application to rabbits of 150 mg/kg as a 43.8% aqueous solution for 13 weeks caused no adverse effects.[9] The LD_{50} for rabbits was 0.45 ml/kg (0.40 g/kg) when confined to the skin for 24 hours.[1] The liquid is not significantly irritating to the skin and is not a skin sensitizer; instilled directly into the eye it produces pain, conjunctival irritation, and transient corneal injury.[1,12]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for ethylene glycol monobutyl ether is 20 ppm (97 mg/m^3) with a notation for skin absorption.

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ETHYLENE OXIDE

CAS: 75-21-8

C_2H_4O

Synonyms: 1,2-Epoxyethane; oxirane; dimethylene oxide

Physical Form. Colorless gas

Uses. Sterilizing agent; fumigant; insecticide; reagent in organic chemical synthesis

Exposure. Inhalation

Toxicology. Ethylene oxide is an irritant of the eyes, respiratory tract, and skin; at high concentrations it causes central nervous system depression; it is carcinogenic in female mice.

In humans the early symptoms are irritation of the eyes, nose, and throat and a peculiar taste; effects that may be delayed are headache, nausea, vomiting, dyspnea, cyanosis, pulmonary edema, drowsiness, weakness, and incoordination.[1]

Contact of solutions of ethylene oxide with the skin of human volunteers caused characteristic burns; after a latent period of 1–5 hours, effects were edema and erythema and progression to vesiculation, with a tendency to coalescence into blebs, and desquamation. Complete healing without treatment usually occurred within 21 days with, in some cases, residual brown pigmentation. Application of the liquid to the skin caused frostbite; three of the eight volunteers were said to have become sensitized to ethylene oxide solutions.[2] The undiluted liquid or solutions may cause severe eye irritation or damage.

Exposure of several species of animals to concentrations calculated to be greater than 1000 ppm for 2 hours caused lacrimation and nasal discharge followed by gasping and labored breathing; corneal opacity was observed in guinea pigs. Delayed effects occurred after several days and included vomiting, diarrhea, dyspnea, pulmonary edema, paralysis of hindquarters, convulsions, and death; at autopsy, findings were degenerative changes of the lungs, liver, and kidneys.[3] The LC_{50} values for mice, dogs, and rats exposed for 4 hours were 835, 960, and 1460 ppm, respectively.[4]

A number of cases of subacute sensory motor polyneuropathy have been described among sterilizing workers exposed to ethylene oxide.[5,6] Findings have included weakness with bilateral foot drop, sensory loss, loss of reflexes, and neuropathologic changes on EMG in the lower extremities. In some cases, sural nerve biopsy showed axonal degeneration. Removal from exposure resulted in resolution of symptoms in 1–7 months. The abnormalities have

been consistent with a distal "dying-back" axonopathy with secondary demyelination, similar to that seen with other peripheral neurotoxins, such as *n*-hexane.[5] An animal model of distal axonal degeneration with pathologic confirmation has been described in rats exposed to 500 ppm ethylene oxide 3 times/week for 13 weeks.[7] No significant neurophysiological effects were found in nonhuman primates after chronic exposures at 50 or 100 ppm.[8]

Two epidemiological studies of workers exposed to ethylene oxide revealed increased rates of leukemia.[9,10] In one study, two cases of leukemia (0.14 expected) and three stomach cancers (0.4 expected) were observed. The other study found three cases of leukemia (0.2 expected). Because these workers had exposures to other potential carcinogens, the findings cannot be linked with certainty to ethylene oxide. The small cohort size, the small number of deaths, and uncertainties about exposure level have also been noted.[11] A number of other studies have not found an increased rate of cancer mortality from ethylene oxide exposure. A mortality study of over 18,000 ethylene oxide workers from 14 plants producing medical supplies and foodstuffs did not find an excess of leukemia or brain, stomach, or pancreatic cancers.[12] There was, however, an increase in non-Hodgkin lymphoma in male workers. A follow-up of 1896 ethylene oxide production workers did not find an increase in mortality from leukemia, non-Hodgkin lymphoma, or brain, pancreatic, or stomach cancers.[13]

In a chronic inhalation bioassay in rats exposed for 6 hours/day, 5 days/week for 2 years to 100, 33, or 10 ppm ethylene oxide, there was a dose-related increased occurrence of mononuclear cell leukemia in both sexes at all concentrations. There was also an increased occurrence of primary brain tumors at 100 and 33 ppm in both sexes and peritoneal mesotheliomas arising from the testicular serosa at 100 and 33 ppm in male rats.[14]

The IARC has determined that there is limited evidence in humans for the carcinogenicity of ethylene oxide and sufficient evidence in experimental animals.[15]

Hospital staff exposed to ethylene oxide in sterilizing operations during pregnancy were found to have a higher frequency of spontaneous abortions (16.7%) compared with a control group (5.6%) by a questionnaire study. Analysis of a hospital discharge register confirmed the findings. The association persisted after analysis for potential confounding factors, such as age and smoking status.[16] Adverse reproductive effects were also noted in ethylene oxide-exposed dental assistants who had a twofold increase in spontaneous abortions and preterm and postterm births compared to unexposed dental assistants.[17] There is animal evidence of adverse reproductive effects, including decreased fertility and reduced sperm count and motility in males and increased fetal losses and malformed fetuses in females.[18]

Ethylene oxide is a potent genotoxic agent in a wide variety of prokaryotic and eukaryotic assays and induces dose-related increases in the formation of adducts with DNA and hemoglobin.[11] In humans it causes increases in the frequency of chromosomal aberrations and sister chromatid exchange in peripheral lymphocytes after acute, high exposures with sampling a few days after exposure.[19]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for ethylene oxide is 1 ppm (1.8 mg/m^3) with a notation for skin absorption and an A2-suspected human carcinogen designation.

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ETHYLENE THIOUREA

CAS: 96-45-7

$C_3H_6N_2S$

Synonyms: ETU; imidazolidinethione; 2-imidazoline-2-thiol; 2-mercaptomidazoline

Physical Form. White crystalline solid

Uses. Accelerator in the curing of polychloroprene (neoprene) and polyacrylate rubber; intermediate in the manufacture of antioxidants, insecticides, fungicides, dyes, pharmaceuticals, and synthetic resins

Exposure. Inhalation

Toxicology. Ethylene thiourea (ETU) is an antithyroid substance and animal carcinogen.

Clinical examination and thyroid function tests carried out over a period of 3 years on 13 exposed workers showed one subgroup, the mixers, to have significantly lower levels of total thyroxine than other workers; one person had an appreciably raised level of thyroid-stimulating hormone and was considered to be hypothyroid.[1] There was no evidence of any clinical effect in any of the workers. Background air concentrations at the plants generally ranged up to 240 µg/m^3, but levels up to 330 µg/m^3 were registered on one individual's personal sampler.

Two previous studies found only slight

differences in total thyroxine and triiodothyronine in exposed workers (concentrations unspecified).

In groups of rats fed 125 or 625 ppm for up to 90 days, marked increases in serum thyroid-stimulating hormone were found.[2] The high-dose group also exhibited decreases in iodide uptake by the thyroid and in serum triiodothyronine and thyroxine levels. The majority of rats at both these exposure levels had enlarged, red thyroids. Clinical signs of poisoning included excessive salivation, hair loss, and scaly skin texture by day 8 in the 625 ppm group. The no-effect level for dietary ETU in rats was considered to be 25 ppm.

In rats, ETU produced a high incidence of follicular carcinoma of the thyroid after oral administration in three studies.[3–5] Doses in one of these studies were 5, 25, 125, 250, or 500 ppm.[2] At the two highest dose levels, animals of both sexes had thyroid carcinomas, although male rats had a higher incidence. The lower dose levels produced thyroid follicular hyperplasia. ETU is believed to induce thyroid tumors through the suppression of thyroxin synthesis, which in turn triggers hypersecretion of thyroid stimulating hormone by the pituitary; prolonged thyroid-stimulating hormone secretion may result in follicular cell hypertrophy, hyperplasia, adenomas, and carcinomas of the thyroid.[1] In mice, repeated oral administration of the maximal tolerated dose of 215 mg/kg ETU produced liver tumors.[6]

A recent study confirmed that ethylene thiourea was carcinogenic in male and female rats as shown by increased incidences of thyroid follicular cell neoplasms after treatment of up to 250 ppm in the diet for 2 years.[7] In mice, concentrations ranging from 100 to 1000 ppm for 2 years caused liver and pituitary tumors in addition to thyroid tumors. Perinatal exposure up to 8 weeks followed by a control diet for 2 years was not carcinogenic in rats or mice. Combined perinatal-adult ETU exposures produced the same carcinogenic effects as adult-only exposures.

The IARC has determined that there is inadequate evidence in humans for the carcinogenicity of ethylene thiourea and sufficient evidence in experimental animals. The agency further notes that because ethylene thiourea produces thyroid tumors in animals by non-genotoxic mechanisms it would not be expected to produce thyroid cancer in humans exposed to concentrations that do not alter thyroid hormone homeostasis.[8]

ETU was a potent teratogen in rats at doses that produced no maternal toxicity or fetal deaths.[9] At doses greater than 10 mg/kg, there were neural tube closure defects, hydrocephalus, and other brain malformations and limb defects.[9] Neural tube defects appear to be the result of secondary reopening from excessive fluid pressure rather than lack of original closure of the neural tube.[10] Other anomalies observed in rats included the urogenital and ocular systems. Treatment only on gestation day 11 with ETU primarily caused hydronephrosis.[11] Doses of 80 mg/kg decreased the brain weight of rabbits. ETU was also teratogenic after oral dosing in cats and mice and after skin and inhalation exposures in rats.[11]

ETU was not a potent genotoxic agent in a variety of assays.[8] At present, there is no threshold limit value (TLV) for ETU.[12]

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ETHYLENIMINE

CAS: 151-56-4

$(CH_2)_2NH$

Synonyms: Aziridine; ethyleneimine; azirane; azacyclopropane; dihydroazirine;

Physical Form. Colorless liquid

Uses. Organic syntheses; production of polyethyleneimines used in the paper industry and as flocculation aids in the clarification of effluents

Exposure. Inhalation; skin absorption

Toxicology. Ethylenimine is a severe irritant of the eyes, mucous membranes, and skin and causes pulmonary edema; in experimental animals it is carcinogenic.

More than 100 cases of significant acute effects after exposure have been reported in the past 30 years, including fatalities from inhalation and skin contact.[1] The effects of overexposure are usually delayed for ½ to 3 hours and include nausea, vomiting, headache, dizziness, irritation of eyes and nose, laryngeal edema, bronchitis, dyspnea, pulmonary edema, and secondary bronchial pneumonia.[1,2] In experimental human studies, eye and nose irritation occurred at concentrations of 100 ppm and above.[3]

Severe corneal damage and death resulted from placing 0.005 ml of the liquid in the eyes of rabbits; severe eye burns in humans have resulted from direct contact. On the skin, the liquid is a potent irritant and vesicant that may produce sensitization.[4]

The LC_{50} in mice was 2236 ppm for 10 minutes; signs of exposure were irritation of eyes and nose, delayed-onset pulmonary edema, and renal tubular damage with proteinuria, hematuria, and elevated blood urea nitrogen.[5] In other exposed animals, a decrease in the white blood cell count and a depression of all blood elements have also been observed.[1]

The carcinogenicity of ethylenimine has been investigated in animal studies. Rats given subcutaneous injections twice weekly for 33 weeks developed sarcomas at the injection site.[6] Administered to mice by gavage for 3 weeks, followed by dietary administration for 77 weeks, it caused a significant increase in hepatomas and pulmonary tumors.[6]

Although animal studies have found ethylenimine to be carcinogenic, an epidemiological study of 144 workers with up to 40 years experience showed no evidence of carcinogenicity.[7] The IARC has determined that there is limited evidence of carcinogenicity of ethylenimine in experimental animals and that it is possibly carcinogenic to humans.[8]

Ethylenimine is a direct-acting alkylating agent that is mutagenic in a wide range of test systems.[8]

The odor and irritant thresholds do not provide sufficient warning of overexposure.[4] The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for ethylenimine is 0.5 ppm (0.88 mg/m^3) with a notation for skin absorption.

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ETHYL ETHER
CAS: 60-29-7

$C_2H_5OC_2H_5$

Synonyms: Diethyl ether; ethoxyethane; ethyl oxide; ether; anesthesia ether; sulfuric ether

Physical Form. Colorless liquid

Uses. Solvent in the manufacture of dyes, plastics, and cellulose acetate rayon; anesthetic agent

Exposure. Inhalation

Toxicology. Ethyl ether causes eye and respiratory irritation, and, at high concentrations, it produces central nervous system depression and narcosis.

Concentrations of ethyl ether ranging from 100,000 to 150,000 are required for induction of human anesthesia; however, exposure at this concentration may also produce fatalities from respiratory arrest.[1,2] Maintenance of surgical anesthesia is achieved at 50,000 ppm, and the lowest anesthetic limit is 19,000 ppm.[1] Continued inhalation of 2000 ppm in human subjects may produce dizziness; however, concentrations up to 7000 ppm have been tolerated by some workers for variable periods of time without untoward effects.[3] Initial symptoms of acute overexposure include vomiting, respiratory tract irritation, headache, and either depression or excitation. In some persons, chronic exposure results in anorexia, exhaustion, headache, drowsiness, dizziness, excitation, and psychic disturbances.[2] Albuminuria has been reported.[1] Tolerance may be acquired through repeated exposures.[2]

Ethyl ether is a mild skin irritant; repeated exposure causes drying and cracking.[2] The vapor is irritating to the eyes, and the undiluted liquid in the eyes causes painful inflammation of a transitory nature.[3] Human subjects found 200 ppm irritating to the nose, but not to the eyes or throat.[4]

Rats gavaged daily with 3500 mg/kg/day for up to 13 weeks showed marked toxicity including mortality, decreased food intake, and body weight loss.[5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for ethyl ether is 400 ppm (1210 mg/m^3) with a short-term excursion limit (STEL) of 500 ppm (1520 mg/m^3).

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ETHYL FORMATE

CAS: 109-94-4

$HCOOC_2H_5$

Synonyms: Formic ether; ethyl methanoate; ethyl formic ester

Physical Form. Clear liquid

Uses. As a food flavoring; in organic syntheses; as a fumigant

Exposure. Inhalation

Toxicology. Ethyl formate causes irritation of the eyes and nose; at very high concentrations it causes narcosis in animals, and it is expected that severe exposure will produce the same effect in humans.

In humans, a concentration of 330 ppm caused slight irritation of the eyes and rapidly increasing nasal irritation.[1] No chronic systemic effects have been reported in humans.[2]

Rats survived 4 hours of inhalation at 4000 ppm, but 8000 ppm was fatal to five of six animals.[3] Cats exposed to 5000 ppm for 20 minutes showed eye irritation; 10,000 ppm for 80 minutes caused narcosis followed by death.[1] Pulmonary edema and death were observed in dogs exposed to 10,000 ppm for 4 hours.[4]

When applied to the skin of mice, ethyl formate showed no evidence of tumorigenic activity in 10 weeks.[4]

The liquid is only slightly irritating to the skin, but dropped into the eye it causes moderate injury to the cornea.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for ethyl formate is 100 ppm (303 mg/m^3).

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2-ETHYLHEXYL ACRYLATE

CAS: 103-11-7

$C_{11}H_{20}O_2$

Synonyms: EHA, 2-propenoic acid 2-ethylhexyl ester

Physical Form. Colorless liquid; commercial form contains hydroquinone (1000 ppm) or hydroquinone methyl ether (15 or 200 ppm) to prevent polymerization

Uses. As a plasticizing co-monomer for the production of resins used in adhesives, latex, paints, textile and leather finishes, and coatings for paper

Exposure. Inhalation; skin contact

Toxicology. By analogy to effects caused by other acrylates, 2-ethylhexyl acrylate (EHA) is expected to be an irritant of the eyes, nose, and skin.

Dermal sensitization to EHA has been documented from exposure to its presence in adhesive tape.[1] This potential has been confirmed in the guinea pig.[2]

In a lifetime dermal oncogenesis study in mice, 20 mg EHA in acetone was applied 3 times weekly for their lifespan.[3] There were 40 mice in the group at the start of the study. Two animals developed squamous cell carcinomas, and four other animals had squamous cell papillomas. The first tumor was observed after 11 months of treatment. None of the acetone-treated controls developed tumors. There was an apparent increase in the frequency of chronic nephritis in the EHA-treated mice (68% compared with 15% in controls). Treatment with EHA may have exacerbated the onset and development of this condition, which is normally seen in aged mice.

In another study, skin tumors, including papillomas, squamous cell carcinomas, and malignant melanomas, were seen in mice receiving skin applications of 21% or 86.5% EHA in 25 µl of acetone three times per week for 2 years.[4]

No skin tumors were observed in another strain of mice receiving up to 85% EHA in acetone for up to 2 years. Hyperkeratosis and hyperplasia occurred in all treated groups.[5]

The IARC has determined that there is limited evidence in experimental animals and inadequate evidence in humans for the carcinogenicity of ethylhexyl acrylate.[6]

Administered to pregnant rats 6 hours/day during days 6–20 of gestation, doses of 50, 75, or 100 ppm caused no evidence of maternal toxicity or significant developmental effects.[7]

An ACGIH threshold limit value has not been established for EHA.

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ETHYLIDENE NORBORNENE

CAS: 16219-75-3

C_9H_{12}

Synonyms: Ethylidenebicyclo(2,2,1)hep-2-ene; ENB; 2-norbornene, 5-ethylidene

Physical Form. Colorless liquid (stabilized with 100 ppm of *tert*-butyl catechol because of its reactivity with oxygen)

Uses. As third monomer in EPDM (ethylene-propylene diene monomer)

Exposure. Inhalation

Toxicology. Ethylidene norbornene is an irritant of the eyes and mucous membranes and at high concentrations causes central nervous system effects in animals.

Humans noted some irritation of the eyes and nose when exposed to 11 ppm for 30 minutes and transient eye irritation at 6 ppm.[1]

The 4-hour LC_{50} values varied in different species from 730 ppm for mice to 3100 ppm for rabbits.[1] In rats lower concentrations of vapor produced narcotic and irritant effects including hypoactivity, ataxia, prostration, lacrimation, and nasal discharge. Higher, near-lethal concentrations caused tremors and convulsions.[2]

Beagle dogs exposed at 93 ppm for 7 hours/day, 5 days/week for a total of 89 exposures showed testicular atrophy, hepatic lesions, and slight blood changes.[1] Less marked effects were seen at 61 ppm and no effects were seen at 22 ppm. Rats similarly exposed to 237 ppm exhibited testicular atrophy, hepatic lesions, and hydrothorax. In a more recent study, rats exposed 6 hours/day for 14 weeks at concentrations up to 150 ppm showed histopathologic changes in the thyroid gland.[3]

Minimal fetoxicity (skeletal variations) was observed in the offspring of rats treated at 100 and 354 ppm for 6 hours/day on gestation days 6–15; maternal toxicity was also evident at these doses.[4]

Applied to the skin of animals a 4-hour occluded dose produced mild to moderate erythema and edema.[2] Similar contact for 24 hours resulted in marked erythema, necrosis, and ulceration.[5] Instilled in rabbit eyes, the liquid has caused mild conjunctival hyperemia.

Ethylidene norbornene was not mutagenic or clastogenic in a variety of *in vitro* assays.[6]

The 2003 ACGIH ceiling-threshold limit value (C-TLV) for ethylidene norbornene is 5 ppm (25 mg/m^3).

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ETHYL MERCAPTAN
CAS: 75-08-1

C_2H_5SH

Synonyms: Ethanethiol; ethyl hydrosulfide; ethyl sulfhydrate; ethyl thioalcohol; thioethanol; thioethyl alcohol

Physical Form. Colorless liquid with a persistent leeklike odor

Uses. Stenching agent for liquefied petroleum gases; adhesive stabilizer; manufacture of plastics, insecticides, and antioxidants

Exposure. Inhalation

Toxicology. Ethyl mercaptan causes irritation of mucous membranes; at high concentrations it causes narcosis in animals, and it is expected that severe exposure will cause the same effects in humans.

At concentrations below those necessary to produce toxic effects, ethyl mercaptan is extremely malodorous and voluntary exposure to high concentrations is unlikely to occur. Observations on humans are limited to a single brief report of exposure of workers to 4 ppm for 3 hours daily over 5–10 days; the workers experienced headache, nausea, fatigue, and irritation of mucous membranes.[1]

In animals, ethyl mercaptan vapor causes mucous membrane irritation, narcosis, and, at near-lethal levels, by analogy to other mercap-

tans, it may produce pulmonary edema. It appears to be severalfold less acutely toxic than hydrogen sulfide or methyl mercaptan.

In rats, the LD_{50} for 4 hours was 4420 ppm; effects included irritation of mucous membranes, increased respiration, incoordination, staggering gait, weakness, partial skeletal muscle paralysis, light to severe cyanosis, and mild to heavy sedation.[2]

Animals that survived single near-lethal doses by the intraperitoneal and oral routes frequently had liver and kidney damage at autopsy up to 20 days after treatment.[2] The liquid dropped in the eyes of rabbits caused slight to moderate irritation. Chronic inhalation exposures in rats, mice, and rabbits over 5 months showed no significant effects at 40 ppm.[1]

The odor threshold of ethyl mercaptan is approximately 0.25 ppb.[3] The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for ethyl mercaptan is 0.5 ppm (1 mg/m^3).

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N-ETHYLMORPHOLINE

CAS: 100-74-3

$C_6H_{13}NO$

Synonyms: 4-Ethylmorpholine

Physical Form. Colorless, flammable liquid with ammonia-like odor

Uses. Catalyst in polyurethane foam production

Exposure. Inhalation; skin absorption

Toxicology. *N*-ethylmorpholine is an irritant of the eyes and mucous membranes; prolonged exposure to low concentrations causes corneal edema.

In an experimental study, humans exposed to 100 ppm for 2.5 minutes experienced irritation of eyes, nose, and throat, whereas 50 ppm produced lesser irritation.[1] Distortion of vision can occur at levels much lower than those that cause irritation. Workers exposed to low vapor concentrations (3–11 ppm) for several hours reported temporary fogged vision with rings around lights.[2] Corneal edema has been observed in workers when air concentrations of substituted morpholines exceed 40 ppm. The symptoms usually appear at the end of the workday and clear within 3–4 hours after cessation of exposure.[3]

The liquid instilled in the eye of a rabbit caused corneal haziness with sloughing and irregularities of the surface characteristic of severe desiccation.[3] On the skin of a rabbit, the undiluted liquid produced no reaction, surprisingly unlike unsubstituted morpholine, which is a severe skin irritant.[4]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for *N*-ethylmorpholine is 5 ppm (24 mg/m^3) with a notation for skin absorption.

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ETHYL SILICATE
CAS: 78-10-4

$Si(OC_2H_5)_4$

Synonyms: Tetraethyl orthosilicate; tetraethoxysilane; ethyl orthosilicate; silicic acid, tetraethyl ester

Physical Form. Colorless liquid

Uses. For arresting decay and disintegration of stone; for manufacture of weatherproof and acid-proof mortars and cement

Exposure. Inhalation

Toxicology. Ethyl silicate is an irritant of the eyes and the mucous membranes; in animal studies it causes adverse effects to the kidneys.

In humans, the eyes and the nose are affected by brief exposures, as follows: 3000 ppm is extremely irritating and not tolerable; 1200 ppm causes lacrimation and stinging; 700 ppm produces mild stinging; and at 250 ppm there is slight tingling.[1] Repeated or prolonged skin contact with the liquid may cause dermatitis because of its solvent effect.[2]

Exposure of guinea pigs to 2530 ppm for 4 hours was lethal to more than half of the animals; death usually was delayed and a result of pulmonary edema; effects were irritation of the eyes and the nose, lacrimation, tremor, dyspnea, and narcosis; some surviving animals developed a delayed but profound anemia.[1]

Gavage administration of 1300, 2800, or 4300 mg/kg to rats caused significant mortality in the two highest dose groups. Acute toxic changes to the kidneys included tubular necrosis, accumulation of silicates, and superficial necrotizing papillitis, which were dose and time dependent.[3] Exposure to 1000 ppm for up to three 7-hour periods was fatal to 4 of 10 rats; autopsy findings were marked tubular degeneration and necrosis of the kidneys, mild liver damage, and slight pulmonary edema and hemorrhage.[2] In rats exposed to 125 ppm, 7 hours/day for 15–20 days, slight to moderate kidney damage was observed, but no pathologic changes were detected in the liver or the lungs.

Mice exposed to 100 or 50 ppm 6 hour/day, 5 days/week for 2 or 4 weeks developed tubulointerstitial nephritis at the high dose; kidney lesions were not observed in the mice exposed to 50 ppm, but histopathologic changes in the nasal mucosa were evident.[4]

Instillation of the liquid into the rabbit eye caused immediate marked irritation that was reversible.[2]

The 2003 threshold limit value-time-weighted average (TLV-TWA) is 10 ppm (85 mg/m^3).

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FENTHION
CAS: 55-38-9

$C_{10}H_{15}O_3PS$

Synonyms: Baycid; Baytex; Entex; Lebaycid; Mercaptophos; phosphorothioic acid *O*, *O*-dimethyl *O*-(3-methyl-4-(methylthio)phenyl) ester

Physical Form. Yellow to tan oily liquid

Uses. Organothiophosphate insecticide

Exposure. Inhalation; skin absorption

Toxicology. Fenthion is an anticholinesterase agent and may also cause delayed neurotoxicity and ocular damage.

Signs and symptoms of overexposure are caused by the inactivation of the enzyme cholinesterase, which results in the accumulation of acetylcholine at synapses in the nervous system, skeletal and smooth muscle, and secretory glands. The sequence of the development of systemic effects varies with the route of entry. The onset of signs and symptoms is usually prompt but may be delayed up to 12 hours.[1–4]

After inhalation, respiratory and ocular effects are the first to appear, often within a few minutes after exposure. Respiratory effects include tightness in the chest and wheezing due to bronchoconstriction and excessive bronchial secretion; laryngeal spasms and excessive salivation may add to the respiratory distress, and cyanosis may also occur. Ocular effects include miosis, blurring of distant vision, tearing, rhinorrhea, and frontal headache.

After ingestion, gastrointestinal effects, such as anorexia, nausea, vomiting, abdominal cramps, and diarrhea appear within 15 minutes to 2 hours. After skin absorption, localized sweating and muscular fasciculations in the immediate area usually occur within 15 minutes to 4 hours; skin absorption is somewhat greater at higher ambient temperatures and is increased by the presence of dermatitis.[3]

With severe intoxication by all routes, an excess of acetylcholine at the neuromuscular junctions of skeletal muscle causes weakness aggravated by exertion, involuntary twitchings, fasciculation and, eventually, paralysis. The most serious consequence is paralysis of the respiratory muscles. Effects on the central nervous system include giddiness, confusion, ataxia, slurred speech, Cheyne–Stokes respiration, convulsions, coma, and loss of reflexes. The blood pressure may fall to low levels, and cardiac irregularities, including complete heart block, may occur.[2]

An intermediate syndrome of neurotoxic effects in humans has been described for fenthion, in which effects developed 24–96 hours after poisoning.[5] Patients developed paralysis of proximal limb muscles, neck flexors, motor cranial nerves, and respiratory muscles.

Fenthion has also exhibited delayed neurotoxicity in which the initial cholinergic crisis was delayed 5 days and recurred 24 days after ingestion.[6,7] Psychosis was a persistent manifestation. Because of the high lipid solubility of fenthion, toxin analysis of repeated fat biopsies was an essential component of patient management.[6]

In a study designed to determine the potential retinal changes in 79 subjects exposed to fenthion, 15 of the 79 workers examined had macular changes, characterized by perifoveal irregularity of pigmentation and hypopigmentation of 1/8–1/3 disk diameter.[8] Symptoms reported were diminution of vision, bright light aversion, flashes of light, black dots in front of eyes, and visual blurring. Other causes of macular involvement in these workers was excluded. Mean exposure duration of subjects with macular involvement was 7.9 years.

A series of studies originating from Japan reported a more advanced visual disease syndrome, Saku disease, which correlated with increasing organophosphate exposure.[9] Ocular effects are dose dependent and range in severity from lentricular changes to the more serious histopathologic changes in the ciliary body and retina.

Although the association between Saku disease and organophosphate exposure remains controversial (lack of similar reports from around the world, poor quality of some of the Japanese studies, and the similarity of Saku disease symptoms with common ocular diseases) animal studies have also shown the occurrence of ocular toxicity from organophosphate exposure.[10] Acute exposure to fenthion in rats has been associated with long-term changes in electroretinograms, whereas chronic exposure has produced permanent ocular degeneration. A single 100 mg/kg dose of fenthion administered subcutaneously to rats caused a long-lasting perturbation in muscarinic receptor function.[11]

Two-year feeding studies in rats (3–

75 ppm) and mice showed no indication of carcinogenic effects.[12,13] Fenthion was not teratogenic in tests on mice and rats.[12,14]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 0.2 mg/m^3 with a notation for potential skin absorption.

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FERBAM
CAS: 14484-64-1

$[(CH_3)_2NCS_2]_3Fe$

Synonyms: Ferric dimethyldithiocarbamate; Cormate; Fermacide

Physical Form. Black solid

Uses. Fungicide

Exposure. Inhalation

Toxicology. Ferbam is an irritant of the eyes and respiratory tract; in animals it causes central nervous system depression, and it is expected that severe exposure will cause the same effect in humans.

In humans, the dust is irritating to the eyes and the respiratory tract; it causes dermatitis in some individuals.[1] Large oral doses cause gastrointestinal disturbances.[1]

In guinea pigs given ferbam by stomach tube, the lethal range was 450–2000 mg/kg; the animals became stuporous and died in coma.[2] Ten of 20 rats died from a diet containing 0.5% ferbam for 30 days; there was a slight and ill-defined tendency toward anemia. At autopsy, there was no evidence of a regularly appearing tissue injury; minor abnormalities of the lung, liver, kidney, and bone marrow were observed in a few animals.[2] Animal experiments revealing an increased acetaldehyde level after ingestion of alcohol suggest that ferbam, like other dithiocarbamates, may be capable of causing an Antabuse-like reaction.[3]

Rats fed at dietary concentrations of 0, 25,

250, or 2500 ppm for 2 years had depressed growth rate, shortened life span, neurological changes, cystic brain lesions, and testicular atrophy at the highest dose. Carcinogenicity was not demonstated, but the IARC has concluded that the data are insufficient to fully evaluate the carcinogenicity of this compound.[3]

In a three-generation study of reproductive toxicity no effect was seen on fertility, viability, or litter size in rats fed dietary concentrations of 250 ppm.[4] A statistically significant increase in sperm abnormalities was seen in mice after oral administration of ferbam at 1000 mg/kg body weight per day for 5 days.[5] No effects were seen after intraperitoneal administration, indicating that active metabolites were responsible for the teratospermia.

The liquid was mildly irritating to the eyes of rabbits but practically nonirritating after 4-hour exposure to the skin.[4] It has weak skin-sensitizing properties in guinea pigs.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for ferbam is 10 mg/m^3.

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FERROVANADIUM DUST
CAS: 12604-58-9

FeV

Synonyms: None

Physical Form. Gray to black dust

Uses. Added to steel to produce fineness of grain, toughness, and resistance to high temperature and torsion

Exposure. Inhalation

Toxicology. Ferrovanadium dust is a mild irritant of the eyes and respiratory tract.

Workers exposed to unspecified concentrations developed slight irritation of the eyes and respiratory tract.[1] Systemic effects have not been reported from industrial exposure.

Animals exposed for 1 hour on alternate days for 2 months to very high concentrations (1000–2000 mg/m^3) developed chronic bronchitis and pneumonitis.[2] No active intoxication occurred in animals exposed at concentrations as high as 10,000 mg/m^3.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for ferrovanadium dust is 1 mg/m^3, with a short-term excursion limit (STEL) of 3 mg/m^3.

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FIBROUS GLASS/GLASSWOOL

CAS: none

Synonyms: Glass wool (finely fibrous or filamentous matter suggestive of sheep wool, made from glass fibers); synthetic vitreous fibers; SVF; AAA fine glass fiber; JM 100; JM104; JM106; JM110; B-1; B-2; B-3; MMMF, an older name that includes glass fibers with man-made mineral fibers or MMMF; man-made vitreous (amorphous) fibers or MMVF, is a newer generic term and is more consistent with the actual source of the material.[1–2] Other closely related terms are rockwool and slagwool, made by blowing steam or air through molten rock or slag.

Physical Form. Fiber (particle with a length-to-diameter aspect ratio of 3 to 1 or greater). Respirable fibers have mass median aerodynamic diameters of approximately 3.5 µm or less. Fibers less than 1 µm in diameter have the highest probability for alveolar deposition.[1] Fibrous glass is a manufactured fiber in which the fiber-forming substance is glass. Glasses are made from silicon dioxide with oxides of various metals and other elements (aluminum, boron, sodium, potassium, magnesium, titanium, iron, barium, and zinc). Glasswool is produced by drawing, centrifuging, or blowing molten glass and comprises cylindrical fibers of relatively short length, with silicone dioxide content of 55–70%.[2] Rock wool is 45–48% silicone dioxide, and slag wool is 38–52% silicone dioxide.

Uses. Glasswool is used for thermal and acoustical insulation in construction and ship building; for air filtration in furnaces and air-conditioning systems.

Exposure. Inhalation; skin contact

Toxicology. Glass fibers cause skin, eye, and upper respiratory tract irritation; although earlier classified by IARC to be a Group 2B carcinogen,[1] *possibly carcinogenic to humans*, more recent evaluations indicate the human risk, if any, to be minimal.[3,4]

In assessing the health evidence concerning synthetic vitreous fibers (SVF) in general, the chemical composition, surface activity, durability, and size of fibers must be taken into account.[3] Special-purpose fine glass fibers must be separated from the insulation wools (glass, rock, and slag wool). SVFs include a very broad variety of inorganic fibrous materials with an amorphous molecular structure. Traditionally, SVFs have been divided into three subcategories based on composition: fiberglass, mineral wool (rock, stone, and slag wools), and refractory ceramic fiber. The epidemiological evidence is sufficient to conclude that there has been no mesothelioma risk to workers producing or using glasswool, rockwool, or slagwool. The epidemiological studies have been large and powerful, and they show no evidence of a cause-effect relationship between lung cancer and exposure to glasswool, rockwool, or slagwool fibers. There is some evidence of a small cancer hazard attached to the manufacturing process in slagwool plants 20–50 years ago, when asbestos was used in some products and other carcinogenic substances were present. However, this hazard is not associated with any index of exposure to slagwool itself. Animal inhalation studies of ordinary insulation wools also show that there is no evidence of hazard associated with exposure to these relatively coarse, soluble fibers. The evidence of carcinogenicity is limited to experiments with special-purpose fine durable glass fibers or experimental fibers, and only when these fibers are injected directly into the pleural or peritoneal cavity. Multiple chronic inhalation studies of these same special-purpose fine glass fibers have not produced evidence of carcinogenicity.

SVFs have been widely used as insulation material in places in which asbestos was used many years ago, and therefore the hazards have been compared. Because the three principal types of asbestos fibers types have caused lung cancer at high exposures, there is a widely held belief that all fibers are carcinogenic if inhaled in large enough doses.[4] Hence, on a morpho-

logic basis, SVFs have been studied for their carcinogenic potential. Several decades of research using rodents exposed by inhalation have confirmed that SVF pulmonary effects are determined by the "Three Ds," fiber dose (lung), dimension, and durability.[5] Inhaled short fibers are cleared from the lung relatively quickly by mobile phagocytic cells, but long fibers persist until they dissolve or fragment. However, several relatively biopersistent SVFs induced chronic inflammation, lung scarring (fibrosis), and thoracic neoplasms. Thus biopersistence of fibers is now generally recognized as a key determinant of the toxicological potential of SVFs.

Neither the epidemiological studies of human exposure nor the animal studies have shown a marked hazardous effect from glasswool. Any effect that might exist is small. Using estimates of the risk associated with exposure to chrysotile asbestos at high exposures and doses, a determination was made of how much less risky an exposure to glasswool fibers might be.[4] For a given fiber count, glasswool is calculated to be 5–10 times less risky. The risk for a nonsmoking installer of glasswool fiber insulation who wears a respirator is about 6 in a million and might be zero per year. This means that out of a million installers there might be six lung cancers from this cause every year, or out of 10,000 installers there might be one in 16 years. The low risk of 6 in a million per year of a worker blowing glasswool is consistent with the fact that no one has found any cancer attributable to the manufacture or installation of glass wool fibers despite diligent searches. Nonetheless, common sense suggests that any installer of blown glasswool fiber insulation should wear a respirator.

Research demonstrating the relationship between biopersistence and SVF toxicity has provided a scientific basis for hazard classification and regulation of SVFs. For a nonhazardous classification, legislation recently passed by the European Union requires a respirable insulation wool to have a low lung biopersistence or be noncarcinogenic in laboratory rats. US fiberglass and mineral wool industries and the Occupational Health and Safety Administration (OSHA) have formed a voluntary Health and Safety Partnership Program (HSPP) that includes: a voluntary permissible exposure level (PEL) in the workplace of 1 fiber/cc, a respiratory protection program for specified tasks, continued workplace air monitoring, and, where possible, the development of fiber formulations that do not persist in the lung. Refractory ceramic fiber manufacturers have implemented a Product Stewardship Program that includes: a recommended exposure guideline of 0.5 fibers/cc; a 5-year workplace air monitoring program; and research into the development of high-temperature-resistant, biosoluble fibers.

On the skin, fiberglass fibers cause intense pruritis as a result of the fibers penetrating the skin and causing an eruption consisting of small erythematous follicular papules.[6] Fiberglass dermatitis clinically presents as patchy folliculitus or subacute dermatitis.

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FLUORANTHENE
CAS: 206-44-0

$C_{16}H_{10}$

Synonyms: FA; 1,2-benzacenaphthene; benzo (*jk*)fluorene

Physical Form. Yellow solid

Uses. Fluoranthene is a component of polynuclear aromatic hydrocarbons, also known as polycyclic aromatic hydrocarbons, and is usually bound to small particulate matter present in urban air, industrial and natural combustion emissions, and cigarette smoke.

Exposure. Inhalation

Toxicology. Fluoranthene (FA) is a lung carcinogen in mice.

A 24-week lung adenoma bioassay using newborn mice was employed to determine the tumorigenicity of FA.[1] A 6.5-fold elevation of lung tumor incidence (58%) and a 12-fold increase in numbers (1.08 tumors/mouse) was observed in animals treated with the highest dose (3.5 mg/mouse), but no increase in tumor incidence was induced by 700 µg/mouse. Male mice, surviving for 24 weeks in the FA treatment group that developed lung tumors, had 2- to 3-fold more tumors than comparably treated females.

FA induced lung and liver tumors 6–9 months after intraperitoneal injection of 0.7, 1.75, and 3.5 mg of FA into preweanling CD-1 mice.[2] There was a dose-dependent increase in lung tumors, with a maximum tumor incidence of nearly 45%.

FA and FA-DNA adducts in various tissues were isolated in various tissues of male rats 24 h after a single intraperitoneal injection of [^{3}H]FA.[3] Formation and distribution of DNA adducts after chronic administration of FA in the diet were also studied. FA-derived radioactivity was widely distributed throughout the animal after a single dose, and excreta contained the greatest amounts of radioactivity at all dose levels.

The in vitro metabolism of FA was assessed by incubating [^{3}H]FA with rat hepatic microsomal enzymes.[4] The major metabolite produced was FA 2,3-diol, accounting for 29–43% of the total extractable metabolites. This study indicated that a major metabolic activation pathway of FA involved the formation of the FA 2,3-diol and the subsequent oxidation of this diol to a FA 2,3-diol-1,10*b*-epoxide, resulting in the production of mutagenic species. Although FA is mutagenic in bacterial and mammalian *in vitro* cell systems after metabolic activation, it did not show evidence of genotoxicity *in vivo* in either the mouse bone marrow micronucleus assay or the rat unscheduled DNA synthesis test system after acute oral administration at levels up to 2000 mg/kg body weight.[5]

An ACGIH threshold limit value (TLV) has not been established for fluoranthene.

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FLUORIDES

F

Compounds: Sodium fluoride; calcium fluoride; fluorspar; cryolite

Physical Form. Various

Sources/Uses. Grinding, drying, and calcining of fluoride-containing minerals; metallurgical processes such as aluminum reduction and steel making; kiln firing of brick and ceramic materials; melting of raw material in glass making; used as a preservative, rodenticide, and insecticide and as an additive to water to prevent dental caries

Exposure. Inhalation; ingestion

Toxicology. Fluoride causes irritation of the eyes and respiratory tract and gastrointestinal effects; absorption of excessive amounts of fluoride over a long period of time results in skeletal fluorosis.

Workers exposed to an airborne fluoride concentration of 5 mg/m^3 complained of eye and respiratory tract irritation and nausea.[2] The lethal oral dose of sodium fluoride for humans has been estimated to be 32–65 mg F/kg of body weight.[3] Effects from ingestion are diffuse abdominal pain, diarrhea, and vomiting; excessive salivation, thirst, and perspiration; painful spasms of the limbs; and sometimes albuminuria.[4,5] Gastrointestinal effects produced after the acute ingestion of toxic amounts of fluoride likely arise from the corrosive action of hydrofluoric acid, which is produced within the acidic environment of the stomach.[6] Cardiac arrest after accidental exposure to high levels of fluoride has been attributed to the development of hypocalcemia and/or hyperkalemia.[6]

Repeated exposure to excessive concentrations of fluoride over a period of years results in increased radiographic density of bone and eventually may cause skeletal fluorosis.[1] Crippling skeletal fluorosis may be associated with limited movement of the joints, skeletal deformities, intense calcification of ligaments, muscle wasting, and neurological deficits.[6] There is clear evidence from India and China that skeletal fluorosis and an increased risk of bone fractures occur at total intakes of 14 mg fluoride/day and evidence suggestive of an increased risk of bone effects at total intakes above about 6 mg fluoride/day.[6] This condition has not been reported in the United States from industrial exposure.

Mottled appearance and altered form of teeth are produced only when excessive amounts of fluoride are ingested during the period of formation and calcification of teeth, which occurs during the first 8 years of life in humans; after calcification has been completed, fluoride does not have an adverse effect on the teeth.[5]

The morbidity experience of a small cohort of 431 Danish cryolite (AlNa3F6) workers employed for at least 6 months between 1924 and 1961, and followed until 1981, showed an apparent excess number of respiratory cancers.[7] Cancer morbidity showed no apparent correlation with length of employment or time from first exposure. Because detailed information on predictors for respiratory cancer such as smoking habits was not available, a possible contributing effect of fluoride was not excluded by the authors. In a follow-up of this cohort, the increase in lung cancer remained [standard incidence ratio (SIR) 1.35] and an increase in bladder tumors (SIR 1.84) was observed. The cancer incidence was not related to length of exposure, and other confounding effects such as smoking, alcohol, and multiple chemical exposures in addition to fluoride may have contributed to the observed increases.[8]

Three limited early carcinogenicity bioassays in three different strains of mice by oral administration of sodium fluoride (NaF) revealed no exceptional tumor incidences.[8] A subsequent NTP study reported equivocal evidence of carcinogenicity based on osteosarcomas in 4 of 80 male rats administered 175 ppm NaF in the drinking water for 2 years.[9] No evidence of carcinogenicity was found in another

strain of rats that ingested up to 13.7 mg/day for 2 years.[10]

NaF was not mutagenic in bacterial assays. Although fluoride has been shown to be clastogenic in a variety of cell types, the mechanism of clastogenicity has been attributed to the effect of fluoride on the synthesis of proteins involved in DNA synthesis and/or repair, rather than direct interaction between fluoride and DNA.[6] In general, there was no effect on sperm morphology or the frequency of chromosomal aberrations, micronuclei, sister chromatid exchange, or DNA strand breaks in rodents treated *in vivo*.[6]

No adverse effects on fetal development were found in rats or rabbits administered fluoride in the drinking water during gestation.[6]

Fluoride concentration in the urine has been used as a biological indicator of fluoride.[11,12] Most absorbed fluoride is excreted rapidly in the urine. A portion is stored in bone, but a nearly equal amount is mobilized from bone and excreted. Some storage of fluoride occurs from the ingestion of as little as 3 mg/day. Evidence from several sources indicates that urinary fluoride concentrations not exceeding 5 mg/l in preshift samples taken after 2 days off work are not associated with detectable osteosclerosis and that such changes are unlikely at urinary levels of 5–8 mg/l.[11] Preshift urinary fluoride concentration is considered to be a measure of the worker's body (skeletal) burden of fluoride, whereas the postshift sample is taken to be representative of exposure conditions during that work shift.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for fluorides is 2.5 mg/m^3, as F.

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FLUORINE
CAS: 7782-41-4

F_2

Synonyms: None

Physical Form. Yellow gas

Uses. Conversion of uranium tetrafluoride to uranium hexafluoride; oxidizer in rocket fuel systems; manufacture of various fluorides and fluorocarbons

Exposure. Inhalation

Toxicology. Fluorine is a severe irritant of the eyes, mucous membranes, skin, and lungs.

Because fluorine is the most reactive of the elements, free fluorine is rarely found in nature. Fluorine reacts with water to produce ozone and hydrofluoric acid.[1] In humans, the inhalation of high concentrations causes laryngeal spasm and bronchospasm, followed by the delayed onset of pulmonary edema.[2,3] At sublethal levels, severe local irritation and laryngeal spasm will preclude voluntary exposure to high concentration unless the individual is trapped or incapacitated.[2] Two human subjects found momentary exposure to 50 ppm intolerable; 25 ppm was tolerated briefly, but both subjects developed sore throat and chest pain that persisted for 6 hours.[4] Short-term exposures to concentrations up to 10 ppm were tolerated without discomfort.[3]

The LC_{50} in mice for 60 minutes was 150 ppm; effects were irritation of the eyes and nose and the delayed onset of labored breathing and lethargy; autopsy findings included marked pulmonary congestion and hemorrhage.[5] Mice exposed to sublethal concentrations had pulmonary irritation and delayed development of focal necrosis in the liver and kidneys.[5]

A blast of fluorine gas on the shaved skin of a rabbit caused a second-degree burn; lower concentrations cause severe burns of insidious onset resulting in ulceration, similar to those produced by hydrogen fluoride.[1,4]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for fluorine is 1 ppm (1.6 mg/m^3) with a short-term excursion limit of 2 ppm (3.1 mg/m^3).

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FORMALDEHYDE
CAS: 50-00-0

HCHO

Synonyms: Methanal; formic aldehyde; oxomethane; oxymethylene; methylene oxide; methyl aldehyde

Physical Form. Gas (Note: formalin is a 37–50% solution by weight of formaldehyde gas.)

Uses. Manufacture of formaldehyde resins, which are used as adhesives in particle board, plywood, and insulating materials; countertops and wall paneling; coating to fabrics to impart permanent press characteristics; manufacture of rubber, photographic film, leather, cosmetics, embalming fluids, insulation; disinfectants and fumigants

Exposure. Inhalation

Toxicology. Formaldehyde is an irritant of the eyes and respiratory tract; it causes both primary irritation and sensitization dermatitis; at high levels it is carcinogenic in experimental animals and, although results are equivocal in humans, it is considered a suspected human carcinogen.

Mild eye irritation with lacrimation and other transient symptoms of mucous membrane irritation have been observed in some persons at concentrations of 0.1–0.3 ppm. For most people, however, a tingling sensation in the eyes, nose, and posterior pharynx is not experienced until 2–3 ppm.[1,2] Some tolerance occurs, so that repeated 8-hour exposures at this level are possible.[3] At 4–5 ppm irritation of mucous membranes increases and lacrimation becomes evident. This level may be tolerated by some for short periods, but after 30 minutes discomfort becomes quite pronounced.

Concentrations of 10 ppm can be withstood for only a few minutes; profuse lacrimation occurs in all subjects, even those acclimated to lower levels. Between 10 and 20 ppm, it becomes difficult to take a normal breath; burning of the nose and throat becomes more severe and extends to the trachea, producing cough. On cessation of exposure, the lacrimation subsides promptly, but the nasal and respiratory irritation may persist for about an hour. It is not known at which levels serious inflammation of the bronchi and lower respiratory tract would occur in humans; it is expected that 5- or 10-minute exposures to levels of 50–100 ppm would cause very serious injury. Acute irritation of the human respiratory tract from inhalation of high levels of formaldehyde has caused pulmonary edema, pneumonitis, and death.[1]

Solutions of 25–44% splashed in the eyes have caused severe injury and corneal damage.

Formaldehyde is one of the most common causes of occupational skin disease; the major effects of formaldehyde on the skin are irritant dermatitis and allergic contact dermatitis.[4] Irritant dermatitis results from direct injury to the skin and is characterized by redness and thickening of the affected areas. In more severe cases there may be blistering, scaling, and the formation of fissures.

Dermal sensitization to formaldehyde is an often-reported phenomenon. After skin contact, a symptom-free induction period typically ensues for 7–10 days.[4] With subsequent contact there is itching, redness, swelling, multiple small blisters, and scaling in sensitized individuals. Repeated contact tends to cause more severe reactions, and sensitization usually persists for life.

A number of studies have suggested that formaldehyde causes asthma and/or exacerbates preexisting respiratory conditions. Small, transient declines in lung function parameters over the course of a work shift have been the most consistent findings.[4] Statistically significant postshift declines in $FEV1/FVC_{\%}$, $FEF_{25\%–75\%}$, $FEF_{50\%}$, and $FEF_{75\%}$ were observed in workers exposed to less than 3.0 ppm.[5] In this same group of workers, there was no evidence of permanent respiratory impairment after a mean exposure time of 10 years. Although other studies have also failed to implicate formaldehyde as a cause of permanent respiratory impairment, a small group of resin workers exposed more than 5 years had lower $FEV_1/FVC_{\%}$ and $FEF_{50\%}/FVC$ over the workweek, suggesting the possibility of chronic lung function shifts.[6]

A few case reports have suggested that formaldehyde may cause asthmatic symptoms by acting as an immunologic sensitizer.[4] Other investigators feel there is insufficient evidence that formaldehyde causes immunologic disease, because IgG and IgE antibodies to formaldehyde have not been demonstrated and antibodies to formaldehyde-albumin complexes, although present in people exposed to formaldehyde, do not correlate well with clinical symptomatology.[7] In a few anecdotal cases prolonged exposure has been associated with impaired central nervous system function including abnormal balance, constricted visual fields, delayed blink latency, and deficits in cognitive function tests.[8]

In a number of reproductive tests in rodents and dogs, formaldehyde did not cause adverse outcome in the offspring, except at maternally toxic doses.[9] In one report there was a significant increase in the incidence of abnormal sperm in rats after 200 mg/kg administered

as a single gavage dose; in other studies there was no effect on sperm in mice after administration of 100 mg/kg/day for 5 days, nor were there changes in reproductive function in rats treated with 0.1 ppm in the drinking water for 6 months.

Formaldehyde has been shown to be carcinogenic in two strains of rats, resulting in squamous cell cancers of the nasal cavity after repeated inhalation of about 14 ppm. In one study, 51 of 117 male and 42 of 115 female Fischer 344 rats developed this tumor, but no nasal tumors were seen at 0 or 2 ppm. No other neoplasm was increased significantly. In a similar study of mice, this nasal tumor occurred in two male mice at 14.3 ppm. None of the excesses was statistically significant except for the high-exposure rats.[10]

A large number of epidemiological studies have now been completed on persons with potential exposure to formaldehyde. Although a variety of excess cancers, including brain, bladder, colon, skin, kidney, and leukemias, have been reported, the evidence for a possible involvement of formaldehyde is strongest for respiratory cancers.[11] A case-control study of men with histologically confirmed primary epithelial cancer of the nasal cavities or accessory sinuses found an increased relative risk of approximately 2 for nasal cancer, particularly squamous cell carcinoma, in formaldehyde-exposed workers.[12] Another case control study of 759 histologically verified cancers of the nasal cavity showed an association between squamous cell carcinoma and formaldehyde exposure.[13] Among industrial workers exposed to formaldehyde-containing particulates, the risk of death from cancer of the nasopharynx increased with cumulative exposure to formaldehyde from a standardized mortality ratio (SMR) of 192 for <0.5 ppm-years to 403 for 0.5 to <5.5 ppm-years and 746 for >5.5 ppm-years.[14] The five workers with formaldehyde exposure who died from nasopharyngeal cancer had held jobs where exposures had excursions to levels exceeding 4 ppm. An increased risk of nasopharyngeal cancer was found among individuals who resided in mobile homes where exposure to formaldehyde averaged as much as 0.5 ppm and easily reached or exceeded 1 ppm.[4,15] The relative risk went from 2.1 for those who resided in mobile homes for 1–9 years to 5.5 for those who resided for over 10 years. A relative risk of 6.7 for nasopharyngeal cancer was found for people with both occupational and residential exposure.[15,16]

Slight excesses in the occurrence of lung cancer have been noted in several studies. In a large cohort mortality analysis of 26,000 workers there were significant excesses of lung cancer in those with more than 20 years since initial formaldehyde exposure.[17] Reanalysis of these same data has also shown a significant trend of increasing lung cancer risk with increasing formaldehyde exposure.[18] In the other large study of industrial workers there was a significant excess of mortality from lung cancer at one plant where 73% of workers were exposed to formaldehyde at levels estimated to be over 2 ppm.[19] An additional 8-year follow-up of this cohort found no cases of nasopharyngeal cancer (vs. 1.3 expected), one nasal cancer death (vs. 1.7 expected), and slight excesses of lung cancer, respiratory disease, and stomach cancer that did not correlate with estimated cumulative dose or time since first exposure.[20] An enlarged and updated cohort study of formaldehyde-exposed workers from a US chemical plant found statistically significantly elevated SMRs for total mortality, ischemic heart disease, nonmalignant respiratory disease and cancers of the lung, skin, and central nervous system; among long-term workers there was no clear evidence of an association between lung cancer mortality and formaldehyde exposure.[21] The authors suggested that unmeasured occupational or nonoccupational factors may have played a role in the significant excesses found in short-term workers.

Although the results of certain of the published cancer studies have been challenged (concomitant exposure to other chemicals, small sample sizes, smoking habits, inadequate statistical treatment), the IARC has determined that the body of evidence suggests sufficient evidence for carcinogenicity to animals but limited evidence for carcinogenicity to humans.[11,22] It has also been suggested that formaldehyde is not carcinogenic at low levels based on the evidence that formaldehyde is

formed naturally in food, it is a normal human metabolite, and a threshold for carcinogenicity exists in animal experiments.[9]

Formaldehyde was genotoxic in both *in vitro* and *in vivo* assays. *In vitro*, it induced DNA-protein cross-links, DNA single-strand breaks, chromosomal aberrations, sister chromatid exchange, and gene mutations in human and rodent cells. *In vivo* it induced chromosomal anomalies in lung cells and micronuclei in the gastrointestinal mucosa in treated rats. Overall, formaldehyde is considered to be weakly genotoxic, with good evidence of an effect at site of contact, but less convincing evidence at distal sites.[23]

The odor is perceptible to previously unexposed persons at or below 1 ppm.

The 2003 ACGIH threshold limit value-ceiling (TLV-C) is 0.3 ppm (0.37 mg/m^3) with a notation for sensitization and an A2-suspected human carcinogen designation.

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FORMIC ACID
CAS: 64-18-6

HCOOH

Synonyms: Methanoic acid; formylic acid, hydrogen carboxylic acid

Physical Form. Colorless liquid

Uses. Preservative of silage; reducer in dyeing wool; lime descaler; pH adjustor in cosmetic products

Exposure. Inhalation

Toxicology. Formic acid vapor is a severe irritant of the eyes, mucous membranes, and skin.

Exposure causes eye irritation with lacrimation, nasal discharge, throat irritation, and cough.[1] A worker splashed in the face with hot formic acid developed marked dyspnea with dysphagia and died within 6 hours.[2] Workers exposed to a mixture of formic and acetic acids at an average concentration of 15 ppm of each complained of nausea.[3] Twelve farmers exposed to 7.3 mg formic acid/m^3 for 8 hours had increased renal ammoniagenesis and urinary calcium at 30 hours after exposure.[4]

The liquid on the skin causes burns with vesiculation; keloid formation at the site of the burn often results.[2] Although ingestion of the liquid is unlikely in ordinary industrial use, the highly corrosive nature of the substance can produce serious burns of the mouth and esophagus.[3] Other clinical features include gastrointestinal irritation, vomiting, hematemesis, and abdominal pain.[5] Cicatricial stenosis may appear after recovery. The major complications are acute renal failure and disseminated intravascular coagulation; pulmonary aspiration with a secondary pneumonia may occur. Occasionally a direct toxic pneumonitis may also occur.

Formic acid is an inhibitor of cytochrome oxidase at the terminal end of the respiratory chain in mitochondria and causes histotoxic hypoxia at the cellular level.[6,7] Therefore, persons with cardiovascular disease may be considered at special risk to the affects of formic acid.[6]

Both positive and negative results have been reported in mutagenicity studies, although acidic experimental conditions were indicated in most cases of positive mutagenicity.[8]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for formic acid is 5 ppm (9.4 mg/m^3) with a short-term excursion limit of 10 ppm (19 mg/m^3).

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FUEL OILS
Fuel oil no. 1: CAS: 8008-20-6, 70892-10-3

Synonyms: Kerosene, straight-run kerosene, range oil, JP-5 jet fuel; kerosine
Fuel oil no. 1-D: No CAS number

Synonym: Diesel fuel
Fuel oil no. 2: CAS: 68476-30-2

Synonym: Home heating oil; gas oil; no. 2 burner oil
Fuel oil no. 2-D: CAS: 68476-34-6

Synonyms: Diesel fuel no. 2; diesel fuel oil no. 2; diesel oil no. 2
Fuel oil no. 4: CAS: 68476-31-3

Synonyms: Diesel fuel oil no. 4; heavy residual fuel oil; marine diesel fuel; residual fuel oil no. 4

Physical Form. Liquids, yellow to light brown in color. All fuel oils consist of complex mixtures of aliphatic (80–90%) and aromatic (10–20%) hydrocarbons. They may be classified as either a distillate fuel or a residual fuel, depending on the method of production. Fuel oils no. 1 and 2 are distillate fuels that consist of distilled process streams. Residual fuels such as fuel oil no. 4 are residues remaining after distillation or cracking or blends of such residuals with distillates.[1]

Uses. Jet fuel; fuel for domestic and industrial heating; kerosene lamps, flares, and stoves; diesel fuel for diesel engines; road oils

Exposure. Inhalation; ingestion; skin contact

Toxicology. Fuel oils cause gastrointestinal irritation, pulmonary aspiration pneumonia, neurological effects and can be irritants of the skin and eyes.

Abdominal cramps, vomiting, and diarrhea occurred in a truck driver who was exposed to diesel fuel vapor for 10 days while driving a truck with a leaking fuel injector.[2] Acute renal failure was also observed. One case study describes eye irritation in two individuals exposed to JP-5 fuel (kerosene) for approximately 1 hour while flying an airplane.[3] Coordination and concentration difficulties were noted, as were headache, apparent intoxication, and anorexia. Inhalation of 140 mg/m^3 deodorized kerosene by six volunteers caused olfactory fatigue in three subjects and a taste sensation in one.[4]

Numerous case studies have been reported of accidental poisoning in children usually under the age of 5 but as old as 15 years who have ingested kerosene.[5–8] The deaths are usually attributed to pneumonia as a result of aspiration of the kerosene into the lungs during vomiting. Lethal doses in children in these studies have been estimated at 30 and 200 ml of kerosene. Drinking kerosene most commonly causes vomiting but can also cause diarrhea, stomach distension and cramps, cough, drowsiness, restlessness, irritability, and difficulty breathing. Drinking large amounts of kerosene can cause coma, convulsions, and death.

Kerosene on the skin for 20 minutes in a 45-year-old man produced erythema, bullae, burning, and itching.[9] In another case study, three boys (2–15 years old) and 1 girl (2 years old) exhibited blisters, erythema, flaccid bullae, pustules, soreness, burning, and denudation of skin after dermal exposure.[10]

No developmental or reproductive effects were observed in animal studies after inhalation exposures.[11]

Repeated skin contact in mice with fuel oils has caused skin cancer, although information is conflicting. The IARC has determined that residual (heavy) fuels and marine diesel fuel are possibly carcinogenic to humans (Group 2B classification).[1] The IARC has also determined that occupational exposure to fuel oils during

petroleum refining is probably carcinogenic to humans (Group 2A classification).

Inconsistent results have been reported in a variety of genotoxic assays both *in vivo* and *in vitro*.[11]

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FURFURAL
CAS: 98-01-1

$C_4H_4O_2$

Synonyms: 2-Furaldehyde; pyromucic aldehyde

Physical Form. Colorless to reddish brown oily liquid

Uses. Solvent refining of lubricating oils, resins, and other organic materials; as insecticide, fungicide, germicide; an intermediate for tetrahydrofuran, furfural alcohol, phenolic and furan polymers

Exposure. Inhalation; skin absorption

Toxicology. Furfural is an irritant of the eyes, mucous membranes, and skin and is a central nervous system depressant.

Although the vapor is an irritant, the liquid has a relatively low volatility so that inhalation by workers of significant quantities is unlikely.[1] Exposure of workers to levels of 1.9–14 ppm caused complaints of eye and throat irritation and headache.[1] The liquid or vapor is irritating to the skin and may cause dermatitis, allergic sensitization, and photosensitization.[2] Dermal absorption has been found to be significant in humans. A 15-minute whole-hand immersion in the liquid resulted in absorption of an amount equivalent to an 8-hour inhalation exposure of 10–20 mg/m^3 (3–5 ppm) vapor.[3]

Exposure of cats to 2800 ppm for 30 minutes resulted in fatal pulmonary edema.[1] Inhalation of 260 ppm for 6 hours was fatal to rats but produced no deaths in mice or rabbits.[2] Slight liver changes were seen in dogs exposed daily to 130 ppm for 4 weeks.[2] Symptoms after oral administration of 50 to 100 mg/kg in rats were weakness, ataxia, coma, and death.[1]

Rats exposed at 40 ppm 1 hour/day for periods of 7, 15, or 30 days had pulmonary irritation, parenchymal injury, and regenerative proliferation of pneumocytes, the severity of which depended on duration of exposure.

Survival was reduced in groups of rats receiving 90 mg/kg/day for 13 weeks by gavage, and cytoplasmic vacuolization of hepatocytes was increased in exposed males. In mice centrilobular coagulative necrosis and/or multifocal subchronic inflammation of the liver occurred at doses up to 1200 mg/kg.[5]

In 2-year gavage studies there was some evidence of carcinogenic activity in male rats based on increased incidences of cholangiocarcinomas and bile duct dysplasia and fibrosis. There was also some evidence of carcinogenicity in female mice based on increased incidences of hepatocellular adenomas. Male mice showed clear evidence of carcinogenicity based on increased incidences of hepatocellular adenomas and carcinomas.[5] The development of liver tumors may be related to the chronic inflammatory effects noted at this site.[6] In another experiment with hamsters, exposure to furfural vapor 7 hours/day, 5 days/week for 1 year caused irritation of the nasal mucosa and growth retardation but no evidence of carcinogenic effects.[7]

The IARC has determined that there is limited evidence in animals and inadequate evidence in humans for the carcinogenicity of furfural.[8] Overall, furfural is not classifiable as to its carcinogenicity to humans.

Furfural was genotoxic *in vitro* in mammalian cells, causing chromosomal aberrations, gene mutations, and sister chromatid exchanges; it was not mutagenic in a number of bacterial assays.[6,8]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for furfural is 2 ppm (7.9 mg/m^3) with a notation for skin absorption.

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FURFURYL ALCOHOL
CAS: 98-00-0

$C_6H_6O_2$

Synonyms: 2-Furyl carbinol; 2-furanmethanol; furfural alcohol

Physical Form. Colorless liquid that turns dark in air

Uses. Solvent for cellulose ethers, esters, resins, and dyes; liquid propellant; binder in foundry cores; manufacture of resins including furfuryl alcohol resin (furan resin) and furfuryl alcohol-formaldehyde resins

Exposure. Inhalation; skin absorption

Toxicology. Furfural alcohol is an eye, nose, and throat irritant; exposure to high concentrations causes central nervous system depression.

Workers exposed to 8.6 and 10.8 ppm in a foundry core-making operation experienced no discomfort, but two persons exposed to 15.8 ppm (and 0.33 ppm formaldehyde) experienced lacrimation and a desire to leave the area. In another foundry core-making operation, no ill effects were seen after exposures of about 6–16 ppm.[1]

Large doses injected subcutaneously in dogs caused depressed respiration, lowered body temperature, salivation, diarrhea, diuresis, and signs of narcosis.[2]

In rats exposed to 700 ppm, effects included excitement followed by eye irritation and drowsiness.[3] The rat LC_{50} for 4 hours was 233 ppm.[4] Repeated daily exposure of rats to an average of 19 ppm caused moderate respiratory irritation.[3] Intravenous injection into rabbits and cats caused depression of the central nervous system; death occurred at doses of 800–1400 mg/kg.[5]

Eye contact in rabbits resulted in reversible inflammation and corneal injury with opacity.[1] Animal experiments indicated that the liquid is well absorbed through the skin with a dose-related mortality; mild skin irritation may also result from contact.[1] Prolonged inhalation exposures of rats to 25, 50, and 100 ppm resulted in decreased weight gain and, at the two highest doses, biochemical changes in the brain suggestive of mitochondrial damage, glial cell degeneration, and early demyelization.[6]

Rats and mice exposed to 31, 63, or 125 ppm 6 hours/day for 16 days developed lesions in the nasal respiratory epithelium and/or olfactory epithelium, and the severity of the lesions generally increased with increasing exposure concentrations.[7] Clinical findings included dyspnea, hypoactivity, and nasal and ocular discharge. At 250 ppm all animals died within 4 days. In 2-year inhalation studies at doses of 2, 8, or 32 ppm rats and male mice had increased incidences of nonneoplastic lesions of the nose and increased severity of nephropathy; female mice had increased incidences of nonneoplastic lesions of the nose and corneal degeneration.[7] In addition, there was some evidence of carcinogenicity in male rats based on increased incidences of combined neoplasms of the nose and equivocal evidence of carcinogenic activity in female rats based on marginally increased incidences of neoplasms of the nose and renal tubule neoplasms. Male mice had some evidence of carcinogenic activity based on increased incidences of renal tubule neoplasms.

Furfuryl alcohol was not mutagenic in a variety of *Salmonella typhimurium* strains, but it did induce sister chromatid exchanges in cultured Chinese hamster ovary cells.[7] No mutagenic effects were detected in vivo in bone marrow cells of male mice treated with furfuryl alcohol.

The odor is detectable at 8 ppm.[4] Mixing with acids results in polymerization, a highly exothermic reaction that may result in explosions.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for furfural alcohol is 10 ppm (40 mg/m^3) with a short-term excursion limit (STEL) of 15 ppm (60 mg/m^3) and a notation for skin absorption.

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F344/N Rats and B6C3F1 Mice (Inhalation Studies), pp 1–248. US Department of Health and Human Services, NTP TR 482, 1999

GASOLINE

CAS: 8006-61-9

Synonyms: Motor fuel; petrol

Physical Form. Liquid gasoline is a complex mixture of at least 150 hydrocarbons with about 60–70% alkanes, 25–30% aromatics, and 6–9% alkenes. The small-chain, low-carbon-numbered components are more volatile and thus in higher percentages in the vapor phase than the larger and heavier molecules.[1] The concentrations of aromatics, the more toxic of the components, are depleted to about 2% in the vapor phase. The light alkanes, the less toxic components, are enriched to about 90%. Benzene is also present and represents a component of major concern.

Uses. Fuel for spark-ignited internal combustion engines

Exposure. Inhalation

Toxicology. Gasoline is an irritant of the eyes and mucous membranes and is a central nervous system depressant.

Exposure of humans to 900 ppm for 1 hour caused slight dizziness and irritation of the eyes, nose, and throat.[2] At 2000 ppm for 1 hour, there was dizziness, mucous membrane irritation, and anesthesia; 10,000 ppm caused nose and throat irritation in 2 minutes, dizziness in 4 minutes, and signs of intoxication in 4–10 minutes.[2] At high concentrations, coma and death may result in a few minutes without any accompanying respiratory struggle or postmortem signs of anoxia.[3]

On skin contact, gasoline vaporizes rapidly and has little if any irritant effect.[4] If occluded, or if the liquid remains in continued contact with the skin, a severe chemical burn can occur. Repeated exposures may cause defatting of the skin.

On ingestion, gasoline produced local irritation, central nervous system depression, and congestion and capillary hemorrhage in visceral organs.[5] Aspiration of the liquid into the lungs produced chemical pneumonitis. Intentional use of leaded gasoline as an intoxicant has resulted in encephalopathy from the tetraethyl lead.[6] Other neurological effects from chronic exposure include postural tremor, ataxia, abnormal gait, affected speech, headaches, and memory loss.[7] Octane improving additives to gasoline, such as methylcyclopentadienyl manganese tricarbonyl (MMT), do not appear to influence toxicity, based on acute animal tests.[5,8]

Blood dyscrasias have been noted in humans acutely and chronically exposed to gasoline, but these effects are most likely due to benzene, and the incidence of these findings has decreased as the benzene content in gasoline has decreased.[7]

In a 2-year inhalation study, rats and mice were exposed to 0, 67, 292, or 2056 ppm 6 hours/day, 5 days per week.[9] The major finding was a time- and dose-related increase in the incidence of kidney lesions in the male rats. These lesions consisted of cortical multifocal tubular basophilia (indicative of areas of cell regeneration), protein casts, and interstitial inflammation. There was epithelial cell shedding, and the casts were found within dilated renal tubules commonly at the corticomedullary junction.

The pattern of renal tubule degeneration, regeneration, dilation, and hyalin deposition (termed light hydrocarbon nephropathy) is produced in male rats of three strains (Sprague-Dawley, Fischer-344, and Harlan-Wistar), but not in female rats of those strains or in male or female mice, cats, dogs, or monkeys.[5] In three instances, male rats that showed light hydrocarbon nephropathy at 3 months developed tumors after 2 years. The hydrocarbons most likely associated with light hydrocarbon nephropathy were branched-chain aliphatic compounds containing at least 6 and probably

not more than 8–10 carbon atoms.[10] Aromatic hydrocarbons were without activity. Additional mechanistic studies suggest that rat renal tumors involve a rat-specific protein α_{2u}-globulin. This protein binds with branched aliphatics, which then accumulate in renal tubule cells, resulting in cell death and, in turn, a proliferative sequence that increases renal tubule tumors.[5,11] The α_{2u}-globulin protein is species specific to rats and gender specific to males.

It does not appear that the nephrotoxicity attributable to α_{2u}-globulin syndrome is relevant to humans. Most epidemiological studies have not shown an association between gasoline exposure and renal cancer risk.[12] However, a recent case-control study from Finland reported a significant association between renal cell cancer and gasoline that was dose dependent.[13]

In general, gasoline is not considered to be genotoxic.[7]

The IARC concluded that limited evidence exists for the carcinogenicity of unleaded gasoline in animals.[14] The epidemiological studies were inadequate in demonstrating increased carcinogenic risk in humans.[14] The IARC Working Group did note that some components of gasoline, especially benzene, are carcinogenic in humans, and concluded that gasoline is possibly carcinogenic in humans.

Although anecdotal reports have suggested a link between gasoline exposure during pregnancy and developmental effects in humans, animal studies have not confirmed the toxicity of gasoline in the fetus.[13,15] Rats exposed to 1600 ppm during days 6–15 of gestation had no evidence of maternal toxicity or adverse effects on the fetuses. In a two-generation reproductive toxicity study, rats exposed 6 hours daily at concentrations up to 20,000 mg/m^3 (approximately 50% of the lower explosive limit) showed no fertility, reproductive, or fetal effects.[16] There were no treatment-related effects in parental animals and no microscopic changes other than hyalin droplet nephropathy in the kidneys of male rats.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for gasoline is 300 ppm (890 mg/m^3) with a short-term excursion limit of 500 ppm (1480 mg/m^3) and an A3-confirmed animal carcinogen with unknown relevance to humans notation

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GERMANIUM TETRAHYDRIDE

CAS: 7782-65-2

GeH_4

Synonyms: Germane; germanium hydride

Physical Form. Colorless gas

Uses. Doping agent for solid-state electronic components

Exposure. Inhalation

Toxicology. Germanium tetrahydride is reported to be a hemolytic agent; at high concentrations it also causes neurotoxicity and damage to the liver and kidneys.

Although the general toxicity of germanium is low, the tetrahydride gas is highly toxic at a level of 100 ppm and can cause death at 150 ppm from hemolysis.[1] There is little information on the toxicity of this compound to humans. It is reported that inhalation by humans of germanium tetrahyride may cause lung problems, but no details were given.[2]

Germanium tetrahydride was lethal to mice after inhalation of 610 mg/m^3 for 4 hours.[2] Degenerative changes were observed in the liver and kidney of rodents exposed to high one-time concentrations of 0.26–1.4 g/m^3.[2,3] Nonspecific changes in the blood were also observed.[3] Nervous system effects, including excitation, impairment of locomotor activity, listlessness, hypothermia, and convulsions, were observed in mice before death following inhalation exposure to 2 g/m^3.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for germanium tetrahydride is 0.2 ppm (0.63 mg/m^3).

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GLUTARALDEHYDE

CAS: 111-30-8

$OCH–(CH_2)_3CHO$

Synonyms: Cidex (2% alkaline glutaraldehyde aqueous solution); 1,5-pentanedial; glutaric dialdehyde; glutaral

Physical Form. Colorless crystalline solid, soluble in water and organic solvents

Uses. As broad-spectrum antimicrobial cold sterilant/disinfectant for hospital equipment; as tanning agent for leather; as tissue fixative; as cross-linking agent for proteins; as preservative in cosmetics; as therapeutic agent for warts, hyperhidrosis, and dermal mycotic infections; in X ray processing solutions and film emulsion; as a disinfectant in the beauty industry

Toxicology. Glutaraldehyde is an irritant of the upper respiratory tract and may be capable of inducing asthma in some individuals; it is a skin irritant and can cause an allergic contact dermatitis.

Glutaraldehyde has caused an allergic contact dermatitis in hospital workers using it as a cold sterilant or in handling recently processed X ray film. It appears to be a strong sensitizer.[1–3] In general, reactions present as a vesicular dermatitis of the hands and forearms. Rubber gloves do not appear to afford complete protection. In unsensitized individuals it acts as a mild skin irritant.

Glutaraldehyde also can produce eye and skin irritation when its solutions are aerosolized.[4] It has a low vapor pressure at room temperature, which reduces the potential for inhalation exposures.

Four nurses who were sterilizing endoscopes with glutaraldehyde developed symptoms of asthma and rhinitis temporally related to exposures to glutaraldehyde. Three of the four nurses, however, had a prior history of mild seasonal asthma.[4] On specific provocation testing, one patient had an increase in nasal airway resistance, with a dual immediate and late response pattern. Another patient had a delayed 22% decline in FEV_1 80 minutes after the final exposure to glutaraldehyde. The occurrence of late reactions suggested that the underlying mechanism involved sensitization rather than an irritant effect.[4]

Swedish hospital workers exposed to low glutaraldehyde concentrations (below 0.2 ppm) had an increased frequency of reported nose and throat symptoms, skin symptoms such as eczema and rash, and general symptoms such as headache and nausea, compared with unexposed controls.[5]

Positive patch tests have also been reported in hairdressers who used glutaraldehyde as a disinfectant. Presenting signs and symptoms included erythema with papules on the hands and face, dyspnea, and cough.[6]

Animal experiments demonstrate that solutions containing 25% or more glutaraldehyde cause a significant degree of skin irritation and eye injury; dilute solutions (5% or less) have low acute toxicity.[7]

Oronasal exposure of mice to 2.6 ppm led to a 50% decrease in respiratory rate.[8] Mice exposed at 0.3, 1.0, and 2.6 ppm 6 hour/day for 4, 9, and 14 days had lesions of the respiratory epithelium including squamous metaplasia, focal necrosis, and keratin exudate that were dose dependent at the lower exposure levels. Lesions persisted 2 weeks after exposure but were decreasing 4 weeks after the end of exposure. No exposure-related lesions were observed in the lungs of exposed mice.

In chronic 2-year inhalation studies there was no evidence of carcinogenicity in rats exposed to 250, 500, or 750 ppb or in mice exposed to 62.5, 125, or 250 ppb. Incidences of nonneoplastic lesions of the nose were significantly increased in both species.[9]

Results of short-term tests have been variable. Both positive and negative results have been reported in bacterial assays and for induction of sister chromatid exchanges and chromosomal aberrations.[7,9] In vivo, glutaraldehyde induced a significant increase in chromosomal aberrations in mouse bone marrow cells after a single intraperitoneal injection.[9]

There were no effects on parental fertility and mating performance or on pup viability and litter size in two generations of rats administered up to 1000 ppm in the drinking water.[10]

Stock glutaraldehyde (pH 3.1–4.5) is often alkalinized (pH 7.8–8.0) before use.[11] In animal tests both unbuffered glutaraldehyde and buffered glutaraldehyde have similar acute toxicity and skin irritancy; buffered glutaraldehyde has greater corneal injuring potential, whereas unbuffered glutaraldehyde has a greater skin-sensitizing potential.

The 2003 TLV-Ceiling (TLV-C) limit for glutaraldehyde is 0.05 ppm (0.2 mg/m^3) with a notation for skin sensitization.

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GLYCIDOL

CAS: 556-52-5

$C_3H_6O_2$

Synonym: 2,3-Epoxy-1-propanol; oxiranemethanol

Physical Form. Colorless liquid

Uses. Stabilizer in the manufacture of vinyl polymers; chemical intermediate in preparation of glycerol, glycidyl ethers, esters, and amines; in pharmaceuticals; in sanitary chemicals

Exposure. Inhalation

Toxicology. Glycidol is an irritant of the eyes, upper respiratory tract, and skin; at high concentrations it causes narcosis in animals, and it is expected that severe exposure will have the same effect in humans. It is carcinogenic and mutagenic in experimental animals.

The acute hazard to humans from vapor exposure appears to be relatively slight, as ample warning in the form of eye, nose, and throat irritation occurs at low concentrations; no chronic effects have been reported in humans.[1]

The LC_{50} in mice was 450 ppm for a 4-hour exposure; in rats, the LC_{50} for 8 hours was 580 ppm; labored breathing, lacrimation, salivation, and nasal discharge were seen, and pneumonitis was observed at autopsy.[1] Rats repeatedly exposed to 400 ppm showed only slight eye irritation and mild respiratory distress, with no evidence of systemic toxicity.

The oral LD_{50} was 0.45 g/kg for mice and 0.85 g/kg for rats; symptoms included central nervous system depression characterized by incoordination, ataxia, coma, and death.[1] Animals surviving exposure showed reversible excitation and tremor; lacrimation and labored breathing also were observed. In 16-day studies, focal demyelination of the brain occurred in mice given 300 mg/kg/day by gavage.[2] In the same study, male rats receiving 300 mg/kg/day had edema and degeneration of the epididymal stroma and atrophy of the testes. Longer exposures of 13 weeks resulted in cerebellar necrosis and demyelination of the medulla, renal tubular cell degeneration, and thymic lymphoid necrosis in rats and demyelination of the medulla and thalamus and renal tubular cell degeneration in mice. A reduction in sperm count and sperm motility and testicular atrophy occurred in males of both species at doses up to 300 mg/kg/day or 400 mg/kg/day for mice and rats, respectively.[2] Glycidol

was not teratogenic to mice receiving up to 200 mg/kg/day by gavage on days 6–15 of gestation.[3]

In experimental animals, glycidol was a broadly acting, multipotent carcinogen. Rats administered 75 or 37.5 mg/kg, 5 days/week by gavage for up to 2 years developed mesotheliomas (80%), mammary adenocarcinomas (33%), forestomach tumors (22%), tumors of the oral mucosa (14%), zymbal gland tumors (12%), brain gliomas (12%), follicular cell tumors of the thyroid (12%), and intestinal tumors (8%).[2] Mice received a slightly lower dose and developed a smaller spectrum of tumors, including tumors of the mammary gland, harderian gland, and forestomach. In hamsters (20 male and 20 female) administered 12 mg twice weekly by gavage for 60 weeks, there were more tumors in treated animals than in controls.[4] However, the spleen was the only notable target organ and the number of hamsters with spleen hemangiosarcomas was small. (Note: study used only one dose and a small number of animals.) The IARC has determined that there is sufficient evidence for the carcinogenicity of glycidol in animals and that it is probably carcinogenic to humans (Group 2A).[5]

Application of the liquid to animal skin caused moderate irritation. Chronic topical administration of a 5% solution to mice did not cause skin tumors or any visible skin reaction.[6] In the eyes, glycidol produced severe irritation; despite the severity of primary injury, no blindness or permanent defects in the cornea, lens, or iris resulted from the applications.

In *Salmonella typhimurium* glycidol is a potent direct-acting mutagen.[2] *In vitro* it caused an increased number of sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells and human lymphocytes.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for glycidol is 25 ppm (76 mg/m^3).

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GRAPHITE (natural)
CAS: 7782-42-5

C (with traces of Fe, SiO_2, etc)

Synonyms: Plumbago; black lead; mineral carbon

Physical Form. Usually soft, black scales; rarely crystals

Uses. For pencils, refractory crucibles, pigment, lubricant, polishing compounds, electroplating

Exposure. Inhalation

Toxicology. Natural graphite dust causes graphite pneumoconiosis.

The earliest roentgenologic changes may be the disappearance of normal vascular markings with the later appearance of pinpoint and

nodular densities in all lung fields.[1,2] Massive lesions, when present, are caused by large cysts filled with black fluid. The pleura is often involved; hydrothorax, pneumothorax, and pleural thickening may occur.

At autopsy, the lungs are gray-black to black; histologically there are widely scattered particles, spicules, and plates of graphite, often within intra-alveolar phagocytes amid diffuse interstitial fibrosis and occasionally pneumonitis. There are also interwoven bands of collagen, similar to those found in silicosis, that frequently are the most prominent feature of the fibrotic lesions occupying the lung and the bronchial lymph nodes. Symptoms include expectoration of black sputum, dyspnea, and cough.

Of 344 workers in a graphite mine in Sri Lanka, 78 had radiographic abnormalities, including small rounded and irregular opacities, large opacities, and enlargement of hilar shadows. Some affected workers had cough, dyspnea, or digital clubbing.[3] Eighteen of 388 Sri Lankan mine workers were diagnosed with graphite pneumoconiosis between 1987 and 1993; the diagnosed workers had served an average of 20.8 years in the mine.[4]

It has generally been believed that the capacity of inhaled natural graphite dust to cause a disease is largely the result of its crystalline silica component.[5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for graphite (except graphite fiber) is 2 mg/m^3 as respirable dust.

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GRAPHITE (synthetic)
CAS: 7782-42-5

C

Synonyms: None

Physical Form. A crystalline form of carbon made from high-temperature treatment of coal or petroleum products; same properties as natural graphite; it is chemically inert

Uses. Similar to those of natural graphite in refractories and electrical products

Exposure. Inhalation

Toxicology. Pure synthetic graphite acts as an inert or nuisance dust.

In contrast to the several reports of pneumoconiosis in workers exposed to natural graphite (qv), there was until recently only the rare anecdotal report of significant pulmonary findings due to exposure to synthetic graphite.[1,2] One man who had spent 17 years turning and grinding synthetic graphite bars developed simple pneumoconiosis with cough, dyspnea, reduced pulmonary function, and X ray changes.[1] At autopsy, there was emphysema with scattered fine black nodules (microscopic to 5-mm diameter) with some strands of fibrous tissue. Many of the nodules consisted of almost acellular collagen. There were traces of iron in the nodules and the hilar nodes. Ashed material from the lung showed little or no birefringent particles, indicating the absence of siliceous material. The lung contained 8.8–9.5% carbon by dry weight.

Despite a general belief that pneumoconiosis in this industry in the US ceased to be a problem after World War II, five workers

involved in the manufacture of carbon electrodes have now been reported to have developed this condition after exposures after 1940.[3] However, the variability in clinical findings that characterizes these cases suggests a mixed dust exposure.

Synthetic graphite injected peritoneally in mice produces a reaction characteristic of an inert material. On the basis of experimental evidence, and the rarity of reports of adverse effects of exposure in humans, it is concluded that pure synthetic graphite acts only as an inert dust.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for synthetic graphite (except graphite fiber) is 2 mg/m^3.

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HAFNIUM (and compounds)
CAS: 7440-58-6

Hf

Compounds: Hafnium chloride ($HfCl_4$); hafnyl chloride ($HfOCl_4$); hafnium dioxide (HfO_2)

Physical Form. Hard, shiny, ductile stainless steel-colored metal or dull gray powder

Uses/Sources. Obtained in mining and purification of the metal; used in control rods in nuclear reactors and in manufacture of light bulb filaments; found in all zirconium-containing minerals

Exposure. Inhalation

Toxicology. Hafnium dust is very low in toxicity. No health hazards have been recognized from the industrial handling of hafnium powder other than those arising from fire or explosion.[1]

Hafnium salts are mild irritants of the eye and the skin and have produced liver damage in animals.[2] In mice, the LD_{50} of hafnyl chloride by intraperitoneal injection was 112 mg/kg.[2] In cats, intravenous administration of hafnyl chloride at 10 mg/kg was fatal. Rats fed a diet containing 1% for 12 weeks showed slight changes in the liver, consisting of perinuclear vacuolization of the parenchymal cells and coarse granularity of the cytoplasm.[1] The application of 1 mg of hafnium chloride to the eyes of rabbits produced transient irritation. Topical application of hafnium chloride crystals to unabraded rabbit skin produced transient edema and erythema; application to abraded skin caused ulceration.[2]

Cell proliferation and benign local tumors occurred in mice given a single intradermal injection of hafnium oxychloride.[3] Hafnocene dichloride induced DNA adducts when incubated with mammalian DNA.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 0.5 mg/m^3.

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HALOTHANE
CAS: 151-67-7

$CF_3CHClBr$

Synonyms: 2-Bromo-2-chloro-1,1,1-trifluoroethane; bromochlorotrifluoroethane; Fluothane

Physical Form. Colorless liquid

Use. Clinical anesthetic

Exposure. Inhalation

Toxicology. Halothane causes central nervous system depression, affects the cardiovascular system, and occasionally causes hepatitis.

Halothane is used as a clinical anesthetic, and all levels of central nervous system depression can be expected, including amnesia, analgesia, anesthesia, and respiratory depression. Levels ranging from 5000 to 30,000 ppm can induce anesthesia, whereas 5000–15,000 ppm can maintain it.[1] A 30-minute exposure to 4000 ppm caused amnesia and impairment of manual dexterity, whereas similar exposure to 1000 ppm did not alter the outcome on various psychomotor tests.[2]

Levels of halothane associated with anesthesia may also reduce cardiac output by 20–50%.[3] Tachyarrhythmias may occur in the presence of halothane.[4]

Hepatitis occasionally occurs in patients after clinical anesthesia. Typically, 2–5 days after anesthesia, a fever develops, accompanied by anorexia, nausea, and vomiting.[5] There may be a progression to hepatic failure, and death occurs in about 50% of these patients. The incidence of the syndrome is 1 in 10,000 anesthetic administrations, and it is seen most often after repeated administration of halothane over a short period of time.

Epidemiological studies of occupationally exposed populations have examined possible carcinogenic and teratogenic effects of chronic exposure to the operating room environment. In one study, a high rate of miscarriages (18/31) was observed among pregnant anesthetists.[6] Pregnancies among anesthetists and nurses in anesthesiology departments ended in spontaneous abortion or premature delivery approximately twice as often (20% vs. 10%) as among unexposed women.[7] In a third study, female anesthetists were found to have a higher frequency of involuntary infertility (12% vs. 6%) and spontaneous abortion (18.3% vs. 14.7%) than unexposed women.[8] A national study reported that women chronically exposed to the operating room environment had increased risks of cancer, diseases of the liver and the kidney, spontaneous abortion, and congenital anomalies in their children.[9,10] An increase in sister chromatid exchange, chromosomal aberrations, and DNA damage in lymphocytes has been reported in workers with occupational exposure to halothane.[11–13] It has been noted that all of the epidemiological studies to date have involved either mixed exposures or exposure to unmeasured concentrations of halothane. In vitro studies have confirmed the genotoxicity of halothane; DNA strand breaks were increased with halothane exposure as determined by the comet assay.[14]

In animal studies, macroscopically visible injuries to fetuses have occurred after exposure to 1600 ppm, 6 hours/day for multiple days during gestation.[15] Retardations occurred in mice similarly exposed at 1000 ppm, and 3000 ppm caused minor skeletal variations. No visible damage to the offspring was apparent in rabbits treated 1 hour/day to 22,000 ppm during organogenesis. Prenatal exposure of rats to relatively low levels of halothane (50 or 500 ppm) caused slight and transient changes in rat neonatal liver biochemistry as indicated by significant increases in the serum activities of glutamate dehydrogenase and aspartate aminotransferase.[16]

Recent studies suggest that halothane may be able to act on the developing brain by interfering with neurotransmitters during the synaptogenesis period, causing neurons to die by apoptosis; the degree of risk posed to humans by this mechanism has not been determined.[17]

No carcinogenicity in animals has been reported.[18] The IARC has stated that there

is inadequate evidence for carcinogenicity to humans.[19]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for halothane is 50 ppm (404 mg/m^3).

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HELIUM
CAS: 7440-59-7

He

Synonyms: None

Physical Form. Gas

Uses. Inert gas shield in arc welding; air ships; in mixtures with neon and argon for electronic tubes and "neon" signs

Exposure. Inhalation

Toxicology. Helium is a simple asphyxiant.

Helium is among a number of gases that have no significant physiological action and act primarily as simple asphyxiants by displacing oxygen from the environment.[1] Humans are asymptomatic while breathing air containing 16.5–21% oxygen by volume; oxygen concentrations of 12–16% cause tachypnea, tachycardia, and slight incoordination.[2] If oxygen concentrations fall to 10–14%, exhaustion occurs with minimal exertion. In air containing 6–10% oxygen there is vomiting, lethargy, and unconsciousness; at oxygen levels below 6% there are convulsions, followed by apnea and cardiac arrest.[2]

Atmospheres deficient in oxygen do not provide adequate warning.

No threshold limit value (TLV) has been established for helium. The limiting factor is available oxygen, which should be 18% by volume under normal atmospheric pressure.

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HEPTACHLOR
CAS: 76-44-8

$C_{10}H_5Cl_7$

Synonyms: 2-Chlorochlordene; Drinox; E-3314, ENT 15, 152: Velsicol 104

Physical Form. White to tan crystalline solid

Uses. Insecticide for boll weevil control and termite control currently banned or severely restricted in many countries

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Heptachlor is a convulsant in animals and causes liver damage.

There have been occasional anecdotal reports of blood dyscrasias after exposure to heptachlor, but exposure levels are not available.[1]

In rats, the oral LD_{50} was 90 mg/kg; within 30–60 minutes after administration, effects were tremor and convulsions; liver necrosis was noted.[2] Multiple applications to the skin of rats of 20 mg/kg were toxic, indicating a marked cumulative action.[2] Reversible histologic changes in the rat liver have occurred after dosages of 0.35 mg/kg for 50 weeks.[1] Rats given heptachlor in the diet at 6 mg/kg body weight developed cataracts after 4.5–9.5 months of feeding.[3] This observation has not been replicated in a number of subsequent animal studies.[1] In animals, heptachlor is more potent than chlordane, to which it is closely related chemically.[4]

Chronic oral exposure to heptachlor increased the incidence of liver carcinomas in three species of mice and one species of rats.[5] A study of two cohorts of workers exposed to chlordane and heptachlor at two different production facilities failed to demonstrate any overall excess of cancer. There was one death from liver cancer with 0.59 expected. There was a slight excess of lung cancer (12 observed,

9 expected), but this was not statistically significant.[6]

The IARC has determined that there is sufficient evidence in experimental animals for the carcinogenicity of heptachlor and there is inadequate evidence of carcinogenicity in humans.[7] Heptachlor is considered possibly carcinogenic to humans.[7]

Heptachlor was not mutagenic in bacterial assays, but it did cause gene mutations in rodent cells and unscheduled DNA synthesis in human fibroblasts.[7]

Prenatal and perinatal exposure to heptachlor has resulted in developmental effects. Rats exposed from gestational day 12 up to postnatal day 42 (at 3 mg/kg/day) had persistent neurobehavioral changes, most notably in spatial learning and memory.[8] There were also alterations in the cholinergic system as evidenced by a significant decrease in muscarinic acetylcholine receptors.[9] In mice, prenatal exposure resulted in changes in hematopoietic progenitor cell numbers as measured by colony-forming cell assays.[10]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for heptachlor is 0.05 mg/m^3 with an A3-animal carcinogen designation and a notation for skin absorption.

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HEPTACHLOR EPOXIDE
CAS: 1024-57-3

$C_{10}H_5Cl_7O$

Synonyms: Epoxyheptachlor; 1,4,5,6,7,8,8*a*-heptachloro-2,3-epoxy-3*a*,4,7,7*a*-tetra-hydro-4,7-methanoindene

Physical Form. White crystalline solid

Sources. Not commercially produced; formed as a metabolite of heptachlor in mammals

Exposure. Consequent to exposure to heptachlor

Toxicology. Heptachlor epoxide is a liver carcinogen in rodents.

Heptachlor epoxide is a metabolic product of heptachlor.[1]

Heptachlor epoxide is more toxic then heptachlor.[2] The acute oral LD_{50} for heptachlor epoxide in rodents and rabbits ranged from 39 to 144 mg/kg.[2] After dietary exposure of rats, heptachlor epoxide caused hepatic cell vacuolization at all dose levels (0.5–10 ppm for up to 108 weeks). Degeneration, hepatomegaly, and regeneration were also reported. Like heptachlor, the ability of heptachlor epoxide to induce lethality after acute exposure may involve its ability to interfere with nerve action or release of neurotransmitters and to inhibit the function of the receptor for γ-aminobutyric acid.[2]

In two three-generation studies with rats administered heptachlor, heptachlor epoxide, or a mixture of the two in the diet, the number of resorbed fetuses increased and the fertility decreased with succeeding generations. No adverse effects on reproductive capacity were reported in male mice receiving single oral doses of 7.5 or 15 mg/kg heptachlor : heptachlor epoxide (25% : 75%) in a dominant lethal assay.[2] Heptachlor epoxide has been found in tissues of stillborn infants, indicating transplacental transfer.[2]

Mice fed heptachlor epoxide in the diet at 10 mg/kg for 24 months showed a significant excess of liver carcinomas. In another study, an excess of liver carcinomas was observed in female rats given 5 and 10 mg/kg in the diet.[3]

The IARC has concluded that there is sufficient evidence that heptachlor epoxide is carcinogenic in experimental animals and that it is possibly carcinogenic to humans.[3] The majority of genotoxic assays suggest that heptachlor epoxide is not genotoxic.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for heptachlor epoxide is 0.05 mg/m^3 with an A3-confirmed animal carcinogen designation with unknown relevance to humans and a notation for skin absorption.

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n-HEPTANE

CAS: 142-82-5

$CH_3(CH_2)_5CH_3$

Synonyms: Dipropyl methane; heptyl hydride; heptane

Physical Form. Volatile, flammable liquid

Uses. As standard in testing knock of gasoline engines; solvent

Exposure. Inhalation

Toxicology. *n*-Heptane causes central nervous system depression.

Human subjects exposed to 1000 ppm for 6 minutes, or to 2000 ppm for 4 minutes, reported slight vertigo.[1] At 5000 ppm for 4 minutes, effects included marked vertigo, inability to walk a straight line, hilarity, and incoordination, but there were no complaints of eye, upper respiratory tract, or mucous membrane irritation. In some subjects, a 15-minute exposure at 5000 ppm produced a state of stupor lasting for 30 minutes after exposure. These subjects also reported loss of appetite, slight nausea, and a taste resembling gasoline for several hours after exposure.

Dermal application resulted in immediate irritation characterized by erythema and hyperemia. The subjects complained of painful burning sensation, and, after 5 hours, blisters formed on the exposed areas.[2]

n-Heptane induced anesthesia in mice at 8000 ppm; at 32,000 ppm for 5 minutes mice developed irregular respiratory patterns, followed by deep narcosis; at 48,000 ppm three of four mice had respiratory arrest within 4 minutes.[3] Chronic inhalation studies in rats exposed to 400 or 3000 ppm 6 hours/day 5 days/week for 26 weeks found no evidence of neurological disturbances or organ toxicity.[4] Except for increased serum alkaline phosphatase levels in females at 3000 ppm, blood chemistry showed no hematologic, renal, or liver abnormalities.

Although *n*-heptane exposure produces narcotic effects, it has not been shown to cause the type of peripheral neuropathy associated with *n*-hexane at the same exposure levels.[5] A metabolic study of heptane in rats and humans showed that only a very small amount of 2,5-heptanedione, the purportedly neurotoxic metabolite responsible for peripheral neuropathy, is produced.[6] Clinical damage to the peripheral nervous system after *n*-heptane exposure, therefore, seems unlikely.[6]

Heptane was not mutagenic in a number of in vitro assays with bacteria, yeast, and cultured mammalian cells.[7]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for *n*-heptane is 400 ppm (1640 mg/m^3) with a TLV-short-term excursion limit (STEL) of 500 ppm (2050 mg/m^3).

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HEXACHLOROBENZENE

CAS: 118-74-1

C_6Cl_6

Synonyms: Hexachlorobenzol; perchlorobenzene; HCB; pentachlorophenyl chloride

Physical Form. White crystalline solid

Uses. No current commercial use of HCB in the United States; was used as a pesticide until 1985; occurs as a by-product of the production of a number of chlorinated solvents and other industrial chemicals

Exposure. Ingestion; inhalation

Toxicology. Hexachlorobenzene (HCB) causes porphyria, enlarged liver and thyroid, and neurological symptoms; it is a developmental toxin, and in experimental animals it is carcinogenic.

Evidence of the human health effects of HCB exposure comes primarily from Turkey, where, between 1955 and 1959, 4000 people consumed grain treated with HCB. The consumption level was estimated to be 0.05–0.2 g/day for several years. The majority of the affected patients were children.[1] There was a high rate of mortality in infants of lactating mothers known to have ingested the bread, and

children born to porphyric mothers did not survive.[2] Other manifestations included the development of a condition resembling porphyria cutanea tarda, with abnormal porphyrin metabolism and skin lesions, hyperpigmentation, liver enlargement, hirsutism, short stature (in affected children), thyroid enlargement, painless arthritis, and neurological findings, including weakness, paresthesias, cog wheeling, and myotonia.[3] A study of 32 of the affected individuals demonstrated that abnormal porphyrin metabolism and symptoms persisted 20 years after HCB ingestion.[1] More recent occupational studies have also associated inhalation of HCB with immunologic effects including decreased neutrophil activity and increased immunoglobulins and susceptibility to infection.[2]

In rodents, the liver is a primary target organ for HCB effects. Exposure to 2000 ppm in the diet caused increased porphyrin levels, microscopic lesions in the liver, elevation of serum enzyme levels, and induction of liver microsomal enzymes.[4] Male rats exposed at 40 ppm in the diet for 130 weeks developed chronic nephrosis, and renal tubular damage was noted in rats exposed to 10 mg/kg/day for 15 weeks.[5] Nephropathy is dependent upon the presence of α_{2u}-globulin and is specific to male rats.[6] Exposure of animals to 100, 200, or 500 ppm in the diet caused a 2.5- to 3-fold increase in thyroid size.[7] HCB has been demonstrated to cause hyperparathyroidism and osteosclerosis in another study of rats.[5] HCB is immunotoxic in a number of animal studies, interfering with humoral and cellular immune functions in dogs, rats, mice, and monkeys.[2]

There is no information on in utero developmental effects in humans exposed to HCB, but oral exposure of young children has caused small or atrophied hands, short stature, pinched facies, osteoporosis of the carpal, metacarpal, and phalangeal bones, and painless arthritic changes.[2] HCB has been demonstrated to cross the placenta in humans and in rodents.[1] HCB residues have been detected in human milk and adipose tissue and in the blood of the umbilical cord of newborn infants and their mothers. Teratogenic effects were not demonstrated in rats after exposure to up to 120 mg/kg/day during organogenesis. Cleft palate and renal agenesis were observed in mice at 100 mg/kg/day.[1] Parameters such as fertility index and gestational indices have not been affected in rats at HCB doses up to 40 ppm.[8]

No excess of cancer was reported in two follow-up studies of affected individuals in Turkey about 20–30 years after consumption of contaminated grain had ceased.[9,10] In mice, liver tumors were observed after exposure to HCB at 12–24 mg/kg/day in the diet, but not at 6 mg/kg/day.[1] Hepatomas, hepatocellular carcinomas, bile duct adenomas, and renal cell adenomas were observed in rats after dietary administration.[11] Liver tumors were also observed in 100% of surviving females and 16% of males after dietary administration to rats for 90 weeks. In another study, increased incidence of parathyroid adenomas and adrenal pheochromocytomas were observed in male and female rats and liver neoplastic nodules in females of the F_1 generation in a two-generation feeding study.

The IARC has determined that there is sufficient evidence for carcinogenicity of HCB in experimental animals and that it is possibly carcinogenic to humans.[11]

In an *in vivo* experiment in rats, HCB did not induce dominant lethal mutations. Chromosomal aberrations were not induced in cultured Chinese hamster ovary cells, nor were mutations induced in bacteria.[2,11] HCB does not appear to be genotoxic.

In animal studies, HCB is not a skin or eye irritant and does not sensitize the guinea pig.[12]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for hexachlorobenzene is 0.002 mg/m^3 with an A3-confirmed animal carcinogen with unknown relevance to humans designation and a notation for skin absorption.

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HEXACHLOROBUTADIENE

CAS: 87-68-3

C_4Cl_6

Synonyms: HCBD; hexachloro-1,3-butadiene; perchlorobutadiene

Physical Form. Colorless liquid

Uses. Produced as an unwanted by-product during the production of tetrachloroethylene, trichloroethylene, carbon tetrachloride, and chlorine; formerly used as a pesticide in other countries

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Hexachlorobutadiene (HCBD) causes kidney damage including renal cancer in experimental animals; it also produces central nervous system effects and causes hepatic disorders at very high concentrations.

In a report of human exposures, cited by IARC, vineyard workers exposed to HCBD (0.8–30 mg/m^3) and polychlorobutane (0.12–6.7 mg/m^3) showed multiple toxicological effects contributing to the development of hypotension, cardiac disease, chronic bronchitis, disturbances of nervous function, and hepatitis.[1]

In rats, 4- to 7-hour exposures to concentrations ranging from 133 to 500 ppm caused death.[2] Guinea pigs and cats died subsequent to exposures of 160 ppm for 53 minutes or from 7.5-hour exposures to 35 ppm.

Repeated exposures to 250 ppm (twice for 4 hours) or 100 ppm (twelve 6-hour exposures) caused eye and nose irritation and respiratory difficulty in rats; at autopsy, there was degeneration of renal tubules and injury to the adrenals.[3] Fifteen exposures to 5 or 10 ppm resulted in no observed toxic effect, except for retarded weight gain at the higher dose.

Small groups of rats, rabbits, and guinea pigs exposed to 3 ppm, 7 hours/day for approximately 5 months had liver and kidney damage,

whereas those exposed to 1 ppm were not adversely affected.[4]

A 30-day dietary study at 30, 65, and 100 mg/kg/day in rats found renal toxicity in the form of increased kidney-to-body weight ratio and renal tubular degeneration, necrosis, and regeneration. Other adverse effects included reduced body weight gain at 10 mg/kg/day and minimal hepatocellular swelling at 100 mg/kg/day.[2]

In a chronic dietary study, ingestion by rats of 20 mg/kg/day for up to 2 years resulted in a statistically significant increase in renal tubular adenomas and adenocarcinomas, some of which metastasized to the lungs.[5] Other toxicological effects included decreased body weight gain, increased mortality, increased excretion of urinary coproporphyrin, increased terminal weights of the kidneys, and increased renal tubular epithelial hyperplasia. At the intermediate dose level of 2.0 mg/kg/day, effects were limited to an increased excretion of urinary coproporphyrin and increased hyperplasia of the renal tubular epithelium. Lifetime ingestion of the lowest dose level of 0.2 mg/kg/day caused no treatment-related effects.

HCBD did not produce skin tumors after repeated application or show initiating activity in a two-stage initiation-promotion study in mice.[6]

The IARC has determined that there is limited evidence for the carcinogenicity of HCBD in experimental animals and that it is not classifiable as to its carcinogenicity in humans.[6]

Studies of the mutagenicity of HCBD and its metabolites concluded that HCBD exerts genotoxic effects after metabolic activation.[7] This hypothesis may be important for the evaluation of the carcinogenic potential, as it is generally accepted that a minimum risk threshold for genotoxic substances cannot be assigned. Alternatively, it has also been reported that HCBD induces little genotoxicity in vivo and that renal tumors have been observed only at doses that induce severe chronic nephrosis. Accordingly, chronic cytotoxicity to the renal proximal tubular cells by HCBD intermediates formed in the kidney may account for HCBD-induced renal carcinogenesis.[8]

Reproductive indices, including pregnancy rate, gestational survival, neonatal survival, or morphologic alterations in neonates were not affected when male and female rats were fed up to 20 mg/kg/day for 90 days before mating and during gestation and lactation.[9]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for hexachlorobutadiene is 0.02 ppm (0.24 mg/m^3) with a notation for skin absorption and an A3-confirmed animal carcinogen with unknown relevance to humans designation.

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HEXACHLOROCYCLOPENTADIENE

CAS: 77-47-4

C_5Cl_6

Synonyms: HCCPD; HCCP; HEX; perchlorocyclopentadiene

Physical Form. Yellow to amber-colored liquid

Uses. Intermediate in the manufacture of chlorinated pesticides; intermediate in the manufacture of flame retardants

Exposure. Inhalation

Toxicology. Hexachlorocyclopentadiene is a lacrimator and severe irritant of the mucous membranes, respiratory tract, and skin.

A large amount of hexachlorocyclopentadiene was dumped into a municipal sewage system and caused exposure to 145 sewage treatment workers.[1,2] Exposures were estimated to range from less than 0.05 ppm to 20 ppm for several seconds to 15 minutes. The major complaints were eye irritation, headache, and throat irritation. Medical examination of 41 workers 3 days after the exposure showed proteinuria and elevation of serum lactic dehydrogenase levels. These findings had resolved 3 weeks later.

In a recent study of male operators employed in a chemical plant, it was concluded that long-term exposure to a mixture of chlorinated hydrocarbons, including hexachlorocyclopentadiene, below or near the current threshold limit values did not lead to clinically significant effects on the liver or kidney as determined by biochemical function tests.[3]

Hexachlorocyclopentadiene appears to be more toxic when inhaled than when ingested.[4] The reported oral LD_{50} is 425 mg/kg for rats and 680 mg/kg for mice. The 4-hour LC_{50} values range from 1.6 to 3.5 ppm for rats and mice. Rats, rabbits, and guinea pigs exposed to 0.15 ppm for 7 hours/day, 5 days/week, for 30 weeks survived.[5] Exposure at 0.34 ppm caused death in mice and rats after 20 exposures. Effects observed were lacrimation, salivation, gasping respiration, and tremor. Severe pulmonary edema and acute necrotizing bronchitis and bronchiolitis were evident, as were degenerative changes in the brain, heart, liver, adrenal glands, and kidneys. The liquid on the skin of monkeys caused severe irritation.[5]

Exposure of rats to 0.5 ppm 6 hours/day, 5 days/week, for 2 weeks caused lesions in the olfactory and bronchiolar epithelium along with inflammatory exudate in the lumens of the respiratory tract.[6]

In a 13-week oral gavage study in rats and mice at doses up to 150 mg/kg/day, there was irritation of the forestomach in both sexes of both species and a high incidence of toxic nephrosis in the females only of both species.[7]

There was no evidence of carcinogenicity in rats or mice exposed to 0.01, 0.05, or 0.2 ppm for 6 hours/day for 2 years.[8] Pigmentation of the respiratory epithelium occurred in both species, and squamous metaplasia of the laryngeal epithelium occurred in female rats. Genotoxic assays have been uniformly negative.

No evidence of teratogenicity was found after oral exposure in three species.[4]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 0.01 ppm (0.11 mg/m^3).

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HEXACHLOROETHANE

CAS: 67-72-1

CCl_3CCl_3

Synonyms: Carbon hexachloride; perchloroethane

Physical Form. Colorless crystals

Uses. Chemical intermediate in the manufacture of pyrotechnics, insecticides, and other chlorinated materials

Exposure. Inhalation; skin absorption

Toxicology. Hexachloroethane is an eye irritant and causes kidney and central nervous system effects in animals. At high doses, it is carcinogenic to mice.

Exposure of workers to fumes from hot hexachloroethane resulted in blepharospasm, photophobia, lacrimation, and reddening of the conjunctiva but no corneal injury or permanent damage.[1] No chronic effects have been reported from industrial exposure, although significant skin absorption is said to occur.[2]

Rats exposed to 5900 ppm for 8 hours showed ataxia, tremor, and convulsions and two of six died.[1] At 260 ppm for 8 hours there were no toxic signs, but repeated exposure to this concentration 6 hours/day, 5 days/week caused tremor, red exudate around the eyes, and some deaths after 4 weeks. Dogs exposed at 260 ppm developed tremor, ataxia, hypersalivation, and facial muscular fasiculations and held their eyelids closed during the exposure; three of four survived 6 weeks of repeated exposures. No treatment-related effects were found in a number of species repeatedly exposed at 48 ppm.[1]

Rats fed 62 mg/kg/day for 16 weeks exhibited no overt toxicity.[2] Kidney effects characterized by increased kidney weights and microscopic changes (tubular atrophy, degeneration, hypertrophy and/or dilation) were observed in males at 15 and 62 mg/kg/day; in females tubular atrophy and degeneration of the kidneys were observed only at the highest dose. Both sexes also had increased liver weights at 62 mg/kg/day.[2]

The dermal LD_{50} for male rabbits was greater than 32 g/kg.[2] Applied to rabbit skin for 24 hours, the dry material caused no skin irritation whereas a water paste caused slight redness.[1] In the eyes of five of six rabbits, 1 g of the crystal overnight caused moderate corneal opacity, iritis, severe swelling, and discharge.

Gavage administration of 590 and 1179 mg/kg/day to mice for 78 weeks caused a significant increase in the incidence of hepatocellular carcinomas, whereas no increase in these tumors was observed in rats given 212 or 423 mg/kg/day. A nonsignificant increase in renal tumors was seen in rats, and tubular nephropathy occurred in both species.[3] In 2-

year gavage studies, there was clear evidence of carcinogenicity in male rats administered 20 mg/kg, 5 days/week, based on increased incidences of renal neoplasms.[4] Marginally increased incidences of pheochromocytomas of the adrenal gland may also have been related to hexachloroethane administration in males. There was no evidence of carcinogenicity for female rats administered 80 or 160 mg/kg for the 2-year duration, although the severity of nephropathy was increased in dosed females as well as males.[4]

The IARC has determined that there is sufficient evidence for the carcinogenicity of hexachloroethane in animals and that it is possibly carcinogenic to humans.[5] Hexachloroethane was not mutagenic in a variety of *in vitro* assays.[6]

In limited studies hexachloroethane did not appear to be a selective reproductive or developmental toxin at doses below those causing maternal toxicity.[6]

Hexachloroethane has a camphorlike odor, readily sublimes, and, when heated to decomposition, emits phosgene.[1] Sublimation of hexachloroethane may contribute to exposure control problems. Sedimented hexachloroethane dust may accumulate on fluorescent tube illuminators and other warm surfaces and act as an exposure reservoir, adding to exposure levels.[7]

Hexachloroethane exposure can be determined from blood plasma. In one group of workers, plasma levels increased nearly 100-fold despite the use of personal protective equipment.[7]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 1 ppm (9.7 mg/m^3) with an A2-suspected human carcinogen designation and a notation for skin absorption.

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HEXACHLORONAPHTHALENE
CAS: 1335-87-1

$C_{10}H_2Cl_6$

Synonyms: Halowax 1014

Physical Form. Waxy yellow-white solid

Uses. In synthetic wax; in electric wire insulation; in lubricants

Exposure. Inhalation; skin absorption

Toxicology. Hexachloronaphthalene is toxic to the liver and causes chloracne.

Human fatalities due to acute yellow atrophy of the liver have occurred with

repeated exposure to penta- and hexachloronaphthalene.[1,2] Air measurements showed concentrations averaging 1–2 mg/m^3. Other workers experienced jaundice, nausea, indigestion, and weight loss.

The most common problem, a severe acneform dermatitis termed chloroacne, typically occurs from long-term contact with the fume or dust or shorter contact with the hot vapor.[3] The reaction is usually slow to appear and may take months to return to normal.

An excess mortality of cirrhosis of the liver was observed in 9028 workers employed from 1940 to 1944 at a cable manufacturing plant with chlorinated naphthalene exposure. Cirrhosis deaths were similarly elevated in a subcohort of 460 individuals who had shown symptoms of chloracne.[3] A cancer mortality study of this same subcohort found an excess of two rare causes of death, malignant neoplasm of the esophagus and benign and unspecified neoplasms.[4]

Repeated exposure of rats to an average concentration of 8.9 mg/m^3 of a mixture of penta- and hexachloronaphthalene produced jaundice and was fatal; the liver showed a marked fatty degeneration and centrilobular necrosis.[5] At 1.16 mg/m^3, minor liver injury still occurred.

Cattle developed severe systemic disease (bovine hyperkeratosis) during a 5- to 10-day oral exposure to 1.7–2.4 mg/kg/day of the higher-chlorinated napthalenes.[6]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for hexachloronaphthalene is 0.2 mg/m^3 with a notation for skin absorption.

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HEXAFLUOROACETONE

CAS: 684-16-2

C_3F_6O

Synonyms: HFA; acetone, hexafluoro; perfluoro-2-propanone; perfluoroacetone; 1,1,1,3,3,3-hexafluoro-2-propanone

Physical Form. Colorless gas, which reacts vigorously with water to form hydrates

Uses. In the synthesis of polymer, pharmaceutical, and agricultural chemicals; solvent for polyamides, polyesters, and polyacetals; in the synthesis of hexafluoroisopropanol

Exposure. Inhalation; skin absorption

Toxicology. Hexafluoroacetone affects the lungs, liver, and kidneys and causes testicular damage and teratogenesis in rats.

Upper respiratory tract irritation has been reported in humans after exposure to 4 ppm hexafluoroacetone dihydrate.[1]

In dogs 5000 ppm was lethal to one of two animals after a 45-min exposure.[2] Deaths occurred within 3 days after exposure; lung hemorrhage and edema were observed,

whereas the trachea, spleen, liver, kidney, and urinary bladder appeared normal.[2]

The oral LD_{50} for the trihydrate in rats is 190 mg/kg; moderate signs of central nervous system depression were observed that abated in the survivors after 2 days.[2]

LC_{50} values of 900, 570, 275, and 200 ppm have been reported in rats for exposure times of 0.5, 1, 3, and 4 hours, respectively.[1] Exposure of rats to 200 ppm or above for 4 hours caused injury to the liver, kidneys, and thymus.[3] Pulmonary edema and congestion were seen in the lungs, and surviving males had testicles that were small on gross examination and microscopically showed aspermatogenesis, destruction of the stem cells, and effects on the interstitial tissue.

Exposure of rats and beagle dogs to 12 ppm for 6 hours/day, 5 days/week for 13 weeks produced severe testicular damage and slight hypoplasia of the spleen, thymus, lymph nodes, and bone marrow.[4] In the rats both immature and mature spermatids no longer appeared in the seminiferous tubules; no spermatozoa were noted in the epididymal tubules.[5] Normal spermatogenesis was only partly restored at 84 days after exposure.[5] Similar exposure at 0.1 ppm caused no effects.

Hexafluoroacetone sesquihydrate was applied dermally to male rats at doses of 13, 39, or 130 mg/kg/day for 14 days.[6] All rats developed severe testicular atrophy at the highest dose, whereas 50% of the animals at the medium dose had the same effects. No effects were observed at the low dose.

In a teratology study, hexafluoroacetone trihydrate was applied to the skin of pregnant rats from days 6 to 16 of gestation.[7] Teratogenic effects were seen at 5 and 25 mg/kg/day and consisted of gross external, internal soft tissue, and skeletal abnormalities. Malformations (soft cleft palate), external variations (edema and subcutaneous hemorrhages), delayed ossifications, and skeletal variations (extra ribs) were increased in rats exposed by inhalation to 7 ppm, 6 hours/day on gestation days 7–16.[8] Fewer live fetuses, increased resorptions, and lower fetal weights were also observed. Dams exhibited no signs of maternal toxicity except for increased liver weights.

The liquid is a severe skin irritant; one drop of the dihydrate produced marked erythema and blanching to guinea pig skin, but no irritation was seen when diluted to 10%.[1,3] Instilled in rabbit eyes hexafluoroacetone sesquihydrate produced severe, extensive injury including corneal opacity, scar tissue, and chronic conjunctivitis.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for hexafluoroacetone is 0.1 ppm (0.68 mg/m^3) with a notation for skin absorption.

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HEXAMETHYLENE DIISOCYANATE
CAS: 822-06-0

$C_8H_{12}N_2O_2$

Synonyms: HDI; HMDI; 1,6-diisocyanatohexane; 1,6-hexamethylene diisocyanate

Physical Form. Pale yellow liquid

Uses. Cross-linking agent (hardener) in the production of polyurethane materials such as car paints, dental materials, and contact lenses

Exposure. Inhalation

Toxicology. Hexamethylene diisocyanate (HDI) is an irritant of the eyes, mucous membranes, and skin and is a sensitizer of the respiratory tract.

Severe eye injury including conjunctivitis, glaucoma, keratitis, and corneal damage can occur with exposure to HDI.[1] By analogy with toluene diisocyanate (TDI) threshold levels for irritation would be expected to be in the range of 50 ppb.[1] If the breathing zone concentration of diisocyanates reaches 0.5 ppm, the possibility of respiratory response is imminent.[2] Depending on the length of exposure and level of concentrations above 0.5 ppm, respiratory symptoms may develop with a latent period of 4–8 hours. Symptoms include increased secretions, cough, pain of respiration, and, if severe enough, some restriction of air movement owing to a combination of secretions, edema, and pain. On removal from exposure, the symptoms may persist for 3–7 days.

A second type of response to isocyanates is allergic sensitization of the respiratory tract.[3] This usually develops after some months of exposure. The onset of symptoms may be insidious, becoming progressively more pronounced with continued exposure. Initial symptoms are often nocturnal dyspnea and/or nocturnal cough with progression to asthmatic bronchitis.

Productive cough and shortness of breath developed in a spray painter 12–18 months after introduction of a spray paint that contained HDI.[4] When the worker was exposed to a diagnostic spray mist containing 5% HDI for 5 minutes, an 18% drop in respiratory function was noted in 10 minutes and a 41% drop was seen in 3 hours. The worker also had an enhanced nonspecific reactivity to inhaled histamine that persisted for 18 months after the worker ceased to be exposed to HDI.

Cross-reactivity of diisocyanates was investigated in 24 exposed workers with respiratory symptoms.[5] All workers had been exposed to TDI. In inhalation challenge tests, 16 gave asthmatic reactions to TDI at levels ranging from 0.0001 to 0.02 ppm. Five gave nonimmediate (late) reactions only, and 11 gave combined (dual) reactions. Eight of these 16 also reacted to methylene diisocyanate (MDI). Of the eight TDI and MDI reactors, four had histories of exposure only to TDI and two of those four also reacted to HDI. Of nine subjects tested with HDI, three gave asthmatic reactions, and all three also reacted to TDI and MDI. Reactions to MDI and HDI were elicited only in TDI reactors. Among the possible explanations for these findings are cross-reactivity between the different isocyanates, an irritant or pharmacological effect in subjects with hyperreactive airways, or both.

Isocyanates mediate their toxicity through a high degree of chemical reactivity.[1] These reactions can result in cross-linkages of biological macromolecules that lead to the denaturation of proteins, the loss of enzyme function, and the formation of immunologic reactivities.

Chronic 2-year exposure of rats at concentrations up to 0.175 ppm was not carcinogenic but caused lesions to the nasal cavity and lungs.[6]

HDI was not mutagenic against a variety of *Salmonella* assays with or without metabolic activation.[6]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for hexamethylene diisocyanae is 0.005 ppm (0.034 mg/m^3).

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HEXAMETHYL PHOSPHORAMIDE

CAS: 680-31-9

$C_{16}H_{18}N_3OP$

Synonyms: HMPA; HMPT; HPT; hexamethyl phosphoric triamide

Physical Form. Colorless liquid

Uses. Solvent for polymers; polymerization catalyst; stabilizer against thermal degradation in polystyrene; UV stabilizer in polyvinyl and polyolefin resins

Exposure. Inhalation; skin absorption

Toxicology. Hexamethyl phosphoramide (HMPA) causes kidney damage, testicular atrophy, and respiratory tract effects and is carcinogenic in experimental animals.

Effects from human exposures have not been reported.

Nasal tumors were induced in rats by inhalation exposure to HMPA for 6–24 months at levels of 50, 100, 400, and 4000 ppb, 6 hours/day, 5 days week, but not in rats exposed to 10 ppb for 24 months.[1,2] Most nasal tumors were epidermoid carcinomas and developed from the respiratory epithelium or subepithelial nasal glands, both of which revealed squamous metaplasia or dysplasia in the anterior nasal cavity.

Other effects were: keratinized squamous metaplasia of the trachea (4000 ppb); dose-related increases in tracheitis and desquamation of the tracheal epithelium, and bronchitis, desquamation, and regeneration of the bronchial epithelium (100, 400, and 4000 ppb); bone marrow erythropoietic hyperplasia (males, 4000 ppb); testicular atrophy (males, 4000 ppb); and degenerative changes in the convoluted tubules of the kidneys.[2,3]

Dogs also showed squamous metaplasia of the nasal cavity after inhalation exposure to HMPA for 5 months at 400 and 4000 ppb.

In subchronic studies HMPA administered by gavage or in the drinking water of rats caused lesions in the nasal cavity.[4] At 100 ppm in the drinking water for 90 days there was epithelial denudation, regeneration, and squamous metaplasia of the nasal cavity. At 1000 ppm nasal toxicity was more severe and testicular atrophy was induced in males.

In a teratology study, rats were given daily oral doses of 200 mg/kg/day from day 7 to day 20 of gestation; no abnormalities were seen in offspring.[5]

The IARC has determined that there is sufficient evidence for the carcinogenicity of hexamethyl phosphoramide in experimental animals and that it is possibly carcinogenic to humans.[6]

The ACGIH classfies hexamethyl phosphoramide as an A3, confirmed animal carcinogen with unknown relevance to humans, and a notation for skin absorption; a numerical threshold limit value is not recommended.

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n-HEXANE

CAS: 110-54-3

$CH_3(CH_2)_4CH_3$

Synonym: Hexane

Physical Form. Colorless, very volatile liquid solvent and thinner

Uses. Solvent

Exposure. Inhalation; skin absorption

Toxicology. *n*-Hexane is an upper respiratory irritant and central nervous system depressant; chronic exposure causes peripheral neuropathy.

In human subjects, 2000 ppm for 10 minutes produced no effects but 5000 ppm resulted in dizziness and confusion.[1] Other investigators reported slight nausea, headache, and irritation of the eyes and throat at 1500 ppm.[2] In industrial practice, mild symptoms of narcosis such as dizziness have been observed when concentrations of solvents containing various isomers of hexane exceeded 1000 ppm but symptoms were not observed for exposures below 500 ppm.[3]

Dermal exposure to hexane caused immediate irritation characterized by erythema and hyperemia.[4] Subjects complained of painful burning sensations with itching, and after 5 hours, blisters formed on the exposed areas.[4]

Polyneuropathy has been reported after chronic occupational exposure to vapors containing *n*-hexane at concentrations typically in the 400–600 ppm range with some ceiling exposures up to 2500.[4–6] One person developed polyneuropathy after 1 year of exposure at 54–200 ppm.[5] Initial symptoms may include sensation disturbances, muscle weakness, and distal symmetric pain in the legs after 2–6 months of exposure.[5] Clinical changes are muscle atrophy, hypotonic decreased muscle strength, foot drop, and paresthesias in the arms and legs. Characteristic electroneurophysiological findings include a noticeable fall in nerve conduction velocities, profound amplitude reduction of compound muscle action potentials and sensory action potentials, and prolongation of distal latencies.[6] Evoked potential studies show prolongation of conduction times in the visual, auditory, and somatosensory pathways of the central nervous system. Changes in color vision, in retinal pigmentation, and in perifoveal capillaries were found in workers exposed to 420–1280 ppm for more than 5 years.[5] Peripheral nerve biopsies show significant swelling of the nerve with thinning of the myelin sheath. Functional disturbances commonly progress for 2–3 months after cessation of exposure. Recovery may be expected within a year, but, in some cases, clinical polyneuropathy has remained after 2 years.[5] A follow-up of 11 patients with moderate to severe *n*-hexane-induced polyneuropathy

found that sensory functions were regained earlier than motor functions and that abnormal color vision and muscle atrophy persisted up to 4 years.[7]

One anecdotal report has suggested that prolonged exposure (30 years) to low-grade levels of *n*-hexane (10–100 mg/m^3) may also cause polyneuropathy.[8]

Experimental animals continuously exposed to pure *n*-hexane developed the same clinical, electrophysiological, and histopathologic changes found in humans exposed to mixed vapors containing *n*-hexane.[9] Continuous inhalation by rats of 400 ppm caused axonapathy.[10] In contrast, intermittent exposure of rats to 10,000 ppm 6 hours/day, 5 days/week for 13 weeks caused only slight paranodal axonal swelling.[11] It is postulated that 2,5-hexanedione, a metabolite of *n*-hexane and purported neurotoxic agent, must build to an effective concentration. With continuous exposure there is no recovery during each day or week.

Chronic exposure to commercial hexane solvent (51% *n*-hexane) at concentrations up to 9000 ppm was not carcinogenic to F-344 rats or to male B6C3F1 mice but did result in an increased incidence of liver tumors in female mice.[12] It is unclear what components of the hexane mixture caused the neoplasms.[13]

In genotoxic assays, commercial hexane, consisting of *n*-hexane and other six-carbon isomers, did not produce chromosomal mutations either *in vitro* or *in vivo*.[14] Results have generally been negative in bacterial assays and in other mammalian cell assays.[13] Morphologic alterations in sperm were noted in one inhalation study in rats.[13]

In regard to reproductive effects, the o nly difference found in rats exposed to 1000 ppm during gestation was in their offspring, which weighed less than expected at ages 1–6 weeks.[15]

Urinary concentration of 2,5-hexanedione has been used in the biological monitoring of workers exposed to *n*-hexane and is considered to be a reliable indicator of alveolar and percutaneous absorption.[16] Variability between environmental concentrations of *n*-hexane and 2,5-hexanedione levels have been attributed to variable use of protective clothing.

The neurotoxic properties of *n*-hexane are potentiated by exposure to methyl ethyl ketone (qv). Because other compounds may also have this effect, human exposure to mixed solvents containing any neurotoxic hexacarbon compound should be minimized.[9]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for *n*-hexane is 50 ppm (176 mg/m^3).

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sec-HEXYL ACETATE

CAS: 108-84-9

$C_8H_{16}O_2$

Synonyms: Methyl amylacetate; 4-methyl pentyl 2-acetate; 1,3-dimethylbutyl acetate; methyl isoamyl acetate

Physical Form. Clear liquid

Uses. Lacquer industry; fragrances

Exposure. Inhalation

Toxicology. *sec*-Hexyl acetate causes irritation of the eyes and upper respiratory tract; at concentrations approaching saturation it causes narcosis in animals, and it is expected that similar exposure would cause the same effect in humans.

Human volunteers exposed to 100 ppm for 15 minutes experienced eye irritation and objected to the odor and taste; nose and throat irritation occurred at levels greater than 100 ppm.[1] No chronic or systemic effects in humans have been reported.

Four of six rats survived exposure to 4000 ppm for 4 hours, but 8000 ppm was lethal to all animals.[2]

The liquid was poorly absorbed through rabbit skin but did cause moderate irritation.[2,3] Little corneal injury resulted from eye instillation.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for *sec*-hexyl acetate is 50 ppm (295 mg/m^3).

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HEXYLENE GLYCOL

CAS: 107-41-5

$C_6H_{14}O_2$

Synonyms: 2-Methyl-2,4-pentanediol; 2,4-dihydroxy-2-methyl pentane; Isol; Pinakon

Physical Form. Mild-odored liquid

Uses. Fuel and lubricant additive; solvent in cosmetics; solvent in petroleum refining; coupling agent in hydraulic brake fluid and printing inks; gasoline anti-icer additive

Exposure. Inhalation

Toxicology. Hexylene glycol is an irritant of the eyes and mucous membranes and causes narcosis at high levels.

Sensory response evaluations in humans indicated that exposure to 50 ppm for 15 minutes produced slight odor and eye irritation.[1] At 100 ppm for 5 minutes, the odor was plainly detectable and slight nasal and respiratory discomfort was noted by unacclimated subjects. At 1000 ppm for 5 minutes, various degrees of eye irritation and throat and respiratory discomfort were noted.

The irritant and sensitizing properties of hexylene glycol as compared to propylene glycol were investigated in 823 eczema patients by routine patch testing.[2] Edema and erythema reactions occurred in 2.8% of the patients exposed to hexylene glycol compared with 3.8% reacting to propylene glycol.

The oral LD_{50} in rats was 4.79 g/kg, with death being preceded by narcosis.[1] No adverse effects were detected in rats given 590 mg/kg/day for 8 months.

The liquid in the rabbit eye caused appreciable irritation and corneal injury that was slow to heal.[3] Mild to moderate irritation occurred from the liquid applied to the skin of rabbits. Skin absorption is minimal; the dermal LD_{50} for rabbits was 12.3 g/kg.[1]

No effect on fertility was seen in male rats treated orally.[4] Hexylene glycol was not genotoxic in a variety of assays.[4]

The 2003 short-term excursion limit (STEL)/ceiling limit for hexylene glycol is 25 ppm (125 mg/m^3).

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HMX
CAS: 2691-41-0

$C_4H_8N_8O_8$

Synonyms: Octogen; cyclotetramethylenetetranitramine

Physical Form. Colorless solid

Uses. To implode fissionable material in nuclear devices to achieve critical mass; as a component of plastic-bonded explosives and solid fuel rocket propellants and as burster charges in military munitions.

Exposure. Skin contact and absorption; inhalation

Toxicology. HMX may cause hepatic and central nervous system effects in exposed workers.

A study investigated the effects of HMX in 24 male munitions workers who were also exposed to cyclotrimethylenetrinitramine or RDX.[1] Although air levels of RDX were measured (0.28 mg/m^3), levels of HMX were not. Compared with an unexposed control group of 237 men, there were no differences in various hematologic, renal, and hepatic indices. Another study in a group of 558 male and female munitions workers examined the immunologic effects of explosives.[1] The study was prompted by the occurrence of three cases of lupus erythematosus at one munitions plant in 2 years. The workers were exposed to HMX and RDX, either alone or in combination

with other explosives such as trinitrotoluene (TNT). Compared with an unexposed control group of 863 men and women, the prevalence of antinuclear antibodies, a biomarker for lupus erythematosus, was not significantly different in the exposed group.

Several studies have reported hepatic effects in animals after exposure to HMX. Hepatocyte hyperplasia and cytoplasmic eosinophilia were noted in rats and mice orally exposed to 1280 and 300 mg/kg/day, respectively, for 14 days.[2] Clear evidence of hepatotoxicity was observed at a higher dose of 8504 mg HMX/kg/day, which resulted in centrilobular degeneration in male rats exposed for 14 days. Collectively, the data from animal studies indicate that the liver is adversely affected by exposure to moderate to high doses of HMX.

In rabbits administered a single 168 mg/kg dermal dose of HMX there were a number of neurological effects including hyperkinesia, hypokinesia, and clonic convulsions.[3] An increase in the severity of the convulsions and hind leg paralysis occurred at 372 mg/kg. These data suggest that the central nervous system may be a target for HMX.

Because of the lack of appropriate cancer bioassays and epidemiological studies, the EPA has determined that HMX is not classifiable as to its human carcinogenicity.[4]

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HYDRAZINE
CAS: 302-01-2

NH_2NH_2

Synonyms: Hydrazine anhydrous; diamide; diamine; nitrogen hydride

Physical Form. Colorless oily liquid, fuming in air

Uses. Reducing agent; in the production of plastic blowing agents, herbicides, and rocket propellants

Exposure. Inhalation; skin absorption

Toxicology. Hydrazine is a severe skin and mucous membrane irritant, a convulsant, a hepatotoxin, and a moderate hemolytic agent; it is carcinogenic in experimental animals and is considered a possible human carcinogen.

In humans, the vapor is immediately irritating to the nose and throat and causes dizziness and nausea; itching, burning, and swelling of the eyes develop over a period of several hours.[1] Severe exposure of the eyes to the vapor causes temporary blindness, lasting for about 24 hours.[2] The liquid in the eyes or on the skin causes severe burns.[1] Hydrazine and its salts will also produce skin irritation and allergic reactions in humans.

Hydrazine is absorbed through the skin. In one case attributed to hydrazine hydrate exposure, systemic effects included weakness, vomiting, excited behavior, and tremors; the chief histologic findings were severe tracheitis and bronchitis, fatty degeneration of the liver, and nephritis.[3]

The LC_{50} values for rats and mice were 570 and 252 ppm, respectively.[4] The exposed rodents were restless and had breathing difficulties and convulsions. Exposure of mice, rats, dogs, and monkeys to 1.0 and 5.0 ppm, 6 hours/day, 5 days/week, or at levels of 0.2 and 1.0 ppm continuously, had a variety of effects. Increased mortality occurred in mice and was attributed to liver damage; rats showed a dose-

related growth depression; dogs also had increased mortality and developed depressed erythrocyte counts, hematocrit values, and hemoglobin concentrations at higher doses; there were no effects in monkeys.[1] Lipid deposition in the kidneys of monkeys has been reported after intraperitoneal administration of hydrazine.[1]

Studies in rats have shown that acute doses of hydrazine cause hepatic steatosis accompanied by depletion of ATP and reduced glutathione (GSH) and hepatic accumulation of triglycerides. Biochemical effects from repeated exposure, however, included depletion of triglycerides and induction of nitrophenol hydroxylase activity in addition to changes in other microsomal enzymes.[5]

Hydrazine or hydrazine salts are carcinogenic in mice after oral administration (pulmonary adenocarcinoma; hepatocarcinoma) or intraperitoneal injection (pulmonary carcinoma) and in rats after oral administration (pulmonary adenocarcinoma).[6] Hydrazine induced a significantly greater incidence of nasal tumors, primarily benign, in rats and in hamsters after 1 year of intermittent inhalation exposure at levels up to 5.0 ppm.[7]

A group of 427 hydrazine facility workers followed through 1992 showed no increased risk for lung cancer, cancer of the digestive system, other cancers, or mortality from other causes as compared with referent values, regardless of the degree of exposure.[8]

In other case reports, choroidal melanoma was observed in one man who had been exposed to hydrazine for 6 years, and chronic myeloid leukemia was reported in two patients with long-lasting exposure to hydrazine.[9,10]

Hydrazine induces gene mutations in bacteria, yeast and *Drosophila*, and in vivo treatment of rodents results in the formation of DNA adducts.[6]

The IARC has determined that there is sufficient evidence for the carcinogenicity of hydrazine to animals and inadequate evidence for humans.[6]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for hydrazine is 0.1 ppm (0.13 mg/m^3) with a notation for skin absorption. An A3-confirmed animal carcinogen with unknown relevance to humans notation is assigned.

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HYDROGENATED TERPHENYLS
CAS: 61788-32-7

Synonym: Terphenyls, hydrogenated

Physical Form. Liquid; the hydrogenated terphenyls are complex mixtures of *ortho*-, *meta*-, and *para*-terphenyls in various stages of hydrogenation; five such stages exist for each of these three isomers

Uses. Heat-transfer media and plasticizers; as coolants they are 40% hydrogenated (HB-40)

Exposure. Inhalation

Toxicology. Hydrogenated terphenyls have caused lung, kidney, and liver changes in animals.

The oral LD_{50} in rats for 40% hydrogenated terphenyls (reactor coolant) was 17.5 g/kg; for irradiated reactor coolant it was 6 g/kg.[1] Ingestion by mice for 16 weeks of the irradiated mixture at 1200 mg/kg was lethal, whereas the nonirradiated mixture was not lethal but did cause irreversible interstitial nephritis. At 250 mg/kg, no lesions were observed for the 16-week period of exposure.

Rats exposed to a commercial formulation of partially hydrogenated terphenyl vapor at 100 or 500 mg/m^3 for 6 hours/day, 5 days/week for 14 weeks had excessive lacrimation and rough coats.[2] At the highest dose males had slightly reduced body weights and significantly increased absolute and relative liver weights. Administered in the diet for 14 weeks, 2000 ppm caused significantly increased absolute and relative kidney and spleen weights in female rats and significantly increased relative and absolute liver weights in both males and females. No treatment-related gross or histopathologic changes were observed.[2]

Mice exposed for 8 weeks to an irradiated mixture of hydrogenated terphenyl at 2000 mg/m^3 showed transient changes in Type II cells of the alveolar epithelium and some proliferation of the smooth endoplastic reticulum in the liver.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for hydrogenated terphenyls is 0.5 ppm (4.9 mg/m^3).

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HYDROGEN BROMIDE
CAS: 10035-10-6

HBr

Synonyms: Hydrobromic acid; anhydrous hydrobromic acid

Physical Form. Colorless, nonflammable gas

Uses/Sources. Manufacture of organic and inorganic bromides; reducing agent, catalyst in oxidations; alkylation of aromatic compounds; can be generated during the pyrolysis of a variety of materials

Exposure. Inhalation

Toxicology. Hydrogen bromide gas in an irritant of the eyes, mucous membranes, and skin.

There are no systemic effects reported from industrial exposure. Experimental expo-

sure of humans to 5 ppm for several minutes caused nose and throat irritation in most persons, and a few were affected at concentrations of 3–4 ppm.[1] At 35 ppm irritation of the throat has been observed after short exposure; more severe exposures result in pulmonary edema and laryngeal spasm.[2] Concentrations of 1400–2100 ppm were reported to be lethal in exposures lasting a few minutes.[2] Solutions in contact with the eyes, skin, or mucous membranes may cause burns.[3]

The 1-hour inhalation LC_{50} was 2860 ppm for rats and 815 ppm for mice.[4] Rats exposed to 1300 ppm for 30 min and euthanized 24 hours after exposure showed tissue injury confined to the nasal region, including epithelial and submucosal necrosis, accumulations of inflammatory cells and exudates, and the extravasation of erythrocytes.[5] Intratracheal administration of the same dose produced some mortality and major tissue disruption in the trachea, including epithelial, submucosal, glandular, and cartilage necrosis, and accumulations of inflammatory cells and exudates.

The 2003 ACGIH ceiling-threshold limit value (C-TLV) for hydrogen bromide is 3 ppm (9.9 mg/m^3).

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HYDROGEN CHLORIDE

CAS: 7647-01-0

HCl

Synonyms: HCl; hydrochloric acid, aqueous; muriatic acid

Physical Form. Colorless gas (aqueous solution is hydrochloric acid)

Uses. Production of chlorinated organic chemicals; production of dyes and dye intermediates; steel pickling; oil well acidizing operations to dissolve subsurface dolomite or limestone; formed during thermal decomposition of PVC

Exposure. Inhalation

Toxicology. Hydrogen chloride is a strong irritant of the eyes, mucous membranes, and skin.

The major effects of acute exposure are usually limited to the upper respiratory tract and are sufficiently severe to encourage prompt withdrawal from a contaminated atmosphere.[1] Exposure to the gas immediately causes cough, burning of the throat, and a choking sensation. Effects are usually limited to inflammation and occasionally ulceration of the nose, throat, and larynx.[2] Acute exposures causing significant trauma are usually restricted to people who are prevented from escaping; in such cases, laryngeal spasm or pulmonary edema may occur.

In workers, exposure to 50–100 ppm for 1 hour was barely tolerable; short exposure to 35 ppm caused irritation of the throat, and 10 ppm was considered the maximal concentra-

tion allowable for prolonged exposure.[3] In one study, workers chronically exposed to hydrogen chloride did not exhibit the pulmonary function changes observed in naive subjects exposed to similar concentrations; this observation suggests acclimatization of the workers to hydrogen chloride.[4]

Ten young adult asthmatics showed no adverse respiratory health effects after multiple inhalation challenge with 0.8 and 1.8 ppm hydrogen chloride.[5]

Exposure of the skin to a high concentration of the gas or to a concentrated solution of the liquid (hydrochloric acid) will cause burns; repeated or prolonged exposure to dilute solutions may cause dermatitis.[2] Erosion of exposed teeth may also occur from repeated or prolonged exposure. Although ingestion is unlikely, hydrochloric acid causes severe burns of the mouth, esophagus, and stomach with consequent pain, nausea, and vomiting.[6]

Exposure of mice to 1300 ppm for 30 minutes caused tissue injury to the nasal region including epithelial and submucosal necrosis and accumulations of inflammatory cells and exudates.[7] Mice administered the same concentration by tracheal tubes (to simulate mouth breathing) had major tissue damage in the trachea including epithelial, submucosal, glandular, and cartilage necrosis; peripheral lung damage was manifested by histopathologic changes in the larger conducting airways.

Rodent studies may be of limited value in determining human effects because of their increased sensitivity compared with primates. A comparison of the lethality data indicates that the mouse (LLD = 3200 ppm, 5 min) is more sensitive than the rat (LLD = 15,250–32,250 ppm, 5 min) or the baboon (LLD = 16,570–30,000 ppm, 5 min).[8] For longer exposure periods, the LLD for the rat and baboon also diverge: For a 30-minute exposure, the LLD is less than 3000 ppm for rats and greater than 5000 ppm for baboons.

None of three US industry-based case-control studies suggested an association between exposure to hydrogen chloride and cancers of the lung, brain, or kidney.[9,10] This result was consistent with a rodent bioassay in which chronic exposure to 10 ppm, 6 hours/day for life did not cause any neoplastic lesions.[11] The IARC has determined that there is inadequate evidence for the carcinogenicity of hydrogen chloride in experimental animals and humans.[10]

Hydrogen chloride was not mutagenic in bacteria, but it did cause chromosomal aberrations in mammalian cell assays.[10]

Warning properties are good, and most people can detect 5 ppm.[1]

The 2003 short-term excursion limit (STEL)/ceiling for hydrogen chloride is 5 ppm (7.5 mg/m^3).

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HYDROGEN CYANIDE

CAS: 74-90-8

HCN

Synonyms: Hydrocyanic acid; aero liquid HCN; prussic acid; formonitrile

Physical Form. Colorless gas liquefying at 26°C (may be found in the workplace both as a liquid and a gas)

Uses. Rodenticide and insecticide; fumigant; chemical intermediate for the manufacture of synthetic fibers, plastics, and nitrites

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Hydrogen cyanide can cause rapid death due to metabolic asphyxiation.

Cyanide ion exerts an inhibitory action on certain metabolic enzyme systems, most notably cytochrome oxidase, the enzyme involved in the ultimate transfer of electrons to molecular oxygen.[1] Because cytochrome oxidase is present in practically all cells that function under aerobic conditions, and because the cyanide ion diffuses easily to all parts of the body, cyanide quickly halts practically all cellular respiration. The venous blood of a patient dying of cyanide poisoning is bright red and resembles arterial blood because the tissues have not been able to utilize the oxygen brought to them.[2] Cyanide intoxication produces lactic acidosis, the result of an increased rate of glycolysis and production of lactic acid.[3]

A concentration of 270 ppm hydrogen cyanide has long been quoted as being immediately fatal to humans. A more recent study, however, states that the estimated LC_{50} to humans for a 1-minute exposure is 3404 ppm.[1] Others state that 270 ppm is fatal after 6–8 minutes, 181 ppm after 10 minutes, and 135 ppm after 30 minutes.[1]

If large amounts of cyanide have been absorbed, collapse is usually instantaneous, the patient falling unconscious, often with convulsions, and dying almost immediately.[1,2] Symptoms of intoxication from less severe exposure include weakness, headache, confusion, vertigo, fatigue, anxiety, dyspnea, and occasionally nausea and vomiting. Respiratory rate and depth are usually increased initially, and at later stages respiration becomes slow and gasping. Coma and convulsions occur in some cases. If cyanosis is present, it usually indicates that respiration has either ceased or has been very inadequate for a few minutes.

Hydrogen cyanide has recently been recognized in significant concentrations in some fires, as a combustion product of wool, silk, and many synthetic polymers; it may play a role in toxicity and deaths from smoke inhalation.[4]

Most reported cases of chronic cyanide poisoning involve workers with a mixture of repeated acute or subacute exposures, making it unclear whether symptoms resulted simply from multiple acute exposures with acute intoxication or from prolonged, chronic exposure. Some symptoms persisted after cessation of such exposures, perhaps because of the effect of anoxia from inhibition of cytochrome oxidase. Symptoms from chronic exposure are similar to those reported after acute exposures, such as weakness, nausea, headache, and vertigo.[1] A study of 36 former workers in a silver reclaiming facility chronically exposed to cyanide demonstrated some residual symptoms 7 or more months after cessation of exposure; frequent headache, eye irritation, easy fatigue, loss of appetite, and epistaxis occurred in at least 30% of these workers.[5]

Liquid hydrogen cyanide, hydrogen cyanide in aqueous solution (hydrocyanic acid), and concentrated vapor are absorbed rapidly through the intact skin and may cause poisoning with little or no irritant effect on the skin itself.[1] The liquid in the eye may cause some local irritation; the attendant absorption may be hazardous.[6]

Genotoxic studies have shown primarily negative results. Carcinogenicity bioassays are not available for hydrogen cyanide.[7]

The 2003 ACGIH ceiling threshold limit value (C-TLV) for hydrogen cyanide is 4.7 ppm (5 mg/m^3) with a notation for skin absorption.

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HYDROGEN FLUORIDE
CAS: 7664-39-3

HF

Synonyms: Hydrofluoric acid; HF

Physical Form. Gas, liquefying at 19.5°C; aqueous solution is hydrofluoric acid

Uses. Catalyst for production of high-octane gasoline; aqueous solution for frosting, etching, and polishing glass, for removing sand from metal casings, and for etching silicon wafers in semiconductor manufacture

Exposure. Inhalation; skin contact

Toxicology. Hydrogen fluoride (HF), as a gas, is a severe respiratory irritant and, in solution, causes severe and painful burns of the skin and eyes.

From accidental, occupational, and voluntary exposures, it is estimated that the lowest lethal concentration for a 5-minute human exposure to HF is in the range of 50–250 ppm.[1] The LC_{50} values for 5, 15, and 60 minutes are considered to be 500–800 ppm, 450–1000 ppm, and 30–600 ppm, respectively.[1] Inhalation of HF produces transient choking and coughing. After an asymptomatic period of several hours up to 1–2 days, fever, cough, dyspnea, cyanosis, and pulmonary edema may develop.

Death from pulmonary edema occurred within 2 hours in three of six workers splashed with 70% solution, despite prompt showering with water. The HF concentration in the breathing zone was estimated to be above 10,000 ppm.[2] A chemist exposed to HF splashes on the face and upper extremities developed pulmonary edema 3 hours after exposure and died 10 hours later.[3] Persistent respiratory symptoms, including hoarseness, coughing fits, and nosebleeds, but with normal pulmonary function, were observed in one subject who survived a massive exposure. Acute renal failure of uncertain cause has also been documented after an ultimately fatal inhalation exposure.[4]

Significant systemic absorption by dermal or inhalation exposure may result in hypocalcemia and hypomagnesemia; cardiac arrhythmias may result as a consequence.[5,6]

In human subjects, exposure to 120 ppm for 1 minute caused conjunctival and respiratory irritation with stinging of skin.[7] It has been estimated that for most people exposure at 130 ppm for 10 minutes would cause irritation, but effects would not be severe or irreversible.[8] At 30 ppm for several minutes, mild irritation of the eyes, nose, and respiratory tract has occurred; 2.6–4.8 ppm 6 hours/day for periods up to 50 days caused slight irritation of nose, eyes, and skin but no signs or symptoms of pulmonary irritation.[7,9]

Repeated exposure to excessive concentrations of hydrogen fluoride over a period of years may result in an increased radiographic density of bone and eventually may cause crippling fluorosis (osteosclerosis due to deposition of fluoride in bone).[7] The early signs of increased bone density from fluoride deposition are most apparent in the lumbar spine and pelvis and can be detected by X ray.

Biological monitoring of urinary fluoride concentration provides an indication of total fluoride intake. Data indicate that a postshift urinary fluoride level of less than 8 mg/l, averaged over an extended period of time, will not lead to osteosclerosis, although a minimal or questionable increase in bone density might develop after many years of occupational exposure.[7]

HF solutions in contact with skin result in marked tissue destruction; undissociated HF readily penetrates skin and deep tissue, where the corrosive fluoride ion can cause necrosis of soft tissues and decalcification of bone; the destruction produced is excruciatingly painful.[6,10–12] Fluoride ion also attacks enzymes (e.g., of glycolysis) and cell membranes. The process of tissue destruction and neutralization of the hydrofluoric acid is prolonged for days, unlike other acids, which are rapidly neutralized.[10–12] Because of the insidious manner of penetration, a relatively mild or minor exposure can cause a serious burn. When skin contact is with solutions of less than 20%, the burn manifests itself by pain and erythema with a latent period of up to 24 hours; with 20–50% solutions, the burn becomes apparent 1–8 hours after exposure; solutions above 50% cause immediate pain, and tissue destruction is rapidly apparent.[10] Delayed recognition of contact with dilute solutions with consequently delayed irrigation often results in more severe burns.[6] Depending on the severity of the burn, it may demonstrate erythema alone, central blanching with peripheral erythema, swelling, vesiculation, serous crusting, and, with more serious burns, ulceration, blue-gray discoloration, and necrosis may be noted.[5,6]

Severe eye injuries from splashes may occur. In one case of eye burns from a fine spray of hydrofluoric acid in the face, considerable loss of epithelium occurred despite immediate and copious flushing with water and irrigation for 3 hours with a 0.5% solution of benzethonium chloride; within 19 days, there was recovery of normal vision.[13]

The 2003 ACGIH threshold limit value-ceiling (TLV-C) is 3 ppm (2.6 mg/m^3), as F.

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HYDROGEN PEROXIDE (90%)

CAS: 7722-84-1

90% H_2O_2

Synonyms: Dihydrogen dioxide; Peroxide

Physical Form. Liquid

Uses. Synthesis of compounds; bleaching agent, especially for textiles and paper; disinfectant; rocket fuel

Exposure. Inhalation

Toxicology. Hydrogen peroxide is an irritant of the eyes, mucous membranes. and skin.

In humans, inhalation of high concentrations of vapor or mist may cause extreme irritation and inflammation of the nose and throat.[1,2] Severe systemic poisoning may also cause headache, dizziness, vomiting, diarrhea, tremors, numbness, convulsions, pulmonary edema, unconsciousness, and shock.[3]

Exposure for a short period of time to mist or diffused spray may cause stinging of the eyes and lacrimation.[1,2] Splashes of the liquid in the eyes may cause severe damage including ulceration of the cornea; there may be a delayed appearance of damage to the eyes, and corneal ulceration has, on rare occasions, appeared even a week or more after exposure.[1]

Skin contact with the liquid for a short time will cause a temporary whitening or bleaching of the skin; if splashes on the skin are not removed, erythema and the formation of vesicles may occur.[1] Although ingestion is unlikely to occur in industrial use, it may cause irritation of the upper gastrointestinal tract; decomposition of the hydrogen peroxide will result in the rapid liberation of oxygen, which may distend the esophagus or stomach and cause severe damage.

Repeated exposure of dogs to 7 ppm for 6 months caused sneezing, lacrimation, and bleaching of hair; at autopsy, there was local atelectasis.[4]

A number of investigators have shown that hydrogen peroxide *in vitro* leads to genetic damage and cell death through the formation of free radicals.[5] It is not known whether such damage presents a danger to the mammalian organism or whether various enzymes protect against damage.

Chronic studies in mice found adenomas and carcinomas of the duodenum after oral administration. The IARC has determined that there is limited evidence in experimental animals for the carcinogenicity of hydrogen peroxide and inadequate evidence in humans.[6]

An additional hazard is the possibility of explosion when higher-strength hydrogen peroxide is mixed with organic compounds and violent decomposition if contaminated by metallic ions or salts.[3] Because hydrogen peroxide is such a strong oxidizer, it can set fire to combustible materials when spilled on them.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 1 ppm (1.4 mg/m^3).

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HYDROGEN SELENIDE
CAS: 7783-07-5

H_2Se

Synonyms: Selenium hydride

Physical Form. Colorless gas

Sources. Produced by reaction of acids or water with metal selenides

Exposure. Inhalation

Toxicology. Hydrogen selenide gas is an irritant of the eyes and mucous membranes and causes gastrointestinal effects; pulmonary irritation and liver damage have occurred in animals.

In humans, a concentration of 1.5 ppm is said to produce intolerable irritation of the eyes and nose.[1] Five workers exposed to hydrogen selenide (and possibly other selenium compounds as well) at concentrations of less than 0.2 ppm for 1 month developed nausea, vomiting, diarrhea, metallic taste, garlic odor of the breath, dizziness, lassitude, and fatigue; after cessation of exposure, there was a gradual regression of symptoms during the succeeding months.[2] Urinary selenium levels of the workers ranged from 0 to 13.1 µg selenium/100 ml urine; there was no correlation between symptoms and urinary levels of selenium.[2]

An outbreak of acute intoxication attributed to hydrogen selenide in India in 1994 caused intense cough, suffocation, burning and tearing of the eyes, tachycardia, and severe bronchospasm in 31 patients. Improvement occurred in most after 5 days, but some follow-up cases showed restrictive and obstructive changes on pulmonary function tests 18 months later.[3]

Guinea pigs exposed to 10 ppm for 2 hours exhibited immediate irritation of the eyes and nose; a high percentage of the animals died, apparently from pneumonitis.[4] In guinea pigs, the LC_{50} for 8 hours was 1 mg/m^3 (0.3 ppm); pulmonary irritation and liver damage were observed.

On contact with moist mucous membrane surfaces, hydrogen selenide is probably oxidized to elemental selenium.[5] Thus, in considering health effects, the possible chronic effects of absorbed selenium should be considered in addition to the acute effects of hydrogen selenide itself (see separate monograph on selenium).

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for hydrogen selenide is 0.05 ppm (0.16 mg/m^3).

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HYDROGEN SULFIDE

CAS: 7783-06-4

H_2S

Synonyms: Sulfureted hydrogen; hydrosulfuric acid

Physical Form. Gas

Sources. By-product of many industrial processes; around oil wells and in areas where petroleum products are processed, stored, or used; decay of organic matter; occurs naturally in coal, natural gas, oil, volcanic gases, and sulfur springs.

Exposure. Inhalation

Toxicology. Hydrogen sulfide is an irritant of the eyes and respiratory tract at low concentrations; at higher levels, it causes respiratory paralysis with consequent asphyxia and is rapidly fatal.

Hydrogen sulfide intoxication in humans has generally been categorized as acute, subacute, or chronic, depending on the nature of the predominant clinical signs and symptoms.[1] Acute intoxication refers to the effects of a single exposure to massive concentrations that rapidly produce signs of respiratory distress. Inhalation of 1000 ppm or more can cause coma after a single breath and can be rapidly fatal owing to respiratory paralysis.[1–5] At slightly lower levels the gas may be rapidly absorbed through the lungs into the blood, which initially induces hypernea followed by apnea.

The sequelae of acute poisoning appear to be quite variable and depend on duration of exposure as well as level of exposure. Patients who have been unconscious in high levels of hydrogen sulfide atmosphere for longer than 5 min may have persistent neurological and neuropsychological impairment years after exposure as a result of hydrogen sulfide-induced hypoxia.[6]

Subacute intoxication refers to the effects caused by continuous exposure for up to several hours to concentrations ranging from 100 to 1000 ppm.[1–5] Pulmonary edema is a potentially fatal complication of intoxication and is common after exposure to 250 ppm for prolonged periods of time. Symptoms of gastrointestinal disturbances, including nausea, abdominal cramps, vomiting, and severe diarrhea, have been reported and frequently occur in subacute intoxication.

Exposure to levels above 50 ppm for 1 hour can produce acute conjunctivitis with pain, lacrimation, and photophobia; in severe form, this can progress to keratoconjunctivitis and vesiculation of the corneal epithelium. Prolonged exposure to 50 ppm also causes rhinitis, pharyngitis, bronchitis, and pneumonitis.

Reports of adverse effects of hydrogen sulfide on humans due to chronic intoxication are less well established. It has been postulated that exposures below 50 ppm over long periods may cause certain neuroasthenic symptoms such as fatigue, headache, dizziness, and irritability. Others suggest that the signs and symptoms referred to as chronic poisoning are actually the results of recurring acute exposures or the sequelae of acute poisoning.

A number of toxicological mechanisms have been proposed for hydrogen sulfide: At extremely high concentrations it may exert a direct paralyzing effect on respiratory centers; hydrogen sulfide is also known to inhibit cytochrome c oxidase, resulting in altered oxidative metabolism; it can also disrupt critical disulfide bonds in essential cellular proteins.[5]

Skin absorption appears to be minimal in humans.

In one epidemiological study, no significant increase in cancer incidence was found for individuals residing downwind from two natural gas refineries that emit primarily sulfur compounds, including hydrogen sulfide.[7]

Rats exposed to 100 ppm of hydrogen sulfide 6 hours/day during days 6–20 of gestation showed no signs of maternal toxicity or adverse effects on the developing fetus.[8] In another report, rat dams and pups were exposed 7 hours/day to 20, 50, or 75 ppm from day 1 of gestation until day 21 postpartum. Blood glucose was significantly elevated in dams on day 21 postpartum at all exposure levels, but the toxicological significance of this effect has not been established.[9]

Hydrogen sulfide was not mutagenic in Ames assays with or without metabolic activation.[10]

The odor is offensive and characterized as "rotten eggs" with a threshold ranging from 0.0005 to 0.13 ppm; it is unreliable as a warning signal because the gas exerts a paralyzing effect on the olfactory apparatus above 150 ppm; at these concentrations the odor has been characterized as sickeningly sweet.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 10 ppm (14 mg/m^3) with a short-term excursion limit (STEL)/ceiling of 15 ppm (21 mg/m^3).

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HYDROQUINONE
CAS: 123-31-9

$C_6H_4(OH)_2$

Synonyms: 1,4-Benzenediol; 1,4-dihydroxybenzene; *p*-hydroxybenzene; hydroquinol; quinol; Tecquinol

Physical Form. White crystalline solid

Uses. Photographic reducer and developer; antioxidant; stabilizing agent for some polymers; intermediate in the manufacturing of some dyes and pigments; in cosmetic formulations

Exposure. Inhalation

Toxicology. Hydroquinone is moderately toxic and primarily affects the eyes.

Acute exposure to quinone vapor and hydroquinone dust causes conjunctival irritation, whereas chronic exposure produces changes characterized as: (1) brownish discoloration of the conjunctiva and cornea confined to the interpalpebral tissue; (2) small opacities of the cornea; and (3) structural changes in the cornea that result in loss of visual acuity.[1,2] The pigmentation changes are reversible, but the more slowly developing structural changes in the cornea may progress. Pigmentation may appear with less than 5 years of exposure, but this is uncommon and usually is not associated with serious injury to the eye.[2]

Ingestion of 5–12 g of hydroquinone has been reported to be fatal.[3–5] In one nonfatal case of hydroquinone ingestion of approximately 1 g, tinnitus, dyspnea, cyanosis, and extreme sleepiness were observed.[3] Although acute, high-dose oral ingestion produces noticeable central nervous system (CNS) effects in humans, no effects have been observed in workers exposed to lower concentrations in actual industrial situations.[3] No signs of toxicity were found in subjects who ingested 300–500 mg hydroquinone daily for 3–5 months.[6]

Repeated skin contact with hydroquinone creams (generally 5% or more hydroquinone) produced skin irritation, allergic sensitization, dermatitis, and depigmentation.[3] Excessive use of skin-lightening preparations containing hydroquinone has produced severe and irreversible cutaneous damage.[5] Deleterious effects start with darkening and coarsening of the skin, followed by a hyperpigmented papular condition. Histologically there is increased basophilia of the collagen, followed by the formation of yellow fibers that swell and break down to form an amorphous eosinophilic material.

One mortality study of a cohort of workers with at least 6 months' exposure to hydroquinone at exposure concentrations of 0.1–6.0 mg/m^3 for the dust and from less than 0.1 to 0.3 for the vapor (estimated 8-hour time-weighted averages) found statistically significant deficits in total mortality and deaths due to cancer.[7]

Oral LD_{50} values of 70, 200, and 550 mg/kg have been reported for cats, dogs, and guinea pigs, respectively.[5] In 14-day and 13-week studies mice administered up to 500 mg/kg by gavage and rats administered up to 1000 mg/kg had lethargy, tremors, and convulsions.[8] The CNS, forestomach, and liver were identified as target organs in both species, and renal toxicity was identified in rats.

In 2-year studies rats were given 0, 25, or 50 mg/kg hydroquinone by gavage 5 days/week whereas doses for mice were 0, 50, or 100 mg/kg on the same schedule.[8] There was evidence of carcinogenicity in male rats as indicated by increased incidences of tubular cell adenomas of the kidney, in female rats as shown by increases in mononuclear cell leukemia, and in female mice based on increases in hepatocellular neoplasms, mainly adenomas. There was no evidence of carcinogenicity in male mice.

Pellets of cholesterol containing 2 mg of hydroquinone implanted in mice bladders caused an excessive number of bladder carcinomas.[4] In other studies, rats fed up to 1% hydroquinone in their diets for 2 years did not develop tumors, nor did hydroquinone initiate significant numbers of tumors in mice skin painting studies.[3,4]

The IARC has determined that there is inadequate evidence in humans for the carcinogenicity of hydroquinone and limited evidence in experimental animals.[4]

Pregnant rats given up to 300 mg/kg hydroquinone by gavage on the 6th through 15th day of gestation had a slight but significant reduction in body weight gain and feed consumption. This effect was associated with a slightly reduced mean fetal body weight, but no other significant effects were noted in the rat conceptus.[9] In rabbits hydroquinone at 150 mg/kg on gestation days 6–18 produced minimal developmental alterations in the presence of maternal toxicity.[10] On the basis of these studies it was concluded that hydroquinone is not selectively toxic to the develop-

ing conceptus and does not appear to be a developmental toxicant.[9]

Hydroquinone induces alterations of the DNA in eukaryotic cells (micronuclei, chromosomal aberrations and disintegrations) but is nonmutagenic in *Salmonella* tester strains with or without metabolic activation.[5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for hydroquinone is 2 mg/m^3.

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HYDROXYLAMINE (and Salts)
CAS: 7803-49-8

NH_2OH

Synonyms: Oxammonium; hydroxyl ammonium

Physical Form. Colorless flakes or crystals.

Uses. Reducing agent used in photographic processing, leather tanning, manufacturing of nylon and other polymers; as a stabilizer for natural rubber; to prevent the development of objectionable tastes and odors during the refining of fatty materials.

Exposure. Inhalation

Toxicology. Hydroxylamine and its salts are irritants of eyes, mucous membranes, and skin; higher levels cause methemoglobinemia.

Workers exposed to hydroxylamine sulfate for 1 day at unspecified air levels showed blood methemoglobinemia concentrations of 25%.[1] Dusts and mists of hydroxylamine sulfate are irritants of the mucous membranes and eyes. Although details are lacking, repeated exposure to the sulfate is reported to have caused respiratory sensitization with asthma-like symptoms.

Hydroxylamine hydrochloride is highly irritating to the skin, eyes, and mucous membranes and has caused contact dermatitis in workers exposed for 2–60 days.[2] Hydroxylamine itself is only moderately irritating to the skin. Hydroxylamine sulfate on the skin of rabbits was irritating at levels as low as a 10-mg dose.[3] It is considered to be a potential skin sensitizer.

In animal studies single and repeated exposures to hydroxylamine and its salts primarily targeted the hematopoietic system.[4] The oral LD_{50} values for hydroxylamine and its salts range from 400 to 1000 mg/kg body weight in rats and mice. At acutely toxic levels the substances cause central nervous system excitation and convulsions that are considered to be secondary to hypoxemia due to methemoglobin formation. Rats administered 1600 ppm hydroxylamine sulfate in the drinking water for 4 weeks had severe hemolytic anemia with methemoglobinemia and cyanosis. Doses of 50 and 250 ppm for 3 months resulted in decreased red blood cell count and hemoglobin concentration and increased reticulocyte count and Heinz bodies. At the higher concentration there was an increase in spleen, liver, and kidney weights. Treatment of dogs with 50–70 mg/kg for 2–4 months and guinea pigs at 300–500 mg/kg for up to 235 days with hydroxylamine hydrochloride also caused methemoglobin formation and damage to the hematopoietic system.

Carcinogenicity of hydroxylamine and its salts has not been demonstrated. Several studies have shown a decreased incidence of spontaneous mammary tumors in mice exposed to the sulfate and hydrochloride.[3–7] There was some indication of an increase in the incidence of spontaneous mammary tumors when the sulfate was administered to older animals whose mammary glands were already well developed.

Results of genotoxic tests have been mixed. In general hydroxylamine and its salts have shown positive results in *in vitro* assays and negative results in *in vivo* mammalian assays.[4]

Embryotoxic effects have occurred in rabbits exposed to hydroxylamine hydrochloride by intracoelomic injection.[8] Subcutaneous or intravenous injection of pregnant rabbits with 50–650 mg of hydroxylamine hydrochloride on gestational day 12 caused death or euthanasia of all rabbits within 30 hours.[9] All maternally injected rabbits exhibited severe cyanosis, presumably due to methemoglobinemia. At 8 hours all embryos were dead from cardiovascular effects, which are considered to be secondary to the severe maternal toxicity. Hydroxylamine is a direct-acting developmental toxicant only under conditions of direct embryonic exposure; intracoelomic injection into the chorionic cavity of developing embryos of 100 µg of hydroxylamine caused deaths in 31 of 32 embryos. In general, exposure to hydroxylamine would kill the mother before levels within the embryo became sufficiently high to cause direct developmental toxicity.

A threshold limit value-time-weighted average (TLV-TWA) has not been established for this substance.

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2-HYDROXYPROPYL ACRYLATE

CAS: 999-61-1

$C_6H_{10}O_3$

Synonyms: HPA; 1,2-propanediol-1-acrylate; propylene glycol monoacrylate

Physical Form. Clear to light yellow liquid

Uses. Monomer used in manufacture of thermosetting resins for surface coatings.

Exposure. Inhalation; skin absorption

Toxicology. 2-Hydroxypropyl acrylate is an irritant of the eyes, nose, respiratory tract, and skin.

Inhalation exposure of rats, mice, dogs, and rabbits to 5 ppm for 6 hours/day, 5 days/week over 30 days caused nasal and respiratory tract irritation.[1]

The dermal LD_{50} in rabbits was approximately 0.17 g/kg.[2] Animals that survived developed severe irritation, moderate edema, and moderate to severe necrosis. Direct contact with the eye caused severe eye burns.

Sensitization to 2-hydroxypropyl acrylate during routine patch testing has been reported.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 2-hydroxypropyl acrylate is 0.5 ppm or 2.8 mg/m^3 with a notation for skin absorption.

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INDENE

CAS: 95-13-6

C_9H_8

Synonym: Indonaphthene

Physical Form. Colorless liquid

Uses. Preparation of coumarone-indene resins

Exposure. Inhalation

Toxicology. Indene is expected to be an irritant of the mucous membranes.

Oral doses of 2.5 ml of a 1:1 v/v mixture in olive oil were fatal to rats.[1] A historical study indicates that exposure of rats to 800–900 ppm for 7 hours/day for six exposures caused hemorrhagic liver necrosis in some of the rats as well as focal necrosis of the kidneys.[2] No deaths occurred from these exposures.

Indene vapor inhalation exposure of human subjects has not been reported. By analogy to related hydrocarbons, inhalation of indene can be expected to cause irritation of the mucous membranes.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for indene is 10 ppm (48 mg/m^3).

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INDENO(1,2,3-*cd*)PYRENE
CAS: 193-39-5

$C_{22}H_{12}$

Synonyms: IP; 2,3-phenylenepyrene; *o*-phenylenepyrene; indeneopyrene

Physical Form. Yellow solid

Uses. A component of polynuclear aromatic hydrocarbons, also known as polycyclic aromatic hydrocarbons, usually bound to small particulate matter present in urban air, industrial and natural combustion emissions, and cigarette smoke.

Exposure. Inhalation

Toxicology. Indenol(1,2,3-*cd*)pyrene (IP) is a complete carcinogen and an initiator for skin carcinogenesis in the mouse.[1]

Groups of female mice were painted with IP either in dioxane or in acetone, three times weekly for 12 months.[2] A concentration of 0.1% produced a total of six papillomas and three carcinomas, the first tumors appearing at 9 months. A concentration of 0.5% produced a total of seven papillomas and five carcinomas, the first tumors appearing at 3 months.

The same study demonstrated that 10 paintings at 2-day intervals for a total dose of 250 µg IP initiated skin carcinogenesis. In 30 mice subsequently treated with croton oil in acetone, a total of 10 papillomas in 5 animals was produced.

A statistically significant dose-related increased incidence of epidermoid carcinomas of the lung and thorax was seen in rats that received lung implants of IP for life.

IP was mutagenic in bacterial assays and was positive for in vitro cell transformation; in vivo it binds to mouse skin DNA.[3]

The IARC has determined that there is sufficient evidence for the carcinogenicity of IP in animals.[4] No human data are available because exposures typically involve chemical mixtures containing numerous polynuclear aromatic hydrocarbons. IP is considered possibly carcinogenic to humans.

The ACGIH has not assigned a threshold limit value (TLV).

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INDIUM (and Compounds)
CAS: 7440-74-6

In

Synonyms: Indium sesquioxide; indium trichloride; indium nitrate; indium antimonide; indium arsenide; indium phosphide

Physical Form. Solid

Uses. In the manufacture of semiconductors, injection lasers, and solar cells; in the manufacture of glass, graphite, and cathode oscillographs; in metal alloys to prevent corrosion and metal fatigue

Exposure. Inhalation

Toxicology. Indium (In) and compounds cause injury to the lungs, liver and kidneys in animals.

There are no reports of toxicity in humans. When indium was applied to the skin there was no evidence of irritation.

A range of oral LD_{50} values have been reported in animals depending on the route of administration and compound type.[1] Administered parenterally to rats, rabbits, and dogs indium trichloride ($InCl_3$) had an acute lethal dose range from 0.33 to 3.6 mg of In/kg.[2] Indium sesquioxide (In_2O_3) was less toxic, with intraperitoneal doses of 955 mg/kg fatal to all rats within 9 days. Gross signs of In poisoning from intraperitoneal or intravenous administration have included reduced food and water consumption, with accompanying weight loss, and degenerative changes in the liver and kidneys.[1–3]

When ingested by rats In_2O_3 was practically nontoxic; incorporated in the diet 8% for 3 months caused no effects on growth mortality or tissue morphology.[1] $InCl_3$ caused marked growth depression at 4% in the diet over the same period.

A single intratracheal dose of 1.3 mg In/kg as $InCl_3$ given to female Fischer 344 rats caused severe upper and lower pulmonary damage that was present 8 weeks after dosing.[4] In addition, damage to the alveolar and bronchial/bronchiolar epithelial cells initiated inflammatory and repair processes that led to the rapid development of fibrosis.

In another report, rats exposed to the sesquioxide (In_2O_3) dust by inhalation at levels ranging from 24 to 97 mg/m^3 for a total of 224 hours, had widespread alveolar edema and alteration of the alveolar walls resembling alvelolar proteinosis in which alveolar clearance was reduced.[5] The lesion exhibited no change during exposure or after a 12-week postexposure period, including no evidence of wound healing or fibrosis. Lack of a fibrotic response in this study may be due to the relative insolubility of In_2O_3 (compared with $InCl_3$) and less reactivity with biomembranes.[4]

In 2-year inhalation studies of indium phosphide there was clear evidence of carcinogenic activity in male and female F344/N rats based on increased incidences of benign and malignant neoplasms of the lung.[6] Increased incidences of pheochromocytoma of the adrenal medulla in males and females were also considered to be exposure related. There was also clear evidence of carcinogenic activity in B6C3F1 mice based on increased incidences of malignant neoplasms of the lung and benign and malignant neoplasms of the liver in males and increased incidences of benign and malignant neoplasms of the lung in females.[6]

In cellular studies indium exposure has been associated with a general suppression of protein synthesis and the induction of heme oxygenase, which in turn is associated with the reduction of enzyme activities dependent on cytochrome P-450.[7] The significance of these alterations in the synthesis and maintenance of various enzyme systems in relation to a possible carcinogenic response has not been determined.[8]

Indium arsenide and indium phosphide caused testicular damage in hamsters after repeated intratracheal administration. Both materials decreased reproductive organ weight and caudal sperm count and caused severe histopathologic changes in the testes.[9]

Single intravenous injection of $InCl_3$ in pregnant rats caused reduced fetal weights and fetal malformations primarily in the tail.[10] In mice similarly treated, indium did not cause fetal malformations although it reduced fetal weight and caused fetal mortality.

No significant increases in the frequency of micronucleated normochromatic erythrocytes were found in mice exposed to indium phosphide for 14 weeks.[6]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for indium and compounds as In is 0.1 mg/m^3.

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IODINE

CAS: 7553-56-2

I_2

Synonyms: None

Physical Form. Crystalline solid, blue-black scales or plates

Uses. Synthesis of organic chemicals; photographic film; as a disinfectant in drinking water

Exposure. Inhalation; ingestion; skin absorption

Toxicology. Iodine is an irritant of the eyes, mucous membranes, and skin; it is a pulmonary irritant in animals, and it is expected that severe exposure will cause the same effect in humans.

Exposed workers (concentration and time unspecified) experienced a burning sensation in the eyes, lacrimation, blepharitis, rhinitis, stomatitis, and chronic pharyngitis; after brief accidental exposure in a laboratory, technicians reported headache and a feeling of tightness in the chest.[1,2]

Iodine is an essential nutritional element and is required by the thyroid.[3] However, ingestion of as little as 2–3 g may be fatal. Ingestion may cause corrosive effects such as edema of the glottis, with asphyxia, aspiration pneumonia, pulmonary edema and shock, vomiting, and bloody diarrhea.[4] The central nervous system, cardiovascular and renal toxicity following acute iodine ingestion appear to be due to the corrosive gastroenteritis and resultant shock. Vomiting, hypotension, and circulatory collapse may be noted after severe intoxication.

Chronic absorption of iodine causes "iodism," a syndrome characterized by insomnia, conjunctivitis, rhinitis, bronchitis, tremor, tachycardia, parotitis, diarrhea, and weight loss.[4,5] Iodine absorbed by the lungs is changed to iodide and eliminated, mainly in the urine.

In an experimental investigation, four human subjects tolerated 0.57 ppm iodine vapor for 5 minutes without eye irritation but all experienced eye irritation in 2 minutes at 1.63 ppm.[3] In patients exposed to air saturated with iodine vapor for 3–4 minutes for therapeutic purposes, there was brown staining of the corneal epithelium and subsequent spontaneous loss of the layer of tissue; recovery occurred within 2–3 days.[6] Iodine in crystalline form or in strong solutions is a severe skin irritant; it is not easily removed from the skin, and the lesions resemble thermal burns with brown

staining.[5] Cutaneous absorption may be significant and result in systemic symptoms and death.[4]

Both systemic and topical exposure to iodine can give rise to allergic reactions with fever and skin eruptions of varying types.[4]

Intratracheal administration to dogs of the vapor at 36 mg iodine/kg body weight was fatal after about 3 hours; the animals developed cough, difficulty in breathing, and rales; autopsy findings were pulmonary edema, subpleural hemorrhage, and an increased iodine content of the thyroid and urine.[1]

Administered in the drinking water of rats for 100 days, 1, 3, 10, or 100 mg/l of iodine caused no signs of overt toxicity but some modifications of thyroid function occurred.[7] Specifically, there was a dose-related trend in increased plasma thyroxine levels and a statistically significant increase in the thyroxine-to-triiodothyronine ratio.

The 2003 ACGIH ceiling-threshold limit value (C-TLV) for iodine is 0.1 ppm (1.0 mg/m^3).

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IODOFORM
CAS: 75-47-8

CHI_3

Synonym: Triiodomethane; carbon triiodide

Physical Form. Yellow or green-yellow solid

Uses. Formerly used in medicine as a germicide; still used in veterinary medicine as an antiseptic on superficial lesions

Exposure. Inhalation

Toxicology. Iodoform causes central nervous system depression and damage to the kidneys, liver, and heart.

The 7-hour LC_{50} for iodoform in rats was 165 ppm, and death of the animals was attributed to cardiopulmonary collapse.[1] Exposure of rats to 14 ppm for 7 hours/day over 7 consecutive days showed only mineralized deposits in the medullary renal tubules.

When used as a topical anesthetic in medical applications, iodoform produced central nervous system depression with vomiting, coma, and damage to the kidneys, liver, and heart.[2]

A 78-week bioassay for possible carcinogenicity of technical-grade iodoform was conducted with rats and mice.[3] Iodoform in corn oil was administered by gavage to groups of 50 male and 50 female animals of each species. Administration was 5 days/week, for a period of 78 weeks followed by an observation period of 34 weeks for rats and 13 or 14 weeks for mice. The high time-weighted average dosages of iodoform were, respectively, 142 and 55 mg/kg/day for male and female rats and 93 and 47 mg/kg/day for male and female mice. There was no evidence of carcinogenicity.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for iodoform is 0.6 ppm or 10 mg/m^3.

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IRON OXIDE FUME
CAS: 1309-37-1

Fe_2O_3

Synonyms: Ferric oxide fume

Physical Form. Fume

Source. Result of welding and silver finishing

Exposure. Inhalation

Toxicology. Inhalation of iron oxide fume or dust causes a benign pneumoconiosis (siderosis).

Iron oxide alone does not cause fibrosis in the lungs of animals, and it is probable that the same applies in humans.[1] Exposures of 6–10 years are usually required before changes recognizable by X ray occur; the retained dust produces X-ray shadows that may be indistinguishable from fibrotic pneumoconiosis.[2,3] Of 25 welders exposed chiefly to iron oxide for an average of 18.7 (range 3–32) years, 8 had reticulonodular shadows on chest X ray consistent with siderosis, but there was no reduction in pulmonary function; exposure levels ranged from 0.65 to 47 mg/m^3.[4]

In another study, the X-rays of 16 welders with an average exposure of 17.1 (range 7–30) years also suggested siderosis; their spirograms were normal. However, the static and functional compliance of the lungs was reduced; some of the welders were smokers.[5] The welders with the lowest compliance complained of dyspnea.

Welders are typically exposed to a complex mixture of dust and fume of metallic oxides, as well as irritant gases, and are subject to mixed-dust pneumoconiosis with possible loss of pulmonary function; this should not be confused with benign pneumoconiosis caused by iron oxide.[1] Although an increased incidence of lung cancer has been observed among hematite miners exposed to iron oxide, presumably owing to concomitant radon gas exposure, there is no evidence that iron oxide alone is carcinogenic to man or animals.[6]

Iron oxide was not mutagenic in bacterial assays with or without metabolic activation.[7]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for iron oxide fume is 5 mg/m^3 as total particulate as Fe.

REFERENCES

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IRON PENTACARBONYL
CAS: 13463-40-6

$FE(CO)_5$

Synonyms: Pentacarbonyl iron; iron carbonyl

Physical Form. Colorless to yellow liquid

Uses. As strong reducing agent; in manufacture of high-frequency coils used in radios and televisions; as antiknock agent in motor fuels

Exposure. Inhalation

Toxicology. Iron pentacarbonyl is a pulmonary irritant, similar to nickel carbonyl.

Iron pentacarbonyl is approximately one-third as potent as nickel carbonyl when inhaled by rats for 30 minutes.[1] Effects from inhalation of high concentrations of the chemical are expected to be similar to those of nickel carbonyl, which include frontal headache, vertigo, nausea, vomiting, and sometimes substernal and epigastric pain.[2,3] Generally these early effects disappear when the subject is removed to fresh air.

There may be an asymptomatic interval between recovery from initial symptoms and onset of delayed symptoms, which tend to develop 12–36 hours after exposure. Constrictive pain in the chest is characteristic of the delayed onset of pulmonary effects, followed by cough, hyperpnea, and cyanosis, leading to profound weakness. Except for the pronounced weakness and hyperpnea, the physical findings and symptoms resemble those of a viral or an influenzal pneumonia.

In rodent studies iron pentacarbonyl was found to have approximately one-third the acute toxicity of nickel carbonyl. At 33 ppm for 5.5 hours three of eight rats died; at 18 ppm four of eight died after two 5.5-hour exposures.[4] Multiple 5.5-hour exposures at 7 ppm caused no apparent effects.

Iron pentacarbonyl is relatively benign when administered orally. In a study of iron deficiency anemia, single doses of 10 g were tolerated by 20 nonanemic volunteers with no evidence of toxicity and only minor gastrointestinal side effects.[5] Daily doses of up to 3 g/day for 8–28 days resulted in no evidence of toxicity other than gastrointestinal irritation.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 0.1 ppm (0.23 mg/m^3) as Fe with a short-term excursion limit (STEL)/ceiling of 0.2 ppm (0.45 mg/m^3) as Fe.

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ISOAMYL ACETATE
CAS: 123-92-2

$CH_3COOCH_2CH(CH_3)C_2H_5$

Synonyms: Amyl acetate; banana oil; pear oil; amylacetic ester; 3-methyl butyl acetate; 3-methyl-1-butanol acetate

Physical Form. Colorless liquid

Uses. Solvent; flavor in water and syrups

Exposure. Inhalation

Toxicology. Isoamyl acetate is an irritant of the eyes and mucous membranes; at high con-

centrations it causes narcosis in animals, and it is expected that severe exposure will cause the same effect in humans.

Several technical grades of amyl acetate are known; isoamyl acetate is the major component of some grades, whereas other isomers predominate in other grades.[1]

Men exposed to 950 ppm isoamyl acetate for 30 minutes had irritation of the nose and throat, headache, and weakness.[1] Isoamyl acetate may defat the skin, causing irritation.

Cats exposed to 1900 ppm for six 8-hour exposures showed irritation of the eyes, salivation, weakness, and loss of weight; lung irritation was noted at necropsy. A 24-hour exposure to 7200 ppm caused light narcosis and delayed death due to pneumonia.[2] Dogs exposed to 5000 ppm for 1 hour had nasal irritation and drowsiness.[2]

Isoamyl acetate was not mutagenic in a number of assays.[3] It has a banana- or pearlike odor detectable at 7 ppm.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for isoamyl acetate is 100 ppm (532 mg/m^3).

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ISOAMYL ALCOHOL

CAS: 123-51-3

$(C_2H_5)_2CHOH$

Synonyms: 3-Methybutanol-1; isobutyl carbinol; isopentyl alcohol

Physical Form. Colorless liquid

Uses. Solvent; chemical synthesis; manufacture of smokeless powders, artificial silk, and lacquers

Exposure. Inhalation

Toxicology. Isoamyl alcohol is an irritant of the eyes and mucous membranes; at high concentrations it causes narcosis in animals, and it is expected that severe exposure will produce the same effect in humans.

Human volunteers exposed to 100 ppm for 3–5 minutes experienced throat irritation, and at 150 ppm there was also eye and nose irritation.[1,2] No chronic systemic effects have been reported in humans.

Rats survived 8-hour exposure to 2000 ppm. Oral administration of 0.7 g/kg produced stupor and loss of voluntary movement in half the treated rabbits; the LD_{50} was 3.4 g/kg.[3]

Female rats exposed to 4000 and 16,000 ppm in the drinking water for 90 days showed significant increases in prothrombin time; males with similar exposure had a significant dose-dependent increase in red blood cell count and a decrease in mean corpuscular hemoglobin.[4] No clinical signs of toxicity were observed during the exposure period, and no gross or histopathologic lesions were discovered at necropsy.

Instilled in rabbit eyes, isoamyl alcohol caused severe burns with moderately severe corneal necrosis.[5] Topical application produced minimal skin irritation.[5]

No signs of fetotoxicity or teratogenicity were observed in rats or rabbits administered concentrations up to 10 mg/l 6 hours/day by inhalation during gestation.[6] Signs of maternal toxicity at this concentration included eye irritation in the rabbits and slight retardation of body weight gain in both species.[6]

A total of 10 malignant tumors were found in 24 rats injected subcutaneously with 0.04 ml/kg isoamyl alcohol for 95 weeks; control animals had no malignancies.[5]

Isoamyl alcohol has a disagreeable pungent odor.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for isoamyl alcohol is 100 ppm (361 mg/m^3) with a short-term excursion limit (STEL) of 125 ppm (452 mg/m^3).

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ISOBUTANE

CAS: 75-28-5

C_4H_{10}

Synonyms: 2-Methylpropane; trimethylmethane

Physical Form. Colorless gas

Uses. In the production of propylene glycols and oxides and polyurethane foams and resins; as component of motor fuels and aerosol propellants; as an industrial gas carrier and general fuel source

Exposure. Inhalation

Toxicology. Isobutane is of generally low toxicity; at extremely high concentrations, it may produce cardiac effects and narcosis.

Humans exposed to isobutane at concentrations of 250, 500, or 1000 ppm for periods of 1 minute to 8 hours did not exhibit any untoward physiological responses as determined by continuous ECG telemetry, spirometric measures, blood count, urinalysis, and a battery of cognitive tests.[1] Repetitive exposures at 500 ppm for up to 8 hours/day for 10 days also were without any measurable untoward effect.

In mice, exposure to 520,000 ppm was lethal to 100% of the animals within an average of 28 minutes.[2] Near the LC_{50} dose, mice exhibit central nervous system depression, rapid and shallow respiration, and apnea.[3] At concentrations of 350,000 ppm, loss of posture occurred after 25 minutes; exposure to 150,000 ppm for 60 minutes or 230,000 ppm for 26 minutes produced light anesthesia.

In dogs, 450,000 ppm for 10 minutes caused anesthesia; exposure to 200,000 ppm for 10 minutes produced respiratory depression, bronchospasm, and decreased pulmonary compliance.[2,4]

Isobutane has been found to sensitize the myocardium to epinephrine in various animal studies. Concentrations of 50,000 ppm predisposed the dog heart to cardiac arrythmias induced by catecholamines.[5] Monkeys administered 50,000–100,000 ppm for 5 minutes via tracheal cannulation had tachycardia, arrhythmias, and myocardial depression.[6] Cases of sudden death due to fatal cardiac arrhythmias have been reported in humans intentionally inhaling isobutane.[7]

Repeated exposure of monkeys to 4000 ppm for up to 90 days caused no signs of toxicity.[8]

The vapor exerts no effect on the skin or the eyes.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for isobutene is 800 ppm (1900 mg/m^3).

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ISOBUTYL ACETATE
CAS: 110-19-0

$CH_3COOCH_2CH(CH_3)_2$

Synonyms: Acetic acid, isobutyl ester; 2-methylpropyl acetate

Physical Form. Colorless liquid

Uses. Solvent; flavoring

Exposure. Inhalation

Toxicology. At high concentrations isobutyl acetate causes narcosis in animals, and it is expected that severe exposure will cause the same effect in humans; it is considered to be a respiratory tract and eye irritant by analogy with *n*-butyl acetate.

Cause-specific mortality was lower than expected for all causes of death at a weapons facility where isobutyl acetate was one of several commonly used solvents.[1]

Rats survived exposure to 4000 ppm, but 8000 ppm for 4 hours was fatal to four of six rats.[2] Exposure of rats to 21,000 ppm for 150 minutes was fatal to all animals exposed; no symptoms were observed at 3000 ppm for 6 hours.[3]

Isobutyl acetate has a fruity odor.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for isobutyl acetate is 150 ppm (713 mg/m^3).

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ISOBUTYL ALCOHOL
CAS: 78-83-1

$(CH_3)_2CHCH_2OH$

Synonyms: 2-Methylpropanol-1; 2-methyl-1-propanol; 2-methylpropyl alcohol isopropylcarbinol; isobutanol

Physical Form. Colorless liquid

Uses. Lacquers, paint removers, cleaners, and hydraulic fluids; manufacture of isobutyl esters

Exposure. Inhalation

Toxicology. At high concentrations isobutyl alcohol causes narcosis in animals, and it is expected that severe exposure in humans would produce the same effect.

The liquid on the skin of a human subject was a mild irritant and caused slight erythema and hyperemia.[1] No evidence of eye irritation was noted in humans with repeated 8-hour exposures to 100 ppm.[1] The only reported adverse effects in humans relate to the occurrence of vertigo under conditions of severe and prolonged exposure to vapor mixtures of isobutanol and 1-butanol.[2]

Intermittent exposure of mice to 6400 ppm for 136 hours produced narcosis; exposure to 10,600 ppm for 300 minutes or 15,950 ppm for 250 minutes was fatal.[1]

Rats survived a 2-hour exposure to the saturated vapor (about 16,000 ppm), but two of six died after a 4-hour exposure to 8000 ppm.[3]

Oral administration of 1000 mg/kg/day for up to 3 months caused hypoactivity in all treated rats.[4]

One drop of isobutyl alcohol in a rabbit eye caused moderate to severe irritation without permanent corneal injury.[1]

A variety of malignant tumors developed in rats dosed twice weekly for life by oral intubation or subcutaneous injection.[1] Control animals had no malignancies. The carcinogenic risk to humans has not been determined.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for isobutyl alcohol is 50 ppm (152 mg/m^3).

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ISOOCTYL ALCOHOL
CAS: 26952-21-6

$C_8H_{17}OH$

Synonyms: Isooctanol; 2-ethylhexanol; 2-ethylhexyl alcohol

Physical Form. Liquid; a mixture of closely related isomeric, primary alcohols with branched chains

Uses. Intermediate in the manufacture of 2-ethylhexyl acetate, a lacquer solvent; solvent for nitrocellulose, urea, resins, enamels, alkyd varnishes, and lacquers; used in ceramics, paper coatings, textiles, and latex rubbers

Exposure. Inhalation; skin absorption

Toxicology. Isooctyl alcohol is a mucous membrane irritant and central nervous system depressant in animals.

Exposure of mice, rats, and guinea pigs to 227 ppm for 6 hours produced no mortality.[1] Central nervous system depression was observed, as was labored respiration and local irritation of the mucous membranes of the eyes and nose.

Male and female rats fed diets containing 0.01%, 0.05%, 0.25%, or 1.25% for 90 days showed histologic evidence of liver and kidney effects at the highest level.[2]

Dermal application of up to 2.6 g/kg resulted in no deaths and no signs of percutaneous toxicity; moderate irritation of the skin was observed. Instillation of the liquid into the eye of a rabbit produced erythema and edema of the conjunctiva, tearing, and mucous secretion but no corneal injury.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for isooctyl alcohol is 50 ppm (266 mg/m^3) with a notation for skin absorption.

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ISOPHORONE

CAS: 78-59-1

$C_9H_{14}O$

Synonyms: Isoacetophorone; Isoforon; trimethyl cyclohexenone

Physical Form. Water-white liquid

Uses. Solvent for lacquers, resins, and plastics

Exposure. Inhalation; skin absorption

Toxicology. Isophorone is an irritant of the eyes and mucous membranes.

Human subjects exposed briefly to 25 ppm experienced irritation of the eyes, nose, and throat.[1] Workers exposed to 5–8 ppm for 1 month complained of fatigue and malaise, which disappeared when air levels were reduced to 1–4 ppm.[2] Repeated or prolonged skin contact with the liquid may cause dermatitis because of its defatting action.[2] Although it may be more toxic and irritative than lower-molecular-weight ketones at equivalent concentrations, it poses less of an inhalation hazard because of its relatively low volatility.[2]

Repeated exposures of animals at concentrations of 50 ppm or more resulted in evidence of damage to kidney and lung and, to a lesser extent, liver damage. No effects, however, were seen at 25 ppm. More recent feeding studies with pure compound in rats, mice, and beagle dogs have not demonstrated specific toxicity.[3]

A 2-year gavage study at 250 and 500 mg/kg demonstrated a dose-related statistically significant excess of tubular cell adenomas and adenocarcinomas of the kidney in male rats, a number of preputial gland tumors in dosed male rats, and a probable increased incidence of hepatocellular neoplasms in high-dose male mice.[3]

Studies indicate that renal effects may be specific to certain strains of male rats that synthesize α_{2u}-globulin.[4] Monkeys, guinea pigs, dogs, mice, female rats. and male NBR rats that do not synthesize the hepatic form of α_{2u}-globulin do not develop renal disease in response to isophorone.

Isophorone does not induce gene mutations in bacteria, chromosomal aberrations *in vitro*, DNA repair in primary rat hepatocytes, or bone marrow micronuclei in mice. Positive effects were observed only in the absence of an exogenous metabolic system in L5178YTK +/– mouse mutagenesis assays as well as in a sister chromatid exchange assay.[5] The weight of evidence of all mutagenicity data supports the contention that isophorone is not a potent DNA-reactive compound.[5]

Pregnant rats and mice were exposed 6 hours/day on days 6–15 of gestation to atmospheres containing 0, 143, 285, or 656 mg/m^3 (0, 25, 50, or 115 ppm) isophorone. At the highest atmospheric concentration there was evidence of maternal toxicity, which showed as reduced food consumption, alopecia, and cervical or anogenital staining in the rats and reduced body weights in the mice. Comprehensive uterine and fetal examinations did not show any significant teratogenic or fetotoxic effects in F-344 rats or CD-1 mice.[5]

The 2003 ACGIH ceiling-threshold limit value (C-TLV) for isophorone is 5 ppm

(28 mg/m^3) with an A3-animal carcinogen designation with unknown relevance to humans notation.

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ISOPHORONE DIISOCYANATE
CAS: 4098-71-9

$C_{12}H_{18}N_2O_2$

Synonyms: IPDI; 3-isocyanatomethyl-3,5,5-trimethyl cyclohexylisocyanate

Physical Form. Liquid

Uses. Polyurethane paints and varnishes; as an elastomer in casting compounds, flexible textile coatings

Exposure. Inhalation; skin absorption

Toxicology. Isophorone diisocyanate (IPDI) is an irritant and sensitizer of the respiratory tract and the skin.

By analogy to toluene diisocyanate, exposure of humans to sufficient concentrations is expected to cause irritation of the eyes, nose, and throat; a choking sensation; and a productive cough of paroxysmal type with retrosternal soreness and chest pain.[1,2]

Higher concentrations would be expected to produce a sensation of oppression or constriction of the chest. There may be bronchitis and severe bronchospasm; pulmonary edema may also occur. On cessation of exposure, the symptoms may persist for 3–7 days.[3]

Although the acute effects may be severe, their importance is overshadowed by respiratory sensitization in susceptible persons. The onset of symptoms of sensitization may be insidious, becoming progressively more pronounced with continued exposure over a period of days to months. Initial symptoms are often nocturnal dyspnea and/or nocturnal cough with progression to asthmatic bronchitis.[1]

A 50-year-old spray painter developed severe asthma soon after the introduction of a new paint containing IPDI.[3] A bronchial challenge test with the paint gave a positive response.

In another case, a spray painter developed tightness of the chest and dyspnea shortly after using a paint containing IPDI.[4] The symptoms disappeared after a few days off work but recurred shortly after resumption of work.

IPDI has been shown to provoke allergic dermatitis in exposed workers.[5]

Skin and eye irritation in rabbits is considered moderate.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 0.005 ppm (0.045 mg/m^3).

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2-ISOPROPOXYETHANOL

CAS: 109-59-1

$(CH_3)_2CHOCH_2CH_2OH$

Synonyms: IPE; ethylene glycol monoisopropyl ether; Isopropyl Cellosolve®; isopropyl glycol

Physical Form. Liquid

Uses. Solvent in latex paints, lacquers, and other coatings, resins, coalescing aids, and coupling solvents

Exposure. Inhalation

Toxicology. 2-Isopropoxyethanol (IPE) causes hemolytic anemia in experimental animals.

In a subacute inhalation toxicity study, rats of both sexes were exposed for 6 hours/day, 5 days/week for 4 weeks.[1] Recovery groups were kept for an observation period of 14 days without treatment. At 891, 441, or 142 ppm hemolytic anemia was observed. Mild hemolytic anemia was found in female rats exposed to 100 ppm, but it had disappeared after the 14-day recovery period.

Higher plasma bilirubin values were observed in groups exposed to 891 ppm, and decreased urinary pH values occurred in groups exposed to 891 or 441 ppm. A concentration-related increase in absolute and relative spleen weight in the 441 and 891 ppm groups was accompanied by extramedullary hematopoiesis and brown pigment accumulation in the spleen. The no observed adverse effect level was 30 ppm.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 25 ppm (106 mg/m^3) with a notation for skin absorption.

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ISOPROPYL ACETATE

CAS: 108-21-4

$CH_3COOCH(CH_3)_2$

Synonyms: 2-Propyl acetate; acetic acid, isopropyl ester

Physical Form. Colorless liquid

Uses. Solvent

Exposure. Inhalation

Toxicology. Isopropyl acetate is an irritant of the eyes; at extremely high concentrations it causes narcosis in animals, and it is expected that severe exposure will produce the same effect in humans.

Human subjects exposed to 200 ppm for 15 minutes experienced some degree of eye irritation; there was little objection to the odor.[1] No systemic effects have been reported in humans.

Exposure of rats to 32,000 ppm was fatal to

five of six animals after 4 hours; 16,000 ppm for 4 hours was fatal to one of six rats.[2] The oral LD_{50} for rats was 6.75 g/kg.[2]

Isopropyl acetate was negative in most genotoxic test systems but was a weak inducer of aneuploidy.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 250 ppm (1040 mg/m^3) with a short-term excursion limit (STEL)/ceiling of 310 ppm (1290 mg/m^3).

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ISOPROPYL ALCOHOL

CAS: 67-63-0

$CH_3CHOHCH_3$

Synonyms: Isopropanol; 2-propanol; dimethyl carbinol

Physical Form. Colorless liquid

Uses. Manufacture of acetone; solvent; in skin lotions, cosmetics, and pharmaceuticals; most commonly available commercially as rubbing alcohol (70% isopropanol)

Exposure. Inhalation; ingestion

Toxicology. Isopropyl alcohol is an irritant of the eyes and mucous membranes; at very high doses it causes central nervous system depression.

Human subjects exposed to 400 ppm for 3–5 minutes experienced mild irritation of the eyes, nose, and throat; at 800 ppm, the irritation was not severe but the majority of subjects considered the atmosphere uncomfortable.[1]

Occupational poisoning by isopropyl alcohol has not been reported. Toxicity in humans is based largely on accidental ingestion. An oral dose of 25 ml in 100 ml of water produced hypotension, facial flushing, bradycardia, and dizziness. Other symptoms following ingestion have included vomiting, depression, headache, coma, and shock.[2] Renal insufficiency, including anuria followed by oliguria, nitrogen retention, and edema, may be a complication of isopropyl alcohol poisoning. Estimates of fatal doses are between 160 and 240 ml. Death following ingestion often occurs in 24–36 hours from respiratory paralysis.[2] In a recent report, a newborn was exposed for 2 hours to 70% isopropyl that had been accidentally placed in the humidifier of the infant's ventilator.[3] Despite supportive care, he became cyanotic, bradycardic, then asystolic 12.5 hours after exposure and died.

Studies indicate that isopropyl alcohol may be substantially better absorbed by the dermal route than had previously been believed, although significant toxicity by this route would require prolonged exposure.[4] Delayed dermal absorption rather than inhalation may account for a number of pediatric poisonings that have occurred after repeated or prolonged sponged bathing with isopropyl alcohol to reduce fever. In several cases symptoms have included respiratory distress, stupor, and coma.[2] Recovery was complete within 36 hours. Hypersensitivity characterized by delayed eczematous reactions have occasionally been observed after dermal contact with isopropyl alcohol.[2]

Rats exposed to 12,000 ppm for 4 hours survived, but exposure for 8 hours was lethal to half the animals.[5] Mice exposed to 3250 ppm for 460 minutes developed ataxia, prostration, and finally narcosis. Guinea pigs exposed to 400 ppm for 24 successive hours had slight changes in the mucosa of the nose and trachea,

whereas exposure to 5500 ppm for the same amount of time caused severe pathologic degeneration of the respiratory mucosa.[6] In the eye of a rabbit, 70% isopropyl alcohol caused conjunctivitis, iritis, and corneal opacity.[5]

Early epidemiological studies suggested an association between the manufacture of isopropyl alcohol and paranasal sinus cancer.[7,8] The risk for laryngeal cancer may also have been elevated in these workers.[8] The increased cancer incidence, however, appears to be associated with some aspect of the strong-acid manufacturing process rather than the isopropyl alcohol itself. It is unclear whether the cancer risk is due to the presence of diisopropyl sulfate, which is an intermediate in the process, to isopropyl oils, which are formed as by-products, or to other agents, such as sulfuric acid.[8]

In mice and rats exposed to 500, 2500, or 5000 ppm 6 hours/day, 5 days/week for up to 104 weeks, the only neoplastic lesion showing an increased incidence was interstitial cell (Leydig cell) adenomas in male rats. The tumor was not considered to be treatment related because of its occurrence in control rats.[9] The IARC has determined that there is inadequate evidence for the carcinogenicity of isopropyl alcohol in experimental animals and humans.[10]

No evidence of teratogenicity was observed in rats treated with doses of up to 1200 mg/kg/day on gestation days 6–15 or in rabbits administered up to 480 mg/kg/day on gestation days 6–18.[11] No evidence of developmental toxicity, as determined by pathologic findings, organ weights, or behavioral tests, was observed in rats administered up to 1200 mg/kg/day on gestation day 6 through postnatal day 21.[12]

When absorbed, isopropyl alcohol is oxidized in the liver at the hydroxyl moiety and converted to acetone.[13] Occupational exposure to isopropyl alcohol can be biomonitored by means of urinalysis for acetone after exposures as low as 70 ppm.[13] The acetone metabolite may also be responsible for the enhanced toxicity of carbon tetrachloride following pretreatment of animals with isopropyl alcohol.[2] Extra caution is in order when isopropyl alcohol is used concurrently with carbon tetrachloride in an industrial setting.

The odor threshold for isopropyl alcohol is 40–200 ppm.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for isopropyl alcohol is 400 ppm (983 mg/m^3) with a short-term excursion limit (STEL) of 500 ppm (1230 mg/m^3).

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ISOPROPYLAMINE

CAS: 75-31-0

$(CH_3)_2CHNH_2$

Synonyms: 2-Aminopropane

Physical Form. Liquid

Uses. Chemical synthesis of dyes, pharmaceuticals

Exposure. Inhalation

Toxicology. Isopropylamine is an irritant of the eyes, mucous membranes, and skin.

Human subjects experienced irritation of the nose and throat after brief exposure to 10–20 ppm.[1] Workers complained of transient visual disturbances (haloes around lights) after exposure to the vapor for 8 hours, probably due to mild corneal edema, which usually cleared within 3–4 hours.[2] The liquid is also capable of causing severe eye burns that may cause permanent visual impairment.[2] Isopropylamine in both liquid and vapor forms is irritating to the skin and may cause skin burns; repeated lesser exposures may result in dermatitis.[2]

All rats exposed to 8000 ppm for 4 hours died within 14 days, but six of six survived a 4-hour exposure at 4000 ppm.[3]

Isopropylamine was negative in mutagenicity tests using *Salmonella* with and without metabolic activation.[4]

The odor is like ammonia and becomes definite at 5–10 ppm.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for isopropylamine is 5 ppm (12 mg/m^3) with a short-term excursion limit (STEL) of 10 ppm (24 mg/m^3).

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N-ISOPROPYLANILINE

CAS: 768-52-5

$C_9H_{13}N$

Synonym: N-IPA; benzenamine, *N*-(1-methylethyl); *N*-phenylisopropylamine

Physical Form. Liquid

Uses. Dyeing of acrylic fibers and as a chemical intermediate

Exposure. Inhalation; skin absorption

Toxicology. *N*-isopropylaniline absorption causes methemoglobinemia in animals, and the same effect is expected in humans.

By analogy to methemoglobinemia caused by aniline in humans, the formation of methemoglobinemia often is insidious.[1] After skin absorption, onset of symptoms may be delayed for up to 4 hours. Headache commonly is the first symptom and may become intense as the severity of methemoglobinemia progresses. Cyanosis occurs when the methemoglobin concentration is 15% or more. Blueness develops first in the lips, nose, and earlobes and is usually recognized by fellow workers. The individual usually feels well, has no complaints, and is insistent that nothing is wrong until the methemoglobin level approaches approximately 40%. At higher levels there is weakness and dizziness, and at levels near 70% there may be ataxia, dyspnea on mild exertion, and tachycardia. Lethal levels are estimated to be 85–90%.

In rats the oral LD_{50} was 560 mg/kg and the dermal LD_{50} was 3550 mg/kg.[2] Slight eye and skin irritation were noted in acute toxicity studies with rabbits.

Rats exposed to levels of *N*-isopropylamine at 5, 20, or 100 mg/m^3 for 14 weeks showed no mortality or gross toxicity.[3] Elevated methemoglobin levels were observed in all exposure groups. There were slight signs of toxicity in the high-dose group consisting of decreased body weight gain, increased spleen and kidney weights, and increased hemosiderin in the spleen.

Dermal application of 25, 100, or 400 mg/kg/day for 4 weeks to rats was associated with dryness, redness, abrasions, and scabbing at the treatment site; dose-related occurrences of anemia and methemoglobinemia were statistically significant at the midlevel and high doses, whereas splenic changes including increased relative and absolute weight, hematopoiesis, and hemosiderin accumulation were significant in the high-dose animals.[4] Treatment-related elevations of reticulocyte counts and increased hemosiderin pigment in the spleen suggested toxic anemia by increased red blood cell destruction with compensating activity in both the spleen and bone marrow, rather than reduced production by the bone marrow.

Administered by gavage on gestation days 6–15 *N*-isopropylaniline was fetotoxic and teratogenic (increased fetal malformations and postimplantation loss, decreased fetal body weights and extent of fetal ossification) at a dose [350 mg/kg body weight (bw)/day] that caused severe maternal toxicity (decreased body weight gain, excessive salivation, hair loss, decreased activity, brown urine, increased incidence of extramedullary hematopoiesis, and increased mortality).[5] The treatment was not maternally toxic, fetotoxic, or teratogenic at the 30 and 100 mg/kg bw/day doses.

N-isopropylaniline was negative in bacterial mutagenicity assays with and without metabolic activation.[6]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 2 ppm (11 mg/m^3) with a notation for skin absorption.

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ISOPROPYL ETHER

CAS: 108-20-3

$(CH_3)_2CHOCH(CH_3)_2$

Synonyms: Diisopropyl ether; 2-isopropoxypropane

Physical Form. Colorless liquid

Uses. Solvent; chemical intermediate

Exposure. Inhalation

Toxicology. Isopropyl ether is a mild irritant of the eyes and mucous membranes; at high concentrations it causes narcosis in animals, and it is expected that severe exposure will produce the same effect in humans.

Human subjects exposed to 800 ppm for 5 minutes reported irritation of the eyes and nose, and the most sensitive reported respiratory discomfort.[1] Thirty-five percent of the volunteers exposed to 300 ppm for 15 minutes objected to the odor rather than the irritation.[2]

Animals (monkey, rabbit, and guinea pig) survived a 1-hour exposure to 30,000 ppm with signs of anesthesia; 60,000 ppm for 1 hour was lethal.[1] The lethal concentration for rats was 16,000 ppm for a 4-hour exposure.

Rats exposed 5 days/week for 13 weeks to concentrations as high as 7060 ppm showed minimal effects to the nervous system as determined by functional observational battery, automated motor activity, and neuropathology.[3] Rats exposed 6 hours/day for 90 days at 7100 ppm had increased liver and kidney weights; males also had liver cell hypertrophy and increased hyaline droplets in the proximal tubules.[4]

Pregnant rats exposed on days 6–15 of gestation at 0, 430, 3095, or 6745 ppm for 6 hours/day had significant reduction in food consumption and a slight reduction in body weight gain at the highest dose; there was a concentration-related increase in the incidence of rudimentary fourteenth ribs in the offspring, which is of uncertain significance.[4]

In rabbits, repeated skin application of the liquid for 10 days caused dermatitis.[1] The liquid dropped in the eye of a rabbit caused minor injury.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for isopropyl ether is 250 ppm (1040 mg/m^3) with a short-term excursion limit (STEL) of 310 ppm (1300 mg/m^3).

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ISOPROPYL GLYCIDYL ETHER

CAS: 4016-14-2

$C_6H_{12}O_2$

Synonyms: IGE; 1,2-epoxy-3-isopropoxypropane

Physical Form. Colorless liquid

Uses. Reactive diluent for epoxy resins; stabilizer for organic compounds; chemical intermediate for synthesis of ethers and esters

Exposure. Inhalation

Toxicology. Isopropyl glycidyl ether (IGE) causes both primary irritation and sensitization

dermatitis; in animals it causes irritation of the eyes and mucous membranes, and it is expected that severe exposure will cause the same effects in humans.

Systemic effects have not been demonstrated in workers exposed to IGE.[1]

A technician who handled both IGE and phenyl glycidyl ether developed localized dermatitis on the back of the hands; patch testing showed sensitization to both substances.[2] Dermatitis has occurred in workers with repeated skin contact.[3]

In mice, the LC_{50} was 1500 ppm for 4 hours.[2] Rats repeatedly exposed to levels of 400 ppm exhibited slight eye and respiratory irritation. Large oral doses produced central nervous system depression, but this effect was not seen from inhalation exposure.

Moderate irritation resulted from instillation of the liquid in the eyes of rabbits and from application to the skin of rabbits.[2]

IGE was mutagenic in bacterial assays with and without metabolic activation and in the *Drosophila* sex-linked recessive lethal (SLRL) assay.[4,5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 50 ppm (238 mg/m^3) with a short-term excursion limit (STEL)/ceiling of 75 ppm (356 mg/m^3).

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JET FUELS
JP-4 and JP-7
CAS: JP-4 50815-00-4

Synonyms: JP-4; Jet Propellant-4; Jet fuel-4; MIL-T-5624-L-Amd, 1 wide cut; JP-4 military (gasoline type)

JP-7; Jet Propellant-7; Jet fuel-7; MIL-T-38219A-Amd.2, kerosene, low volatility

Physical Form. JP-4 is a colorless to straw-colored liquid with the odor of gasoline and/or kerosene. JP-7 is a liquid, usually colorless and with the odor of kerosene. JP-4 can be made by refining either crude petroleum oil or shale oil. It is called a wide cut fuel because it is produced from a broad distillation temperature range and contains a wide array of carbon chain lengths, from 4- to 16. It consists of approximately 13% (v/v) aromatic hydrocarbons, 1.0% olefins, and 86% saturated hydrocarbons.[1] JP-7 is made by refining kerosene, a product of refined crude petroleum. It was developed for use in advanced supersonic jets because of its thermal stability and high flash point.[2,3]

Aviation fuels consist primarily of hydrocarbons (paraffins and cycloparaffins or naphthenes primarily but also aromatics and olefins). Paraffins have a high hydrogen-to-carbon ratio, with a high heat release per unit of weight and a cleaner burn than other hydrocarbons. Cycloparaffins have a lower hydrogen-to-carbon ratio and produce less heat release but increase the density and reduce the freezing point of the fuel. Aromatic hydrocarbons are a good energy source but produce smoke on burning; therefore, the maximum levels are restricted (20–25% by volume in JP-4, 5% by volume in JP-7). Olefins are similar

to paraffins but are unsaturated (double and triple C-C bonds) with lower hydrogen-to-carbon ratios, are the most reactive of the hydrocarbons, and are allowed at only 5% by volume in JP-4. Benzene is present as a contaminant at less than 0.5% in JP-4. Other ingredients of lesser importance are sulfur and sulfur compounds as well as additives to improve performance (antioxidants, metal deactivators, fuel system icing inhibitors, corrosion inhibitors, static dissipater additives).[2]

Uses. JP-4 and JP-7 (jet propellant-4 and jet propellant-7) are used by the US Air Force as aircraft fuels.

Exposure. Skin contact and absorption; inhalation

Toxicology. JP-4 and J-7 cause central nervous system depression and skin irritation.

Accidental exposure of a pilot during a fuel leak to JP-4 at levels estimated to be between 3000 and 7000 ppm produced signs of neurological intoxication, but cardiovascular and pulmonary function appeared normal on clinical examination.[4] The pilot had a staggering gait, mild muscular weakness, decreased responsiveness to painful stimuli, and slight slurring of speech. The effects were not evident 36 hours after exposure.

Chronic exposure (12 months) of rats and mice to 1000 or 5000 mg/m^3 JP-4 did not cause respiratory tract irritation or pulmonary lesions in rats at the end of the exposure or at 12 months after exposure.[5] An increase of interstitial cell tumors was observed in the testis 12 months after exposure. No effect on the incidence of neoplastic tumors was seen in mice in the same study. A 1-year JP-7 exposure study to rats at 750 mg/m^3 produced no toxicologically significant treatment-related neoplastic lesions in mice or rats except for a small increase in incidence of C-cell adenomas and kidney adenomas in male rats.[6] However, these tumors are of the type that are considered to be specific to the male rat and not relevant to humans or other animals. The exposure period in these two studies was 1 year, rather than the typical 2-year lifetime period. This time period was chosen by the authors as being more typical of military occupational exposure to jet fuels. Nevertheless, the results may suggest that JP-4 and JP-7 are not carcinogenic to humans.

Acute (24 hours) dermal application of 2 g/kg JP-4 or JP-7 to rabbits did not result in mortality. However, they did cause severe skin erythema and edema 24 hours after exposure.[7–9] Somewhat at odds with these irritation potential findings, there was no evidence of primary ocular irritation after application of JP-4 or JP-7 to the eyes of rabbits.[7–10]

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KETENE
CAS: 463-51-4

CH_2CO

Synonyms: Ethenone; carbomethene; ketoethylene

Physical Form. Gas

Uses. Organic chemical syntheses; conversion of higher acids into their anhydrides; for acetylation in the manufacture of cellulose acetate and aspirin

Exposure. Inhalation

Toxicology. Ketene is a severe pulmonary irritant in animals and is expected to produce the same effect in humans.

For mice, monkeys, cats, and rabbits the concentrations that caused death after a 10-minute exposure were 50, 200, 750, and 1000 ppm, respectively.[1] Few signs appeared during the exposure period, but after a latent period of variable duration there was dyspnea, cyanosis, and signs of severe pulmonary damage; death was often preceded by convulsions. Significant pathologic changes were confined to the lungs and consisted of generalized alveolar edema and congestion. Several species tolerated exposure to 1 ppm for 6 hours/day for 6 months without apparent chronic injury.[1] Exposure of mice to concentrations in excess of 5 ppm for 10 minutes protected mice 3–14 days later against otherwise lethal exposures to pulmonary edema-producing agents.[2] A high degree of tolerance to the acute effects of ketene itself has also been reported.[3] Chronic pulmonary changes including fibrosis and emphysema may also result from repeated acute exposures.

By analogy to effects on the skin caused by other severe irritants, repeated or prolonged exposure is expected to cause dermatitis.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for ketene is 0.5 ppm (0.86 mg/m^3) with a short-term excursion limit (STEL) of 1.5 ppm (2.6 mg/m^3).

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LEAD (Inorganic Compounds)
CAS: 7439-92-1

Pb

Synonyms/Compounds: Metallic lead; lead oxide; lead salts; inorganic lead

Physical Form. Solid

Uses. Storage batteries; paint; ink; ceramics; automobile radiator repair; ammunition

Exposure. Inhalation; ingestion

Toxicology. Prolonged absorption of lead or its inorganic compounds results in severe gastrointestinal disturbances and anemia; with

more serious intoxication, there is neuromuscular dysfunction, whereas the most severe lead exposure may result in encephalopathy.

The onset of symptoms of lead poisoning or plumbism is often abrupt; presenting complaints may include weakness, weight loss, lassitude, insomnia, and hypotension.[1–4] Associated with these is a disturbance of the gastrointestinal tract, such as constipation, anorexia, and abdominal discomfort, or actual colic, which may be excruciating. Physical signs are usually facial pallor, malnutrition, abdominal tenderness, and pallor of the eye grounds. The anemia often associated with lead poisoning is of the hypochromic, normocytic type, with reduction in mean corpuscular hemoglobin; stippling of erythrocytes and reticulocytosis are evident. On gingival tissues, a line or band of punctate blue or blue-black pigmentation (lead line) may appear, but only in the presence of poor dental hygiene; this is not pathognomonic of lead poisoning.[3]

Occasionally the alimentary symptoms are relatively slight and are overshadowed by neuromuscular dysfunction, accompanied by signs of motor weakness, which may progress to paralysis of the extensor muscles of the wrist ("wrist drop") and less often of the ankles ("foot drop").[2,3] Encephalopathy, the most serious result of lead poisoning, frequently occurs in children due to the ingestion of inorganic lead compounds, but rarely in adults, except from exposure to organic lead.[1–4]

Subtle, often subclinical, neurological effects have been demonstrated in workers with relatively low blood lead levels, below 40–60 μg/100 ml blood. Performance of lead workers on various neuropsychological tests was mildly reduced, relative to a control group, at mean levels of 49 μg/100 ml blood and, in a prospective follow-up study, at levels between 30 and 45 μg/100 ml blood.[5–7] In some of these studies, the lead-exposed workers reported significantly more complaints of nonspecific subjective symptoms, such as anxiety, depressed mood, poor concentration, and forgetfulness.[5] However, a recent evaluation of 21 studies found inadequate evidence of decreased neurobehavioral test performance in adults with cumulative low-level exposure to lead.[8] In contrast, children are particularly sensitive to lead-related neurobehavioral effects.

Mild neurophysiological changes, including reductions in motor and sensory nerve conduction velocities (sometimes still within the normal range), have been documented in lead-exposed workers compared with control groups, with blood lead levels less than 40 μg/100 ml blood.[9] A prospective follow-up study of workers with blood lead levels of 30–50 μg/100 ml blood demonstrated mild slowing of conduction velocities.[10]

Nephropathy has been associated with chronic lead poisoning.[2,3,11] A study of two large cohorts of heavily exposed lead workers followed through 1980 demonstrated a nearly threefold excess of deaths attributed to chronic nephritis or "other hypertensive disease," primarily kidney disease.[12] Most of the excess deaths occurred before 1970, among men who began work before 1946, suggesting that current lower levels of exposure may reduce the risk. Experimental animal studies suggest there may be a threshold for lead nephrotoxicity, and in workers, nephropathy occurred only in those with blood levels over 62 μg/dl for up to 12 years.[13]

The role of chronic low-level lead exposure in the pathogenesis of hypertension remains controversial. Although results have been mixed, overall, the studies may suggest a small positive association between blood lead and blood pressure.[14]

After absorption, inorganic lead is distributed in the soft tissues, with the highest concentrations being in the kidneys and the liver.[4] In the blood, nearly all circulating inorganic lead is associated with the erythrocytes.[4] Over a period of time, the lead is redistributed, being deposited mostly in bone and also in teeth and hair.[3,4] Lead absorption is cumulative; elimination of lead from the body is slow, requiring considerably longer than the period of storage of toxic amounts.[1,4] Asymptomatic lead workers, when subjected to a sudden increase in exposure to and absorption of lead, often respond with an episode of typical lead poisoning.[1] Removal of the worker from exposure to abnormal quantities of lead often leads to a seemingly sudden and apparently complete

recovery; this has occurred even when the individual has a considerable quantity of residual lead in the body.[1]

Available human epidemiological studies are inadequate to assess lead carcinogenicity because of the lack of quantitative exposure data for lead, the lack of consistency across studies, and the possibility of confounding exposures.[15,16] A study of 4347 lead-exposed workers in a copper smelter failed to demonstrate any significant excess of neoplasms.[17] A study of two large cohorts of lead workers (3519 battery plant workers and 2300 lead production workers) followed through 1980 demonstrated statistically significant elevation in the standardized mortality ratio (SMR) for gastric (SMR = 168) and lung (SMR = 125) cancer in the battery plant workers only. Citing the absence of prior evidence from other studies for these associations, and their inability to assess and correct for possible confounding factors (such as diet, alcohol, and smoking), the authors considered these findings inconclusive. There were no excess deaths from malignancies of the kidney or other sites in either cohort.[12]

There are several reports that certain lead compounds, including lead acetate and lead phosphate, administered to animals in high doses are carcinogenic, primarily producing renal tumors.[18,19] (Note: Those salts demonstrating carcinogenicity in animals are soluble, whereas human beings are primarily exposed to insoluble metallic lead and lead oxide.)

Genotoxic assays both in vivo and in vitro have shown positive and negative results.[16]

Reproductive effects from lead exposure have been documented in animals and human beings of both sexes. High occupational exposure levels in pregnant women have been associated with increased incidences of spontaneous abortions, miscarriages, and stillbirths.[16] Some studies also seem to indicate that prenatal exposure to lower levels of lead may increase the risk of preterm delivery and reduced birth weight.[20] Lead penetrates the placental barrier and has caused congenital abnormalities in animals.[3,21] There is no conclusive evidence, however, that low-level lead exposure leads to an increased incidence of malformations in humans.[22] Excessive exposure to lead during pregnancy has resulted in neurological disorders in infants; low levels of exposure may be related to neurobehavioral deficits or delays.[16]

In battery workmen with a mean occupational exposure to lead of 8.5 (1–23) years, and with blood lead concentrations of 53–75 µg/100 ml of blood, there was an increased frequency of abnormalities of sperm, including hypospermia, compared with a control group.[23]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for lead, including elemental and inorganic compounds as Pb, is 0.05 mg/m^3 with an A3-confirmed animal carcinogen with unknown relevance to humans designation.

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LEAD ARSENATE
CAS: 10102-48-4

$Pb_3(AsO_4)_2$

Synonyms: Arsinette; Ortho L10 Dust; Gypsine; Soprabel; Talbot

Physical Form. White powder (required to be colored pink in most of US)

Uses. Insecticide; control of tapeworms in cattle, goats, sheep

Exposure. Inhalation; ingestion

Toxicology. Lead arsenate may cause lead and/or arsenic intoxication; arsenic symptoms likely predominate in acute intoxication, whereas prolonged inhalation of lead arsenate may induce the symptoms of lead intoxication.[1]

Some of the effects of acute arsenic intoxication are nausea, vomiting, diarrhea, and irritation; inflammation and ulceration of the mucous membranes and skin; and kidney damage.[2] Among the effects of chronic arsenic poisoning are increased pigmentation and keratinization of the skin, dermatitis, and epidermoid carcinoma. Other effects seen after ingestion, but which are not common from industrial exposure, are muscular paralysis, visual disturbances, and liver and kidney damage.[2]

Effects of lead intoxication include damage to the central and peripheral nervous systems, to the kidneys, and to the blood-forming elements, which may lead to anemia.[3] Symptoms include colic, loss of appetite, and constipation;

excessive tiredness and weakness; and nervous irritability. In peripheral neuropathy, the distinguishing clinical feature of lead intoxication is a predominance of motor impairment, with minimal or no sensory abnormalities. There is a tendency for the extensor muscles of the hands and feet to be affected. Lead intoxication has also resulted in kidney damage with few, if any, symptoms appearing until permanent damage has occurred.

A mortality study in 1973 of a cohort of 1231 individuals (primarily orchardists who had participated in a 1938 mortality study) found that excess mortality did not occur consistently from exposure to lead arsenate spray.[4,5] However, in a recent analysis of this same cohort, the causes of death were determined for three different levels of exposure—orchardists (involved in preparing and spraying), intermediates (infrequent exposure to spray), and consumers. In male orchardists and intermediates there was a higher risk of dying from all causes of death, and for exposed male intermediates there was a greater risk of mortality due to coronary heart disease.[6] Two other independent studies reported a significant excess of lung cancer among other cohorts of this same population.[2] In a study of workers engaged in the formulation and packaging of lead arsenate and calcium arsenate, there was an excess of lung cancer, which was dose related.[7] In vineyard workers chronically exposed to lead, calcium, and copper arsenate dust in Germany and France, there are numerous reports of skin cancer, including basal cell and squamous cell carcinomas, as well as lung cancer.[8]

The IARC has concluded that there is sufficient evidence that inorganic arsenic compounds, including lead arsenate, are skin and lung carcinogens in humans.[8]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for lead arsenate as $Pb_3(AsO_4)_2$ is 0.15 mg/m^3.

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LEAD CHROMATE
CAS: 7758-97-6

PbCrO4

Synonyms: Chrome yellow; CI pigment yellow 34; CI 77600

Physical Form. Yellow crystals or powder, insoluble in water

Uses. Pigment

Exposure. Inhalation

Toxicology. Lead chromate is a suspected human lung carcinogen and can cause chronic lead poisoning.

Lead chromate could potentially pose a double hazard and cause signs and symptoms

of chronic lead intoxication (severe gastrointestinal disturbances, anemia, neuromuscular dysfunction, nephritis, and encephalopathy), and chromium VI toxicity (sensitization dermatitis, primary irritant dermatitis, ulcerated nasal mucosa and skin, and nephropathy), although the latter has not been specifically observed from lead chromate.

Lead poisoning from lead chromate in the chromate pigment industry has been documented.[1] Evidence of lung cancer attributable solely to lead chromate in the industry has not been consistent.[2,3] Long-term mortality was studied in a group of 57 chromate pigment workers who suffered clinical lead poisoning, mostly between 1930 and 1945.[1] One death was attributed to lead poisoning, and there were significant excesses of deaths from nephritis and cerebrovascular disease. The deaths from nephritis followed service exceeding 10 years, whereas the risk of cerebrovascular disease was unrelated to duration of exposure and even affected men employed for under 1 year. Other contemporary workers at the factories showed no excess mortality from cerebrovascular disease.

Lung cancer mortality among 1152 men working at three English chromate pigment factories was studied from the 1930s–1940s until 1981.[2] Workers exposed only to lead chromate at one factory experienced no increased risk in cause-specific mortality. Workers at two other factories were exposed to both lead and zinc chromate, and lung cancer mortality was significantly raised among those with high or medium exposure for at least 1 year before 1955. After that time working conditions were improved, and workers starting after that date did not have excess lung cancer deaths. The results provided no indication that lead chromate induced lung cancer, even under conditions conducive to lead poisoning.

In contrast, another study of 548 men at three lead chromate facilities showed that workers exposed at two of the facilities had a threefold excess of lung cancer.[3,4] Workers at the third facility, who had zinc chromate exposure as well as lead chromate exposure, had a significant excess of lung cancer and stomach cancer. An industrial hygiene survey indicated that nearly half of the samples at the three facilities reached or exceeded the OSHA standards for lead and chromium.

Chronic animal studies have also yielded varying results. Intratracheal implantation of lead chromates in rats failed to significantly increase the carcinogenic response after 2 years.[5] Intrapleural administration caused a 9% incidence of lung tumors in rats within 19–21 months.[6] Intramuscular injection resulted in lymphomas, renal tumors, fibrosarcomas, and rhabdomyosarcomas at the site of injection in rats.[7]

The IARC has concluded that there is sufficient evidence in experimental animals and in humans for the carcinogenicity of lead chromate.[8]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for lead chromate is 0.05 mg/m^3 as Pb and 0.012 mg/m^3 as Cr with an A2-suspected human carcinogen designation.

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Chromium, nickel and welding, pp 49–256. Lyon, International Agency for Research on Cancer, 1990

LINDANE
CAS: 58-89-9

$C_6H_6Cl_6$

Synonyms: 1,2,3,4,5,6-Hexachlorocyclohexane, γ isomer; γ-HCH; γ-benzene hexachloride; γ-BHC; Kwell

Physical Form. Crystalline solid

Use. Insecticide

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Lindane causes central nervous system effects.

Exposure to the vapor causes irritation of the eyes, nose, and throat, severe headache, and nausea.[1] Lindane levels in the blood do not appear to increase with increased duration of exposure but primarily reflect recent lindane absorption.[2] Production workers exposed to air levels of 31–1800 μg/m^3 had blood levels of 1.9–8.3 ppb.[1]

Lindane has been suspected as a cause of aplastic or hypoplastic anemia in a number of cases reported from various countries.[3] Although one report tabulated 46 case reports of bone marrow injury temporally associated with environmental exposure to lindane, the authors questioned the association on several grounds.[3] In 17 cases, there was exposure to other toxic agents, including benzene and chloramphenicol. In eight cases, investigation of the bone marrow did not reveal aplasia or hypoplasia. In some cases, documentation of exposure was limited. Moreover, no cases have been reported after the therapeutic use of lindane (Kwell) as a scabicide in children or adults, despite the fact that lindane is well absorbed dermally. Cross-sectional studies of workers chronically exposed to lindane during manufacture have failed to reveal any hematologic conditions or significant differences in hemoglobin or total leukocyte count relative to a control population.[4] Although some statistically significant differences were found in some hematologic parameters, such as increases in polymorphonuclear leukocyte counts and reticulocyte counts compared with the control group, the results were still largely within the reference range and of questionable biological significance. No significant differences were observed for transaminases (AST, ALT) or other liver function studies.[4]

Accidental ingestion has caused fatalities; effects were repeated, violent, clonic convulsions, sometimes superimposed on a continuous tonic spasm. Respiratory difficulty and cyanosis, secondary to the convulsions, were common.[5] After nonfatal accidental ingestions, symptoms have included malaise, dizziness, nausea, and vomiting. Agitation, collapse, convulsions, loss of consciousness, muscle tremor, fever, and cyanosis have commonly been observed. Most patients who survive recover completely over 1–3 days; protracted illness is rare.[2]

Minor liver lesions have been reported in rats at dosages as low as 2.6–5.0 mg/kg/day. After repeated high doses, degenerative changes have been found in the kidney, pancreas, and testes of rodent species.[2] Feeding of 1500 ppm in the diet to rats for 90 days, a maximally tolerated dose, resulted in testicular atrophy, with spermatogenic arrest and apparent inhibition of androgen synthesis by Leydig cells.[6] A single dose of 30 mg/kg to male rats caused histologic damage to Sertoli cells including fragmentation and complete loss of organelles.[7] After oral administration female rabbits had a reduced ovulation rate, and antiestrogenic properties were found in female rats.[8] Adverse developmental effects have not been reported at doses that are not maternally toxic.[8]

Administered to mice for 80 weeks, lindane caused a significant increase in hepatocellular tumors in low-dose males but not in other groups of mice or in rats.[9] Use of lindane by

farmers was associated with a 50% increased risk of non-Hodgkin lymphoma, but a causal relationship could not be established because confounding effects such as use of other pesticides.[8,10] There is limited evidence that lindane is genotoxic in vitro and in vivo assays.[8]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for lindane is 0.5 mg/m^3 with a notation for skin absorption and an A3-confirmed animal carcinogen with unknown relevance to humans designation.

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LIQUEFIED PETROLEUM GAS

CAS: 68476-85-7

Mixture: C_3H_6, C_3H_8, C_4H_8, and C_4H_{10}

Synonyms: LPG; bottle gas; liquefied hydrocarbon gas

Physical Form. Gas or liquid

Uses. As fuel; in production of chemicals

Exposure. Inhalation

Toxicology. Liquefied petroleum gas (LPG) is practically nontoxic below the explosive limits but may cause asphyxia by oxygen displacement at extremely high concentrations.[1]

No chronic systemic effects have been reported from occupational exposure. The vapor is not irritating to the eyes, nose, or throat.[2] Direct contact with the liquid may cause burns or frostbite to the eyes and skin.[3] Olefinic impurities may lend a narcotic effect. At extremely high concentrations, the limiting toxicological factor is available oxygen. Minimal oxygen content should be 18% by volume under normal atmospheric pressure. More recent reports have suggested that accidental deaths from LPG exposure may occur not only from asphyxia due to anoxia but also from central nervous system depression in cases where there is sufficient oxygen.[4]

Generally, flammability and explosive hazards outweigh the biological effects.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 1000 ppm (1800 mg/m^3).

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LITHIUM HYDRIDE
CAS: 7580-67-8

LiH

Synonyms: None

Physical Form. White crystals that darken on exposure to light

Uses. Reducing agent; condensing agent with ketones and acid esters; desiccant; as a source of hydrogen

Exposure. Inhalation; ingestion

Toxicology. Lithium hydride is a severe irritant of the eyes, mucous membranes, and skin.

The toxicity of lithium hydride differs markedly from that of the soluble salts of lithium because of its vigorous chemical reactivity with water, which produces acute irritation and corrosion of biological tissues.[1]

The explosion of a cylinder of lithium hydride led to eye contact and swallowing of a small amount of the dust by a technician.[2] The resulting burns caused scarring of both corneas and strictures of the larynx, trachea, bronchi, and esophagus; death occurred 10 months later.

Exposure of humans in the range of 0.025–0.1 mg/m^3 caused some nasal irritation; tolerance was acquired with continuous exposure.[3] At 0.5–1.0 mg/m^3 severe nasal irritation, cough, and some eye irritation were noted; in the range of 1.0–5.0 mg/m^3 all effects were severe and skin irritation was felt.

Exposure of animals to concentrations above 5 mg/m^3 caused sneezing and cough with secondary pulmonary emphysema; levels of 10 mg/m^3 corroded the body fur and skin of the legs, and there was occasional inflammation of the eyes and nasal septum.[1] The lesions of the nose and legs were attributed to the alkalinity of lithium hydroxide, the hydrolysis product of lithium hydride.

Powdered lithium hydride may ignite spontaneously in humid air or on contact with moist mucous surfaces; resulting tissue effects may have features of both thermal and alkali burns.[4]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 0.025 mg/m^3.

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MAGNESITE
CAS: 546-93-0

$MgCO_3$

Synonyms: Magnesium carbonate

Physical Form. Solid

Uses. Chemical intermediate for magnesium salts; component of pharmaceuticals, cosmetics, dentifrices, free-running table salt; agent in heat insulation and refractory applications

Exposure. Inhalation

Toxicology. Magnesite is considered to be a nuisance dust.

Among 619 workers in a magnesite plant with 6–20 years of employment, 13 cases of pneumoconiosis were observed, mainly among workers exposed to calcined magnesite.[1] The workers were exposed to dust from crude or calcined magnesite that also contained 1–3% silicon dioxide.

In several reports, the severity of the pneumoconioses caused by the action of magnesite ore dusts was found to be a function of the crystalline silica content.[2]

Adverse health effects have not been reported for workers exposed to magnesite containing no asbestos and <1% crystalline silica.[3] No cases of human systemic magnesium intoxication from inhalation of magnesite have been reported.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for magnesite is 10 mg/m^3, total dust containing no asbestos and <1% crystalline silica.

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MAGNESIUM OXIDE FUME
CAS: 1309-48-4

MgO

Synonyms: None

Physical Form. Fume

Sources. From manufacture of refractory crucibles, fire bricks, magnesia cements, boiler scale compounds

Exposure. Inhalation

Toxicology. Magnesium oxide fume is an irritant of the eyes and nose.

Examination of 95 workers exposed to an unspecified concentration of magnesium oxide dust revealed slight irritation of the eyes and nose; the magnesium level in the serum of 60% of those examined was above the normal upper limit of 3.5 mg/dl.[1] No evidence of any pulmonary inflammatory response was found in six volunteers after short-term (36 min) exposure to high concentrations (137.0 mg/m^3) of fine and ultrafine magnesium oxide particles.[2]

In a very early report, experimental subjects exposed to fresh magnesium oxide fume developed metal fume fever, an illness similar to influenza; effects were fever, cough, oppression in the chest, and leukocytosis.[3] After the introduction of a new process resulting in exposure to magnesium oxide fume in the 1980s, several German foundry workers developed recurrent occupational fever that was also interpreted as metal fume fever.[4]

The 2003 ACGIH threshold limit value-

time-weighted average (TLV-TWA) for magnesium oxide fume is 10 mg/m^3.

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MALATHION
CAS: 121-75-5

$C_{10}H_{19}O_6PS_2$

Synonyms: Diethyl mercaptosuccinate, *S*-ester with *O*,*O*-dimethyl phosphorodithioate; Malathon; carbophos; Cythion 4049

Physical Form. Colorless to light amber liquid

Uses. Insecticide

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Malathion is an anticholinesterase agent, but it is of a relatively low order of toxicity in comparison with other organophosphates.

Signs and symptoms of intoxication by anticholinesterase agents are caused by the inactivation of the enzyme cholinesterase, which results in the accumulation of acetylcholine at synapses in the nervous system, skeletal and smooth muscle, and secretory glands.[1–4] After inhalation of extremely high concentrations of malathion, ocular and respiratory effects may appear simultaneously. Ocular effects include miosis, blurring of distant vision, tearing, rhinorrhea, and frontal headache. Respiratory effects include tightness in the chest, wheezing, laryngeal spasms, and excessive salivation. Peripheral effects include excessive sweating, muscular fasciculations, and weakness. Effects on the central nervous system include giddiness, confusion, ataxia, slurred speech, and convulsions. After ingestion, anorexia, nausea, vomiting, abdominal cramps, and diarrhea also appear.

Malathion itself has only a slight direct inhibitory action on cholinesterase, but one of its metabolites, malaoxon, is an active inhibitor.[4] Both malathion and malaoxon are rapidly detoxified by esterases in the liver and other organs. This rapid metabolism is the apparent reason for the lower toxicity of malathion compared with other organophosphates. Malaoxon inactivates cholinesterase by phosphorylation of the active site of the enzyme to form the "dimethylphosphoryl enzyme." Over the following 24–48 hours there is a process, called aging, of conversion to the "monomethylphosphoryl enzyme." Aging is of clinical interest in the treatment of poisoning, because cholinesterase reactivators such as pralidoxime (2-PAM, Protopam) chloride are ineffective after aging has occurred.

The relative safety of malathion to humans has been demonstrated repeatedly. In a group of workers with an average exposure of 3.3 mg/m^3 for 5 hours (maximum of 56 mg/m^3), the cholinesterase levels in the blood were not significantly lowered and no one exhibited signs of cholinesterase inhibition.[5] In a human experiment in which four men were exposed 1 hour daily for 42 days to 84.8 mg/m^3, there was moderate irritation of the nose and the conjunctiva, but there were no cholinergic signs or symptoms.[6]

Almost all reports of fatalities from malathion have involved ingestion.[4] The acute oral lethal dose is estimated to be somewhat below 1.0 g/kg. Nonlethal intoxication has occurred in agricultural workers but usually has been the result of gross exposures with concomitant skin absorption.[4]

Malathion has caused skin sensitization, and dermatitis may occur under conditions of heavy field use.[7]

In rats, malathion was not teratogenic when administered by gastric intubation on days 6 through 15 of gestation at doses as high as 300 mg/kg.[8] There were no effects on clinical signs, food consumption, maternal weight gain during gestation, reproductive performance, fertility indices, gestation length, or parturition in a two-generation reproductive study in rats administered up to 7500 ppm in the diet.[9]

National Cancer Institute studies showed that administration of 4700 or 8150 mg/kg for 80 weeks or 2000 or 4000 mg/kg for 103 weeks in the diets of rats was not carcinogenic.[10–12] Subsequent data reevaluation by NTP confirmed these conclusions.[13] Mice fed diets containing 8000 or 16,000 mg/kg for 80 weeks also had no significant increase in tumor incidence.[10] The IARC determined that there is no available evidence to suggest that malathion is likely to present a carcinogenic risk to humans.[14]

Most studies indicate that malathion is not genotoxic, although some tests indicate that it can produce chromosomal aberrations and sister chromatid exchanges *in vitro*.[9] There was no significant increase in mutation frequency or micronucleus formation in a cohort of California workers involved in application of malathion as ground treatment during the 1990s.[15]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for malathion is 10 mg/m^3 with a notation for skin absorption.

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MALEIC ANHYDRIDE

CAS: 108-31-6

$C_4H_2O_3$

Synonyms: 2,5-Furandione; *cis*-butenedioic anhydride; toxilic anhydride

Physical Form. White crystalline solid

Uses. In the manufacture of polyester resins, fumaric acid, agricultural pesticides, and alkyl resins

Exposure. Inhalation

Toxicology. Maleic anhydride is a severe irritant of the eyes; it is an irritant and sensitizer of both the skin and respiratory tract and may produce asthma on repeated exposure.

Workers exposed to vapors from heated maleic anhydride developed an intense burning sensation in the eyes and throat, with cough and vomiting; exposure to high fume concentrations caused photophobia, double vision, and a visual phenomenon of seeing rings around lights.[1,2] Exposure of humans to a concentration of 1.5–2 ppm resulted in nasal irritation within 1 minute and eye irritation after 15–20 minutes.[3] Among workers repeatedly exposed to 1.25–2.5 ppm, effects were ulceration of nasal mucous membranes, chronic bronchitis, and, in some cases, asthma.[3] In one case, a worker exposed to dust concentrations below 1 mg/m^3 developed cough, rhinitis, breathlessness, and wheezing about 1 month after initial exposure.[4] Symptoms developed within minutes of exposure to the dust, which occurred during the loading of chemicals into a reactor. Within 3 months his symptoms worsened, and he was admitted to the hospital for an acute asthmatic attack. The patient had a positive challenge test to maleic anhydride but was negative to phthalic anhydride, to which he was concomitantly exposed. In another report, occupational allergic IgE-mediated rhinoconjunctivitis and contact urticaria from maleic anhydride was confirmed in a worker who presented with rhinitis, dyspnea, conjunctivitis, and itchy wheals.[5]

The dust on dry skin may result in a delayed burning sensation, but, on moist skin, the sensation is almost immediate, producing erythema, which may progress to vesiculation.[3] Prolonged or repeated exposure also may cause dermatitis.

In rats maleic anhydride has an oral LD_{50} of 1050 mg/kg. It is corrosive to the skin and eyes of rabbits with a dermal LD_{50} of 2620 mg/kg.[6] An inhalation study of rats, hamsters, and monkeys exposed to 1.1, 3.3, or 9.8 mg/m^3, respectively, 6 hours/day, 5 days/week for 6 months revealed dose-related signs of nasal and ocular irritations including discharge, sneezing, gasping, and coughing for all species.[6] No treatment-related effects were observed in hematology, clinical chemistry, urinalysis, and pulmonary function tests. Although microscopic evaluation showed evidence of nasal irritation, there was no evidence of systemic toxicity directly attributable to maleic anhydride.

In a study in which rats were injected subcutaneously with 1 mg of maleic anhydride in oil twice weekly for 61 weeks, two of three surviving animals developed fibrosarcomas, which appeared 80 weeks after the start of the experiment.[7] Administered in the diet of rats for 2 years, it was not carcinogenic.[8]

Pregnant rats treated orally with up to 140 mg/kg/day from day 6 to day 15 of gestation had no treatment-related effects on fetal

development.[9] In a multigenerational study, no adverse effects on fertility or pups were observed at doses up to 55 mg/kg/day over two generations; at 150 mg/kg/day, maleic anhydride was toxic to parental animals, causing renal cortical necrosis in both females and males.[9]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 0.1 ppm (0.4 mg/m^3) with a SEN notation for sensitization.

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MANGANESE (and Compounds)
CAS: 7439-96-5

Mn

Compounds: Manganese dioxide; manganese tetroxide; manganous chloride; manganous sulfate

Physical Form. Elemental manganese is a silver solid

Uses/Sources. Manufacture of alloys, dry cell batteries; glass; inks; ceramics; paints; welding rods; rubber and wood preservatives; fungicides; mining and processing of manganese ores

Exposure. Inhalation

Toxicology. The major concern of humans exposed to manganese is its effects on the central nervous system after chronic exposure.

The neurological disorder known as chronic manganese poisoning or manganism occurs after variable periods of heavy exposure ranging from 6 months to 3 years.[1,2] The disease begins insidiously with headache, asthenia, irritability, and, occasionally, psychotic behavior.[1] The latter, manganese psychosis, occurs most frequently in miners rather than in industrial workers and consists of transitory psychological disturbances such as hallucinations, compulsive behavior, and emotional instability.[3] Severe somnolence, followed by insomnia, often is found early in the disease. As manganese exposure continues, symptoms include generalized muscle weakness, speech impairment, incoordination, and impotence; tremor, paresthesia, and muscle cramps have been noted.[1,3,4] In the advanced stage, the subject exhibits excessive salivation, inappropriate emotional reactions, and Parkinson-like symptoms, such as masklike facies, severe muscle rigidity, and gait disorders.[1] Manganism is reversible if it is limited to psychological disturbances and the subject is removed from exposure. Established neurological signs and

symptoms tend to persist or even progress in the absence of additional exposure.[5]

Exposure levels associated with advanced manganism typically have been very high; 150 cases were found in three mines where levels reached 450 mg/m^3.[2] More recent studies report cases showing neurological symptoms and a few signs at lower concentrations. Of 36 workers exposed to magnesium dioxide dust ranging from 6.8 to 42.2 mg/m^3, 8 exhibited symptoms of manganism.[6] Neurological screening of 117 workers with exposures greater than 5 mg/m^3 revealed 7 cases with definite signs and symptoms.[7] Comparison of 369 workers exposed to 0.3–20 mg/m^3 suggested that slight neurological disturbances may occur at exposures less than 5 mg/m^3, but the disturbances seem to be more prevalent at higher exposures.[8] Low-level exposure to manganese ranging from 0.19 to 1.39 mg/m^3 for 1–45 years has reportedly caused alterations in neurophysiological and psychological parameters that were interpreted as preclinical signs of manganism.[9] Neurological testing of manganese oxide-exposed workers showed reduced hand steadiness and reaction times, which were significantly associated with blood manganese and with years of manganese exposure, respectively.[10]

One of the striking aspects of manganism is its similarity to Parkinson disease.[11] In both conditions neuropathologic changes occur in the basal ganglia with selective destruction of dopaminergic neurons.

An association between manganese exposure and pulmonary effects including pneumonia, chronic bronchitis, and airway disability has been observed. Extrapolation from animal studies suggests that it is unlikely that manganese could be the sole etiologic agent responsible for serious pathologic changes in the lungs. Instead, it is possible that susceptibility to infection is increased.[1]

Acute poisoning by manganese is rare but may occur after ingestion of large amounts of manganese compounds or from inhalation. Inhaled manganese compounds tend to produce more severe toxicity than ingested manganese compounds. This is probably attributable to the difference in route-specific uptake of manganese from the lung (often assumed at 100%) compared with the gastrointestinal tract (3–5%).[12] Freshly formed manganese oxide fumes at high concentrations may cause metal fume fever. This influenza-like illness is characterized by chills, fever, sweating, nausea, and cough. The syndrome begins 4–12 hours after exposure and lasts for 24 hours without causing permanent damage.[13]

Anecdotal reports have suggested that exposure to high levels of manganese dusts results in decreased libido, impotence, and decreased fertility.[11] In animal studies, growth and maturation of the testes was delayed after oral exposure.[14] Intratracheal administration of a single dose of 160 mg manganese/kg in rabbits resulted in degeneration of the seminiferous tubules with loss of spermatogenesis and complete infertility within 8 months.[15]

Repeated subcutaneous or intraperitoneal injection of manganese dichloride caused increased incidences of lymphosarcomas in mice.[16] Chronic oral exposure of rats to manganese sulfate led to a slight increase in pancreatic tumors that was not dose responsive.[11] There is no information relating manganese exposure to cancer occurrence in humans.[11] Genotoxic assays have yielded mixed results.[11]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for manganese as Mn is 0.2 mg/m^3.

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MANGANESE CYCLOPENTADIENYL TRICARBONYL

CAS: 12079-65-1

C_5H_5-$Mn(CO)_3$

Synonyms: MCT; cymantrene; cyclopentadienyl manganese carbonyl

Physical Form. Liquid

Uses. Octane enhancer for gasoline

Exposure. Inhalation; skin absorption

Toxicology. Manganese cyclopentadienyl tricarbonyl (MCT) causes convulsions and pulmonary edema in laboratory animals.

The oral LD_{50} in rats was 22 mg/kg, and the expected dose for convulsions was 32 mg/kg.[1] Phenobarbital pretreatment prevented the convulsions and pulmonary damage ordinarily caused by a 50 mg/kg intraperitoneal dose of MCT.

The pneumotoxicity of MCT in rats was compared with that of manganese methylcyclopentadienyl carbonyl by subcutaneous administration of 0.5, 1.0, or 2.5 mg/kg of both compounds.[2] MCT was twice as potent in causing large increases in pulmonary lavage albumin and protein content.

The Russian literature indicates that rats exposed 4 hours/day to 1 mg/m^3 for 11 months showed no outward indications of toxicity, but there was decreased diuresis, as well as some protein excretion in the urine.[3] MCT penetrated the tails of rats and caused death.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for manganese cyclopentadienyl tricarbonyl is 0.1 mg/m^3 as Mn with a notation for skin.

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MANGANESE TETROXIDE
CAS: 1317-35-7

Mn_3O_4

Synonyms: Manganese oxide; trimanganese tetroxide

Physical Form. Powder

Source. Fume generated whenever manganese oxides are heated in air; ferromanganese fume, generated in the pouring and casting of molten ferromanganese, is largely manganese tetroxide.

Exposure. Inhalation

Toxicology. Manganese tetroxide affects the central nervous system, and toxicity occurs mostly in chronic form (manganism).

The neurological disorder known as chronic manganese poisoning occurs after variable periods of heavy exposure ranging from 6 months to 3 years.[1,2] The disease begins insidiously with headache, asthenia, and irritability. As exposure continues, symptoms include generalized muscle weakness, speech impairment, incoordination, and impotence. Tremor, paresthesia, and muscle cramps have been noted.[3] In the advanced stage, the subject exhibits excessive salivation, inappropriate emotional reactions, and Parkinson-like symptoms, such as masklike facies, severe muscle rigidity, and gait disorders.

In a report of five cases of manganism in a steel plant, three resulted from exposure to ferromanganese fume and two from exposure to ferromanganese dust.[4] As indicated above, ferromanganese fume is primarily manganese tetroxide. Two of the workers exposed to the fume worked in a pig casting operation where the exposure was estimated to have been 13.3 mg/m^3 for 5 years.

Inhalation of manganese tetroxide dust can lead to an inflammatory response in the lung.[5] Symptoms may include cough, bronchitis, pneumonitis, and occasionally pneumonia. It has been noted that this type of inflammatory response is characteristic of nearly all inhalable particulate matter and not unique to manganese-containing particles.

It is generally held that manganese fume is more hazardous than equivalent concentrations of manganese-containing dust.

A slight decrease in pregnancy rate was observed in female rats exposed to 130 mg manganese/kg body weight per day as manganese tetroxide in the diet for 90–100 days before breeding.[6]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for manganese fume is 1 mg/m^3 with a short-term excursion limit (STEL)/ceiling of 3 mg/m^3.

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MERCURY
CAS: 7439-97-6

Hg

Synonyms: Quicksilver; mercury vapor; mercury liquid; mercury salts

Physical Form. Silver-white heavy liquid metal

Uses. Electrical apparatus; measurement and control systems such as thermometers and sphygmomanometers; agricultural and industrial poisons; catalyst; antifouling paint; dental practice; gold mining

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Acute exposure to high concentrations of mercury vapor causes severe respiratory damage, whereas chronic exposure to lower levels is primarily associated with central nervous system damage and renal effects.

Inhalation of mercury vapor may produce a metal fume fever-like syndrome, including chills, nausea, general malaise, tightness in the chest, and respiratory symptoms.[1] High concentrations cause corrosive bronchitis and interstitial pneumonitis.[2] In the most severe cases, the patient will succumb because of respiratory insufficiency.[2] In one episode involving four workers, it was estimated that mercurial pneumonitis resulted from exposure for several hours to concentrations ranging between 1 and 3 mg/m^3.[3]

With chronic exposure to mercury vapor, early signs are nonspecific and include weakness, fatigue, anorexia, loss of weight, and disturbances of gastrointestinal function.[2] This syndrome has been termed asthenic-vegetative syndrome, or micromercurialism. At higher exposure levels, a characteristic mercurial tremor appears, beginning with intentional tremors of fingers, eyelids, and lips, and may progress to generalized trembling of the entire body and violent chronic spasms of the extremities.[2,4] Parallel to the development of tremor, mercurial erethism develops. This is characterized by behavioral and personality changes, increased excitability, loss of memory, insomnia, and depression. In severe cases, delirium and hallucination may occur. Another characteristic feature of mercury intoxication is severe salivation and gingivitis. Chronic changes in the cornea and lens have also been described.[5]

It has been estimated that the probability of manifesting typical mercurialism with tremor and behavioral changes will increase with exposures to concentrations of 0.1 mg/m^3 or higher.[2]

On significant inhalation of metallic mercury vapors, some people (primarily children) exhibit a syndrome known as acrodynia, or pink disease. Symptoms include severe leg cramps, irritability, erythema, and subsequent peeling of the hands, nose, and soles of the feet.[6]

Renal damage has been reported after both acute and chronic exposure.[6,7] Mercury is known to accumulate in the kidneys, and case studies have described increased creatinine excretion, proteinuria, hematuria, and degeneration of the convoluted tubules in exposed individuals. Increased levels of the urinary enzyme NAG (*N*-acetyl-β-glycosaminidase), compared with controls, have been observed in chronically exposed workers.[8,9]

Ingestion of mercuric salts causes corrosive ulceration, bleeding, and necrosis of the gastrointestinal tract, usually accompanied by shock and circulatory collapse.[2,4] If the patient survives the gastrointestinal damage, renal failure occurs within 24 hours owing to necrosis of the proximal tubular epithelium, followed by oliguria, anuria, and uremia. Chronic low-dose exposure to mercury salts, or probably even elemental mercury vapor, may also induce an immunologic glomerular disease.[2,4]

Applied locally, mercury may cause sensitization dermatitis.[1,2]

In several epidemiological studies, no increased risk for congenital abnormalities, stillbirths, or spontaneous abortions was observed with occupational exposure to mercury.[6] Exposure of pregnant rats on gestational days 10–15 at 0.5 mg/m^3 resulted in an increased incidence of resorptions; gross cranial defects occurred at this dose when it was administered throughout the entire gestational period.[10]

Intraperitoneal injection of metallic mercury in rats has produced sarcomas.[1] The sarcomas develop without exception at those sites in direct contact with the metal, suggesting a foreign body reaction rather than chemical carcinogenesis. Mercuric chloride was tested for carcinogenicity in 2-year gavage studies in mice and rats.[11] Three of 49 high-

dose male mice had renal tubule tumors, and in rats there was an increase in squamous cell papillomas of the forestomach in males.

There is no conclusive evidence from epidemiological studies that mercury increases cancer risk in humans.[12] In the few studies in which increases have been reported, concomitant exposure to other known carcinogens has confounded the results. The IARC has determined that there is inadequate evidence in humans for the carcinogenicity of mercury and mercury compounds.[12] In animals there is inadequate evidence for carcinogenicity of metallic mercury and limited evidence for the carcinogenicity of mercuric chloride.

Genotoxic assays have given both positive and negative results.[6]

Blood and urine mercury concentrations are commonly used as biomarkers of mercury exposure.[6]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for elemental and inorganic mercury is 0.025 mg/m^3, as Hg, and for aryl mercury compounds is 0.1 mg/m^3, as Hg; there is a notation for skin absorption and an A4-not classifiable as a human carcinogen designation.

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MERCURY (Alkyl Compounds)
CAS: Varies with compound

RHgX

Compounds: Methyl mercury; ethyl mercury chloride, dimethyl mercury

Physical Form. Colorless liquids

Uses. Fungicides in seed dressings, folial sprays; preservative solutions for wood, paper pulp, textiles, and leather

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Organo (alkyl) mercury compounds cause dysfunction of the central nervous system (CNS) and kidneys and are irritants of the eyes, mucous membranes, and skin; methyl mercury causes developmental effects in humans.

Methyl and ethyl mercury compounds have similar toxicological properties, and there is no sharp demarcation between acute and chronic poisoning.[1] Once a toxic dose has been absorbed and retained for a period of time, functional disturbances and damage occur. The latency period for a single toxic dose may vary from one to several weeks; longer latency periods on the order of years have been reported for chronic exposures.[1,2]

Symptoms of poisoning include numbness and tingling of the lips, hands, and feet (paresthesia); ataxia; dysarthria; concentric constriction of the visual fields; impairment of hearing; and emotional disturbances.[3]

With severe intoxication, clonic seizures may occur, and the symptoms are usually irreversible.[1,3] Severe intoxication also results in incontinence, periods of spasticity and jerking movements of the limbs, head, or shoulders, and bouts of groaning, moaning, shouting, or crying; less frequent symptoms are dizziness, hypersalivation, lacrimation, nausea, vomiting, and diarrhea or constipation.[4] The pathologic changes in the CNS are characterized by general neuron degeneration in the cerebral cortex, especially the visual areas of the occipital cortex, and gliosis.[1]

An epidemic of intoxication from ingestion of fish contaminated with methyl mercury occurred in the Minamata district in Japan, and, as a result, methyl mercury intoxication is often referred to as Minamata disease.[4] Infants born to mothers with exposure to large amounts of methyl mercury had microencephaly, mental retardation, and cerebral palsy with convulsions. In an incidence in Iraq, ingestion of wheat products contaminated with methyl mercury fungicide by pregnant women caused similar symptoms of neurological damage and mental retardation.[2] The fetus is particularly sensitive to the effects of methyl mercury, which interferes with organ development. Toxic concentrations inhibit the normal migration of nerve cells from the central parts of the neurotube toward the peripheral parts of the brain cortex and thus inhibits the normal development of the fetal brain.[1] Differences between fetal and adult hematocrits may result in differing mercury concentrations in the two; studies suggest that the difference in sensitivity between the fetus and the adult organism is close to a factor of 2.[1] It has been suggested that women of childbearing age should have no occupational exposure to alkyl mercury.[2]

The biological half-life in humans for methyl mercury is about 70 days; because elimination is slow, irregular, and individualized, there is a considerable risk of an accumulation of mercury to toxic levels.[3] A precise relationship between atmospheric levels of alkyl mercury and concentrations of mercury in blood or urine has not been shown.[3] Clinical observations indicate that concentrations of 50–100 μg mercury/100 ml of whole blood may be associated with symptoms of intoxication; concentrations around 10–20 μg mercury/100 ml are not associated with symptoms.[3] In a study of 20 workers engaged in the manufacture of organic mercurials and exposed for 6 years to mercury concentrations in air between 0.01 and 0.1 mg/m^3, there was no evidence of physical impairment or clinical laboratory abnormalities.[5] Low levels of methyl mercury in the blood do not seem to affect the results of behavioral performance tests.[6]

Methyl mercury concentrations in hair can be used as an indicator of mercury concentration in blood, with a ratio of blood to hair of 1:250.[2] Under occupational conditions, the possibility of external contamination of hair should be kept in mind.

The alkyl mercury halides are irritating to the eyes, mucous membranes, and skin and may cause severe dermatitis and burns; skin sensitization has occasionally occurred.[7,8]

Epidemiological studies of methyl mercury-exposed populations have not shown any evidence of a carcinogenic effect.[9] In chronic animal studies, methyl mercury chloride in the diet caused an increase in renal

adenomas and adenocarcinomas in male mice.[9] The IARC has determined that there is inadequate evidence in humans for the carcinogenicity of mercury compounds but there is sufficient evidence for the carcinogenicity of methyl mercury chloride in experimental animals.[10] Organomercury compounds exert a direct effect on chromosomes by inhibiting the spindle mechanism, resulting in clastogenic effects.[10]

Methyl mercury vapor is detectable by smell at concentrations well below those that on intermittent exposure could prove hazardous.[11]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 0.01 mg/m^3, as Hg, with a short-term exposure limit (STEL) of 0.03 mg/m^3 and a notation for skin absorption.

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MESITYL OXIDE

CAS: 141-79-7

$(CH_3)_2CCHCOCH_3$

Synonyms: Methyl isobutenyl ketone; isopropylideneacetone; 4-methyl-3-pentene-2-one

Physical Form. Oily, colorless liquid

Uses. Solvent; chemical intermediate

Exposure. Inhalation

Toxicology. Mesityl oxide is an irritant of the eyes and mucous membranes; at high concentrations it causes narcosis in animals, and it is expected that severe exposure will produce the same effect in humans.

Human subjects exposed to 25 ppm for 15 minutes experienced eye irritation; at 50 ppm, there was also nasal irritation and a persistent unpleasant taste that remained with many subjects 3–6 hours after the exposure.[1] Liquid mesityl oxide produces dermatitis with sustained skin contact.[2]

Rats and guinea pigs exposed 8 hours/day to 500 ppm for 10 days had nose and eye irritation and developed slight kidney injury; slight liver and lung injury were observed in a few animals; 13 of 20 animals died from 30 exposures of 8 hours each at 500 ppm, whereas all animals tested at 250 ppm survived.[3,4] Guinea pigs exposed to 2000 ppm for up to 422 minutes died during or after exposure. Signs of eye and respiratory tract irritation with gradual loss of corneal and auditory reflexes preceded coma and death.

Exposure of rats to irritant levels of mesityl oxide (above 137 ppm) caused leucopenia.[5] This hematologic effect was regarded as an associative response to the sensory irritation, which can act as a stressor to laboratory animals.

The strong peppermint or honeylike odor is detectable at 12 ppm; severe overexposure is unlikely because of local irritation and odor; however, olfactory fatigue may occur.[3,6]

The irritation and systemic effects resulting from mesityl oxide exposure appear to be more serious than those produced by the lower ketones.[7]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 15 ppm (60 mg/m^3) with a short-term excursion limit (STEL)/ceiling of 25 ppm (100 mg/m^3).

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METHACRYLIC ACID
CAS: 79-41-4

$C_4H_6O_2$

Synonyms: 2-Methyl-2-propenoic acid; 2-methylenepropionic acid; α-methacrylic acid

Physical Form. Colorless liquid

Uses. Manufacture of methacrylic resins and plastics

Exposure. Inhalation; skin absorption

Toxicology. Methacrylic acid is an irritant of the eyes, nose, throat, and skin and is corrosive on contact.

Rats exposed to 1300 ppm 5 hours/day for 5 days showed nose and eye irritation but no adverse findings in blood and urine tests.[1] Exposure of rats to 300 ppm 6 hours/day for 20 days resulted in no clinical signs, but histopathologic findings showed slight renal congestion.

Applied to the depilated guinea pig abdomen for 24 hours under an occlusive wrap, the liquid produced severe irritation.[2] The liquid also produced severe irritation when instilled in rabbit eyes.

Rats exposed to 300 ppm, 6 hours/day, during gestation days 6–20 showed no sign of developmental toxicity; maternal toxicity was evidenced by a significant decrease in body weight gain and food consumption.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 20 ppm (70 mg/m^3).

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METHANE
CAS: 74-82-8

CH_4

Synonyms: Marsh gas, methyl hydride

Physical Form. Colorless gas

Uses/Sources. As a constituent in cooking and illuminating gas; in the production of ammonia, methanol, and chlorohydrocarbons; it occurs in natural gas and is produced by the decomposition of organic matter.

Exposure. Inhalation

Toxicology. Methane acts as a simple asphyxiant by causing oxygen deprivation at very high concentrations.

Methane is practically inert and has no demonstrated physiological or toxicological effects.[1,2] Methane can cause asphyxiation in healthy individuals only when it is present in very high concentrations or when atmospheric oxygen has been otherwise reduced. Humans are asymptomatic while breathing air containing 16–21% oxygen by volume.[3] Oxygen concentrations of 12–16% cause tachypnea, tachycardia, and slight incoordination; concentrations of 10–14% cause exhaustion on minimal exertion; and at 6–10% nausea, vomiting, and unconsciousness occur.[3] At concentrations less than 6% convulsions and cardiac arrest ensue.[3]

Methane exposure can occur in coal miners when methane is trapped within coal seams. Because methane is lighter than air, it accumulates first at the top of an enclosed space; loss of consciousness and collapse thus can be lifesaving.[2]

On the skin, liquefied methane can cause frostbite.[1,2]

The ACGIH has not assigned a numerical threshold limit value (TLV) for occupational exposure to methane because the limiting factor is the available oxygen, the minimal content of which should be 18% by volume under normal atmospheric pressure; at concentrations below those required to produce any severe oxygen deprivation, methane presents an explosive and flammable hazard.[4]

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METHOMYL
CAS: 16752-77-5

$C_5H_{10}N_2O_2S$

Synonyms: Lannate; DuPont 1179; methyl-*N*[(methylcarbamoyl)oxy]thioacetimidate

Physical Form. Crystalline solid

Uses. Carbamate insecticide for broad-spectrum control of pests

Exposure. Inhalation

Toxicology. Methomyl is a short-acting carbamate anticholinesterase agent that is rapidly metabolized and demonstrates little evidence of cumulative toxicity.

Exposure to methomyl can result in inhibition of cholinesterase activity in blood and at nerve synapses of muscles, secretory organs, and nervous tissue in the brain and spinal cord.[1] Central nervous system signs and symptoms include anxiety, restlessness, depression of respiratory and circulatory centers, ataxia, convulsions, and coma.

Nicotinic signs of intoxication include muscle weakness, tremor and fasciculations, and involuntary twitching. Muscle weakness that affects the respiratory muscles may contribute to dyspnea and cyanosis. Tachycardia may result from stimulation of sympathetic ganglia in cardiac tissue and may mask the bradycardia due to the muscarinic action on the heart. Nicotinic action at the sympathetic ganglion may also result in pallor, high blood pressure, and hyperglycemia. Muscarinic signs include miosis, increased salivation, sweating, urination and defecation, vomiting and nausea, and increased bronchial secretions.

In a survey of occupationally acquired disease in workers at a pesticide plant, 11% of 102 workers were hospitalized from exposure to methomyl and 3,4-dichloroaniline.[2] On clinical evaluation, 5 (46%) of 11 packaging workers, the group with the highest exposure to methomyl, had experienced blurred vision or pupillary constriction. In cases of accidental ingestion by humans, doses of 12–15 mg/kg body weight have proven lethal.[3]

Methomyl has high acute oral and inhalation toxicity in rats with an oral LD_{50} of 17–45 mg/kg body weight and a 4-hour LC_{50} of 0.26 mg/l in aerosol form.[3] Signs of acute intoxication are consistent with cholinesterase inhibitors and include profuse salivation, lacrimation, tremor, and pupil constriction. The most consistent findings in longer-term studies at the higher dietary levels were decreases in body weight gain in rodents and reduced red blood cell indices in rodents and dogs.[3] Long-term carcinogenicity studies in mice and rats administered methomyl up to 1000 ppm in the diet showed no evidence of carcinogenic effects.[4] Methomyl did not show mutagenicity or cause primary DNA damage in bacterial or mammalian cells in vitro. It showed cytogenetic potential in human lymphocytes *in vitro* as indicated by an increase in micronuclei and chromosomal aberrations.[3]

Methomyl did not produce embryotoxic or teratogenic effects in rats or rabbits at doses that caused maternal toxicity.[3] No effects on fertility, gestation, or lactation indices were found in three-generation reproduction studies in rats.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for methomyl is 2.5 mg/m^3.

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methyl *N*[[(methylamino)carbonyl]oxy]ethanimidothioate. *Toxicol Appl Pharmacol* 40:1–17, 1970

METHOXYCHLOR

CAS: 72-43-5

$C_{16}H_{15}Cl_3O_2$

Synonyms: 1,1,1-Trichloro-2,2-bis(*para*-methoxyphenyl)ethane; methoxy-DDT; Marlate; Prentox; Methoxcide

Physical Form. Crystalline solid

Use. Insecticide

Exposure. Inhalation; ingestion

Toxicology. Methoxychlor at high concentrations is a convulsant; in animals it causes effects to the reproductive system.

No adverse effects on health or clinical laboratory data were found in groups of volunteers given 2 mg/kg/day for 8 weeks.[1]

The oral LD_{50} in rats ranged from 5.0 to 7.0 g/kg.[2] Dogs fed a daily diet containing 4 g/kg body weight developed signs of chlorinated hydrocarbon intoxication, including fasciculations, tremor, hyperesthesia, tonic seizures, and tetanic convulsions after 5–8 weeks. Most of the dogs died within 3 weeks after onset of effects.[3] Rabbits given oral daily doses of 200 mg/kg died after 4–15 doses; autopsy findings included mild liver damage and nephrosis.[4] In mice given 5 mg orally over 3 days and in rats given 20 mg, there was a uterotrophic effect manifested as a marked increase in weight of the uterus.[5]

Methoxychlor is a weakly estrogenic compound that has been shown to alter fertility in male and female rats and cause development effects. Administration of 1000 mg/kg in the diet of pregnant rats caused vaginal defects in their offspring.[6] Reduced fertility in both sexes was also noted when the offspring reached maturity.[6] Subchronic administration of methoxychlor in the diet of rats at 25, 50, 100, or 200 mg/kg/day from weaning through adulthood produced a variety of effects: In females, methoxychlor accelerated the age at vaginal opening (a morphologic indicator of puberty), cycles were in constant estrus, ovarian luteal function was inhibited, and implantation was blocked; in males, treatment reduced growth, seminal vesicle weight, cauda epididymal weight, caudal sperm content, and pituitary weight.[7] Puberty was delayed in the two highest dosage groups, but the fertility of treated males was not reduced when they were mated with untreated females.[7]

Administered to orally to pregnant rats on gestational days 6–19 at doses up to 150 mg/kg/day or to rabbits at doses up to 45 mg/kg/day, methoxychlor resulted in decreased fetal weights and an increased incidence of fetal resorptions and skeletal variations at maternally toxic doses.[8] Reproductive studies have shown that female mice exposed only during their first pregnancy, and then allowed to mate again, delivered second litters (F_{1b}) with reproductive alterations in the form of significant advancement in vaginal opening time even though the F_{1b} litters had not been directly exposed to methoxychlor.[9]

Female mice fed up to 2000 mg/kg and males given 3500 mg/kg in the diet for 78 weeks showed no statistically significant increase in the incidence of benign and malignant tumors that could be attributed to methoxychlor.[10] Chronic feeding studies in rats, at 850 and 1400 mg/kg for males and females, respectively, also showed no significant carcinogenic responses, although high tumor rates in controls may have masked detection.[10] Based on NCI results and several earlier animal studies, the IARC has determined that there is insufficient evidence that methoxychlor is carcinogenic in experimental animals and that it is not classifiable as to its carcinogenicity to humans.[11]

Studies on the genotoxicity of methoxychlor have generally yielded negative results in prokaryotic assays, mixed results in *in vitro* eukaryotic systems, and negative results in *in vivo* studies.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for methoxychlor is 10 mg/m^3.

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2-METHOXYETHANOL

CAS: 109-86-4

$CH_3OCH_2CH_2OH$

Synonyms: 2ME; Ethylene glycol monomethyl ether; EGME; methyl cellosolve; Dowanol EM

Physical Form. Flammable, colorless, liquid

Uses. Solvent; jet fuel anti-icing additive; in the semiconductor industry in manufacture of printed circuit boards

Exposure. Inhalation; skin absorption

Toxicology. 2-Methoxyethanol (2ME) affects the central nervous system and depresses the hematopoietic system; in animals, it causes adverse reproductive effects, including teratogenesis, testicular atrophy, and infertility.

Cases of toxic encephalopathy and macrocytic anemia have been reported from industrial exposures that may have been as low as 60 ppm.[1] Symptoms were headache, drowsiness, lethargy, and weakness. Manifestations of central nervous system instability included ataxia, dysarthria, tremor, and somnolence. These effects were usually reversible. In acute exposures, the central nervous system effects were the more pronounced, whereas prolonged exposure to lower concentrations primarily produced evidence of depression of erythrocyte formation. When exposure was reduced to 20 ppm, no further cases occurred.

Two workers exposed primarily through skin contact showed signs of encephalopathy; one had bone marrow depression, whereas the other had pancytopenia.[2]

The LC_{50} for a 7-hour exposure of rats was 1480 ppm; death was due to lung and kidney injury.[3] Rabbits exposed to 800 and 1600 ppm for 4–10 days showed irritation of the upper respiratory tract and lungs, severe glomerulonephritis, hematuria, and albuminuria.[3] Oral doses of 100 mg/kg/day for 4 days produced hemorrhagic bone marrow, thymic

atrophy, lymphocytopenia, and neutropenia in rats.[4] Instilled in rabbit eyes, 2ME caused immediate pain, conjunctival irritation, and slight corneal cloudiness, which cleared in 24 hours.[3]

Adverse reproductive effects have been reported in a number of species.[5] Testicular atrophy was observed in rats and mice exposed at 1000 ppm for 9 days and in rabbits exposed for 13 weeks at 300 ppm.[5,6] Slight to severe microscopic testicular changes occurred at 30–100 ppm in rabbits. At 500 ppm for 5 days, there was temporary infertility in male rats and abnormal sperm head morphology in mice.[5]

Exposure of pregnant rabbits to 50 ppm 6 hours/day on gestational days 6 through 18 induced significant increases in the incidence of malformations, especially of the skeletal and cardiovascular systems, and in the number of resorptions.[7] At this exposure level, decreases in maternal body weight gain, as well as decreased fetal weight, occurred.[7] Only slight fetotoxicity was observed in mice and rats similarly exposed. In another study, fetal cardiovascular and skeletal defects occurred in rats exposed at the 50 ppm level on days 7–15 of gestation.[5] By gavage, 250 mg/kg on days 7–14 caused increased embryonic deaths and gross fetal defects in mice.[8] Further studies on developmental phase-specific effects in mice showed exencephaly to be related to exposure between gestation days 7–10, whereas paw anomalies were maximal after administration on gestational day 11.[9] In rabbits, the most sensitive species tested to date, the minimally toxic fetal dose was 10 ppm, and the no-observed-effect level was 3 ppm.[5] Recent studies with pregnant cynomolgus monkeys showed that 12 mg/kg given by daily gavage throughout organogenesis (days 20–45) induced embryonic death; at 36 mg/kg, all eight pregnancies ended in death of the embryo, and one of the dead embryos was missing a digit on each forelimb.[10] A single dermal dose of 500 mg/kg or greater, administered to pregnant rats, also produced significant increases in external, visceral, and skeletal malformations in the offspring.[11]

A clinical and cytogenetic evaluation of 41 offspring of 28 females occupationally exposed to 2ME for an average duration of 4.6 years found 6 offspring of 5 women who exhibited characteristic dysmorphic features that were not observed in 35 offspring of 23 women who worked in the same facility but were not pregnant at the time of exposure. Persistent cytogenetic damage was observed exclusively in all 6 in utero-exposed offspring but not in their 12 matched non-in utero-exposed controls.[12] In several studies, increased frequency of spontaneous abortions, disturbed menstrual cycle, and subfertility have been demonstrated in women working in the semiconductor industry; however, the contribution of 2ME in relation to other exposure factors in the semiconductor industry is unclear.[13] A survey of 73 painters who worked in a large shipyard found an increased prevalence of oligospermia and azoospermia and an increased odds ratio for a lower sperm count per ejaculate.[12] The authors attributed these effects to exposure to 2ME and 2-ethoxyethanol, although it should be noted that shipyard painters may be exposed to a variety of other agents, including cadmium, zinc, iron, and lead, which may affect sperm quality.

Recent studies have focused on the immunotoxic effects of glycol ethers; some investigators have suggested that the immune system may be more sensitive than the reproductive system to the toxic effects of 2ME.[14] Rats receiving 50–20 mg/kg/day for 10 days had decreases in thymus weights in the absence of decreased body weights, and lymphoproliferative responses to concanavalin A and phytohemagglutinin were also reduced. In another report, dose-related increases in natural killer cell cytotoxic activities and decreases in specific antibody production were observed after 2ME exposure in the drinking water.[15] Recent studies in rats showed that dermal exposure to 2ME also compromises the ability of the immune system to mount an effective humoral immune response.[16]

NIOSH recommended exposure limits of 0.1 ppm as a time-weighted average for up to 10-hour days during a 40-hour workweek; it is also recommended that dermal contact be prohibited.[17]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 2-

methoxyethanol is 5 ppm (16 mg/m^3) with a notation for skin absorption.

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2-METHOXYETHYL ACETATE
CAS: 110-49-6

$CH_3COOCH_2CH_2OCH_3$

Synonyms: Ethylene glycol monomethyl ether acetate; EGMEA; 2-MEA; methyl cellosolve acetate; methyl glycol acetate

Physical Form. Colorless liquid

Uses. Lacquer industry; textile printing; manufacture of photographic film, coatings, and adhesives

Exposure. Inhalation; skin absorption

Toxicology. 2-Methoxyethyl acetate affects the central nervous system, the hematopoietic system, and the reproductive system in animals.

In a recent report, shipyard painters with mean exposure concentrations of 3.03 ppm had significantly lower white blood cell counts than controls, and 6 of 57 painters were leukopenic.[1]

Mice and rabbits tolerated 1-hour exposure to 4500 ppm with only irritation of mucous membranes; guinea pigs survived the 1-hour exposure but succumbed days later.[2] Repeated exposure to 500 ppm for 8 hours/day caused narcosis and death in cats, and 1000 ppm for 8 hours/day was lethal to rabbits; all animals showed kidney injury.[2] Anemia was observed in cats repeatedly exposed to 200 ppm for 4–6 hours.

Dose-related increases in testicular atrophy and leukopenia have been reported in mice after administration of 63–2000 mg/kg 5 days/week for 5 weeks.[3]

2-Methoxyethyl acetate is hydrolyzed in vivo to form 2-methoxyethanol, which is subsequently metabolized to 2-methoxyacetic acid, a proported teratogenic substance.[4] Consequently, the acetate is expected to show profiles of developmental and reproductive toxicity similar to those of 2-methoxyethanol (qv). In a case report, a woman who was extensively exposed to 2-methoxyethyl acetate, both dermally and probably by inhalation during pregnancy, gave birth to two sons with hypospadias.[5] Because family history and medical examination showed no overt risks other than the significant exposure of the mother, and because 2-methoxyethyl acetate can cause teratogenic effects in animals, the malformations were attributed to the exposure.

The liquid is mildly irritating to the eyes of rabbits, but not to the skin; prolonged contact can result in significant absorption.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 2-methoxyethyl acetate is 5 ppm (24 mg/m^3) with a notation for skin absorption. NIOSH has recommended exposure limits of 0.1 ppm as a time-weighted average for a 10-hour day during a 40-hour workweek and also has recommended that dermal contact be prohibited.[6]

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4-METHOXYPHENOL

CAS: 150-76-5

$C_7H_8O_2$

Synonyms: Hydroquinone monomethyl ether; 4-hydroxyanisole

Physical Form. Solid

Uses. Inhibitor for acrylic monomers; stabilizer for chlorinated hydrocarbons and ethyl cellulose; UV inhibitor

Exposure. Inhalation

Toxicology. 4-Methoxyphenol is expected to cause liver and renal toxicity with narcosis, but only at high levels of exposure.

4-Methoxyphenol is moderately potent acutely, as evidenced by an oral LD_{50} of

1600 mg/kg for the rat.[1] The gross signs of acute intoxication included paralysis and anoxia at lower doses and narcosis at higher doses.

During the industrial handling of 4-methoxyphenol, two of eight process workers developed skin depigmentation.[2]

In medicine, 4-methoxyphenol is known as 4-hydroxyanisole. It is a depigmenting agent that has been shown to have activity against malignant melanoma when given intra-arterially in humans.[3] An intravenous dose escalation study was carried out with the aim of obtaining maximum plasma concentrations in a 5-day schedule. Eight patients entered this study, which was stopped because of drug toxicity after three patients had been treated at the third dose escalation of 15 g/m^2. Two patients had WHO grade 4 liver toxicity, one also had grade 4 renal toxicity, and another had grade 4 hemoglobin toxicity. Extrapolated plateau plasma levels between 112 and 860 µmol/l were obtained, which in vitro studies suggested would be cytotoxic.

Rats administered diets containing 2% 4-methoxyphenol for 2 years had atypical hyperplasias, papillomas, and squamous cell carcinomas in the forestomach.[4] Cytotoxicity and cell proliferation appeared to be important factors for this nongenotoxic carcinogen.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 4-methoxyphenol is 5 mg/m^3.

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METHYL ACETATE
CAS: 79-20-9

$CH_3C(O)OCH_3$

Synonyms: Acetic acid, methyl ester

Physical Form. Colorless, highly volatile liquid

Uses. Solvent for lacquers, oils, and resins

Exposure. Inhalation

Toxicology. Methyl acetate is irritating to the eyes and mucous membranes; at high concentrations it causes narcosis in animals, and it is expected that severe exposure will produce the same effect in humans.

Human exposure to 10,000 ppm for a short period of time resulted in eye, nose, and throat irritation, which persisted after cessation of exposure.[1] In a man exposed to unmeasured concentrations, effects were general central nervous system depression, headaches, and dizziness, followed by blindness of both eyes caused by atrophy of the optic nerve.[2] The toxic action on the optic nerve is possibly related to the presence of methanol after hydrolysis of methyl acetate.[3]

Cats exposed to 5000 ppm showed eye irritation and salivation; at 18,500 there was dyspnea, convulsions, and narcosis; 54,000 ppm was lethal within minutes.[1] Repeated exposure at 6600 ppm resulted in weight loss and weakness.

Prolonged contact with the liquid may cause dryness, cracking, and irritation of the skin.

Methyl acetate was not mutagenic in a number of bacterial strains with or without metabolic activation.[4]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 200 ppm (606 mg/m^3) with a short-term excursion limit (STEL)/ceiling of 250 ppm (757 mg/m^3).

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METHYL ACETYLENE
CAS: 74-99-7

CH_3CCH

Synonyms: Allylene; propyne; propine

Physical Form. Colorless gas

Uses. Propellant; welding

Exposure. Inhalation

Toxicology. At high concentrations methyl acetylene causes narcosis in animals, and it is expected that severe exposure will produce the same effect in humans.

Rats exposed to 42,000 ppm became hyperactive within the first 7 minutes, and at the end of 7 minutes they appeared lethargic and ataxic.[1] After 95 minutes, the animals were completely anesthetized. There was no mortality when the exposure was terminated at the end of 5 hours, and most of the animals recovered completely within 40 minutes. Edema and alveolar hemorrhage were present in animals killed at termination of the single exposure, whereas bronchiolitis and pneumonitis were observed in rats killed 9 days after exposure.

Two dogs and 20 rats were exposed to 28,700 ppm, 6 hours/day, 5 days/week for 6 months; after 7 minutes of exposure ataxia was noted in the rats, and after 13 minutes, ataxia and mydriasis were observed in the dogs. Within 15 minutes, the dogs also exhibited staggering, marked salivation, and muscular fasciculations. There was a 40% mortality rate among exposed rats versus a 10% mortality rate in the control animals.

Methyl acetylene has a "sweet" odor similar to acetylene.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 1000 ppm (1640 mg/m^3).

REFERENCE

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METHYL ACRYLATE
CAS: 96-33-3

$CH_2CHCOOCH_3$

Synonyms: 2-Propenoic acid methyl ester; acrylic acid methyl ester; methyl propenoate

Physical Form. Colorless liquid

Uses. As a monomer, polymer, and copolymer in the manufacture of acrylic fibers

Exposure. Inhalation; skin absorption

Toxicology. Methyl acrylate is a lacrimating agent and an irritant of the skin and mucous membranes.

The lowest dose reported to have any irritant effect in humans is 75 ppm.[1]

Skin sensitization has been reported and may be elicited by systemic exposure after dermal contact.[2]

The liquid is readily absorbed by mucous membranes and through the skin. The dermal

LD_{50} in rabbits was 1.3 g/kg. It was moderately to severely irritating to rabbit skin. The liquid tested in the eye caused mild reversible injury.

In rats, the LD_{50} for 4 hours was 1350 ppm.[3] Behavior of the animals suggested irritation of the eyes, nose, and respiratory tract, with labored breathing. At necropsy, there were no discernible gross abnormalities of the major organs. In the same study, rats were exposed to methyl acrylate at 110 ppm 4 hours/day, 5 days/week, for 32 days. There were no overt signs of central nervous system or respiratory effects, although the animals huddled with their eyes closed, possibly indicating some eye discomfort.

No exposure-related clinical signs or lesions of systemic toxicity and no oncogenic responses were observed in rats exposed by inhalation at concentrations of 0, 15, 45, or 135 ppm 6 hours/day, 5 days/week, for 24 consecutive months.[4] Dose-related changes occurred in the anterior portion of the olfactory epithelium and consisted of atrophy of the neurogenic epithelial cells followed by progressive hyperplasia of the reserve cells and ultimately loss of the upper epithelial cell layer. Opacity and neovascularization of the cornea were also observed in methyl acrylate-exposed animals.

Methyl acrylate was not found to be mutagenic in the *Salmonella* assay, but it increased chromosomal aberrations *in vitro* and tested positive in the micronucleus assay in mice.[4]

The IARC has determined that there is inadequate evidence for the carcinogenicity of methyl acrylate to experimental animals and that it is not classifiable as to its carcinogenicity to humans.[5]

No treatment-related increases in embryo/fetal mortality or fetal malformations were observed in rats after exposures of up to 100 ppm, 6 hour/day, during days 6–20 of gestation.[6] Fetal and maternal toxicity were evidenced by reduced weights.

The 2003 ACGIH threshold limit value-time-weighted average TLV-TWA is 2 ppm (7 mg/m^3) with a notation for skin absorption and sensitization.

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METHYLACRYLONITRILE
CAS: 126-98-7

$CH_2C(CH_3)CN$

Synonyms: 2-Methyl-2-propenenitrile; 2-cyanopropene-1; isopropene cyanide; isopropenylnitrile; methacrylonitrile

Physical Form. Colorless liquid

Uses. Widely used monomer in the production of plastic elastomers and coatings

Exposure. Inhalation; skin absorption

Toxicology. Methylacrylonitrile is a potent neurotoxin.

The approximate LC_{50} for mice exposed to airborne concentrations for 1 hour was 630 ppm, and for a 4-hour exposure it was 400 ppm.[1] Exposure to 75 ppm for 8 hours caused no deaths, but respiratory difficulties and convulsions were observed. In a study with rats exposed at concentrations between 3180 and 5700 ppm the clinical symptoms, rapid unconsciousness with convulsions and lethality, suggested that the acute toxicity is predominantly caused by metabolically formed cyanide.[2] Cyanide reacts readily with cytochrome oxidase in mitochondria and inhibits cellular respiration. Cyanide antidotes were also effective against methylacrylonitrile toxicity. Metabolic studies have suggested that methylacrylonitrile may also exert toxic effects by directly interacting with the cytoplasmic (hemoglobin) and membrane proteins of red blood cells.[3] A significant decrease in the red blood cell count and in the level of hemoglobin, probably from hemolysis, has been observed after methacrylonitrile administration.[4]

The oral LD_{50} was 20–25 mg/kg in mice and 25–50 mg/kg in rats.[5] Symptoms included weakness, tremors, cyanosis, and convulsions. When beagle dogs were exposed 7 hours/day, 5 days/week to 13.5 ppm over a period of 90 days, two of three animals exhibited convulsions and loss of motor control in the hind limbs about halfway through the exposure period.[6] No effects occurred at 3.2 ppm.

In 2-year gavage studies of mice (administered 1.5, 3, or 6 mg/kg/day) and rats (administered 3, 10, or 30 mg/kg/day) there was no evidence of carcinogenic activity.[7] Significant increases in nonneoplastic lesions of the nose and liver occurred in high-dose rats.[7]

Methacrylonitrile was not mutagenic in *Salmonella* or *Drosophila* assays; it was also negative in the micronucleus test.[7]

Prenatal exposure of rats and rabbits to doses of methylacrylonitrile that did not induce toxicity in the adults also did not induce developmental toxicity in the fetus.[8] Methylacrylonitrile was also determined not to be a selective reproductive toxin. In a continuous breeding study in rats, doses that caused decreases in epididymal sperm density of F_1 males occurred concomitant with reduced body weight.[9]

The liquid was rapidly absorbed through the skin of a rabbit and caused death after 3 hours at a dose of 2.0 ml/kg.[1] Skin irritation at the site of application was negligible. One drop in the eye of a rabbit caused transient irritation.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for methylacrylonitrile is 1 ppm (2.7 mg/m^3) with a notation for skin absorption.

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METHYLAL
CAS: 109-87-5

$CH_2(OCH_3)_2$

Synonyms: Dimethoxymethane; formal; methylene dimethyl ether

Physical Form. Colorless liquid

Uses. Solvent; fuel; in perfume

Exposure. Inhalation

Toxicology. Methylal is an irritant of the eyes and mucous membranes, and, at high concentrations, it causes central nervous system depression.

In humans, methylal has been used as an anesthetic in a number of surgical operations; however, anesthesia was produced more slowly than with ether, and the effect of methylal was more transitory.[1]

In guinea pigs exposed to a concentration near 154,000 ppm, effects included vomiting, lacrimation, sneezing, cough, and nasal discharge; coma occurred in 20 minutes and death in 2.5 hours.[1]

The LC_{50} for a 7-hour exposure of mice was 18,354 ppm.[1] Exposure 7 hours/day to 11,300 ppm for 1 week caused mild eye and nose irritation, incoordination, and light narcosis after 4 hours; the exposure was fatal to 6 of 50 mice. Animals exposed to toxic concentrations often developed marked fatty changes in the liver, kidney, and heart and inflammatory changes in the lungs.[1] Rats were unaffected by eight 6-hour exposures to 4000 ppm.[2]

Methylal can cause superficial irritation of the eyes.[1] Frequent or prolonged skin contact with the liquid may cause dermatitis due to a defatting action.

The liquid has a chloroform-like odor and pungent taste.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 1000 ppm (3110 mg/m^3).

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METHYL ALCOHOL
CAS: 67-56-1

CH_3OH

Synonyms: Methanol; wood spirit; carbinol; wood alcohol; wood naphtha; methylol; Columbian spirit; colonial spirit

Physical Form. Colorless liquid

Uses. In production of formaldehyde; in paints, varnishes, cements, inks, and dyes

Exposure. Inhalation; skin absorption

Toxicology. Methyl alcohol causes optic neuropathy, metabolic acidosis, and respiratory depression.

Although methyl alcohol poisoning has occurred primarily from the ingestion of adulterated alcoholic beverages, symptoms also can occur from inhalation or absorption through the skin.[1,2] Impairment of vision and death from absorption by the latter routes were reported in the early literature.[2] Typically, within 18–48 hours after ingestion, patients develop nausea, abdominal pain, headache, and abnormally slow, deep breathing. These are accompanied by visual symptoms ranging from blurred or double vision and changes in color perception to constricted visual fields and complete blindness.[1,3] The most severely poisoned patients become comatose and may die; those who recover from coma may be found blind.[3] One of the most striking features of methyl alcohol poisoning is acidosis; the degree of aci-

dosis has been found to closely parallel the severity of poisoning.[1] Accumulated evidence suggests that chronic exposure to 1200–8300 ppm can lead to impaired vision.[1] Exposure to vapor concentrations ranging from 365 to 3080 ppm may result in blurred vision, headache, dizziness, and nausea.[4]

In the eyes, the liquid has caused superficial lesions of the cornea that were of a nonserious nature.[1] Prolonged or repeated skin contact will cause dermatitis, erythema, and scaling.[1]

The presence of an asymptomatic latent period after ingestion suggests that methyl alcohol must be metabolized before toxicity is fully manifest.[1] This concept also explains the discrepancy between plasma concentrations of methyl alcohol and clinical signs of toxicity.[5] Furthermore, methyl alcohol poisoning is ameliorated by ethanol, a substance with greater affinity than methyl alcohol for alcohol dehydrogenase, which is responsible for the initial step in metabolism.[5] The metabolite formate appears to be the mediator of ocular injury and acidosis.[6] The individual variations in activity of the alcohol dehydrogenase systems, which are responsible for the oxidative metabolism of methyl (and ethyl) alcohol, may well account for the wide variation in the individual responses observed with methyl alcohol poisoning.[1]

Metabolic differences also account for the great species variability in methyl alcohol toxicity with humans and nonhuman primates being uniquely sensitive.[7] (A relatively poor ability to metabolize the methanol-metabolized formate in these species leads to increased blood formate levels and subsequent metabolic acidosis and neuronal toxicity.)

In developmental animal studies, methyl alcohol produced malformations in mice and rats after inhalation of 15,000 or 20,000 ppm, respectively, for 6–7 hours/day during gestation; slight maternal toxicity was also observed.[8] A recent study in *Macaca fasicularis* monkeys exposed to 200, 600, or 1800 ppm methyl alcohol before and during pregnancy found exposure-associated effects in the offspring including low arousal of neonates, changes in visual recognition memory, delays in sensorimotor development in males, and a severe wasting syndrome in females after 1 year.[9]

There is no evidence from animal studies to suggest that methyl alcohol is carcinogenic, but the lack of an appropriate animal model is noted.[7] In general, it was not genotoxic in a variety of *in vivo* and *in vitro* assays.[7,8]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for methyl alcohol is 200 ppm (262 mg/m^3) with a short-term excursion limit (STEL) of 250 ppm (328 mg/m^3) and a notation for skin absorption.

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methanol in nonhuman primates. *Govt Reports Announcements & Index (GRA&I)*, Issue 10, 2002

METHYLAMINE

CAS: 74-89-5

CH_3NH_2

Synonyms: Monomethylamine; aminomethane

Physical Form. Gas

Uses. Tanning and dyeing industries; fuel additive; chemical intermediate in the production of pharmaceuticals, insecticides, and surfactants

Exposure. Inhalation

Toxicology. Methylamine is a severe irritant of the eyes and skin; in animals repeated inhalation causes upper respiratory tract irritation.

In humans, brief exposure at 20–100 ppm is said to produce transient irritation of the eyes, nose, and throat.[1] No symptoms of irritation are produced from longer exposures at less than 10 ppm. On the basis of the irritant properties of methylamine, it is possible that severe exposure may cause pulmonary edema.

In rats, when administered orally as the base in a 40% aqueous solution, the LD_{50} was 0.1–0.2 g/kg.[1] Repeated exposures of rats at 750 ppm 6 hours/day, 5 days/week for 2 weeks caused severe body weight loss, liver damage, hematopoietic abnormalities, and some deaths.[2] Histopathologic effects, which were also observed with similar dosing at 250 ppm, included necrosis and ulceration of the respiratory mucosa of the nasal turbinates and atrophy with regeneration of the olfactory mucosa. Repeated exposures at 75 ppm produced marginal changes in the olfactory mucosa.

Inhalation exposure of rats to 19 µmol/l caused pulmonary edema at 1 week; associated interstitial pneumonitis progressed to fibrosis.[3] (The authors note that methylamine, a metabolite of methyl isocyanate, may contribute to the pulmonary fibrosis found in Bhopal victims who were exposed to massive amounts of methyl isocyanate.)

In the eyes of rabbits, one drop of a 5% aqueous solution caused conjunctival hemorrhage, superficial corneal opacities, and edema.[4] On the skin of animals, a 40% solution caused necrosis.[1]

The ammonia-like odor is detectable at less than 5 ppm.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 5 ppm (6.4 mg/m^3) with a short-term excursion limit (STEL)/ceiling of 15 ppm (19 mg/m^3).

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METHYL *n*-AMYL KETONE

CAS: 110-43-0

$CH_3COC_5H_{11}$

Synonym: 2-Heptanone; methyl pentyl ketone

Physical Form. Liquid

Uses. Organic solvent

Exposure. Inhalation

Toxicology. Methyl *n*-amyl ketone irritating to the eyes and mucous membranes; at high concentrations it causes narcosis in animals, and it is expected that severe exposure will produce the same effect in humans.

There have been no reports of effects in humans, and the concentration at which irritation may be produced is not known.[1]

However, both sensory and pulmonary irritation can be expected with sufficient exposure. Sensory irritation is characterized by immediate eye and nose irritation that may increase to sensations of burning and pain and is due to interaction between the substance and receptors in the trigeminal nerve.[2] Vapors reaching the lower respiratory tract as well as the lungs may interact with the nerves in these regions, causing dyspnea and breathlessness or pulmonary irritation.

In guinea pigs, exposure to 4800 ppm caused narcosis and death in 4–8 hours; 2000 ppm was strongly narcotic, and 1500 ppm was irritating to the mucous membranes.[3]

Rats and monkeys exposed to 1025 ppm methyl n-amyl ketone for 6 hours/day, 5 days/week for 9 months showed no evidence of neuropathy or clinical signs of illness. Microscopic examination revealed no tissue damage.[4]

Applied full strength to intact or abraded rabbit skin for 24 hours under occlusion, the liquid was not irritating; on the uncovered rabbit belly it produced a moderate degree of irritation. The liquid has a marked fruity odor and a pearlike flavor.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 50 ppm (233 mg/m^3).

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N-METHYL ANILINE

CAS: 100-61-8

$C_6H_5NHCH_3$

Synonyms: Monomethylaniline; *N*-methylaminobenzene

Physical Form. Colorless or slightly yellow liquid that becomes brown on exposure to air

Uses. Chemical syntheses

Exposure. Inhalation; skin absorption

Toxicology. *N*-methyl aniline causes anoxia in animals because of the formation of methemoglobin.

There are no reports of human intoxication from exposure to *N*-methyl aniline. Overexposure would be expected to produce the effects of methemoglobinemia, including cyanosis (especially in the lips, nose, and earlobes), weakness, dizziness, and severe headache.

Animal fatalities occurred from daily exposure to 7.6 ppm; signs of intoxication included prostration, labored breathing, and cyanosis. Methemoglobinemia developed promptly in rabbits and cats; the rabbits also exhibited mild anemia and bone marrow hyperplasia.[1] Animals

that died had pulmonary involvement ranging from edema to interstitial pneumonia, as well as occasional centrilobular hepatic necrosis and moderate kidney damage.

Applied to the skin of rabbits 3 g/kg of body weight caused death.[2] The minimum lethal dose in rabbits was 280 mg/kg when administered orally; signs of intoxication included weight loss, dyspnea, prostration, cyanosis, and occasional terminal convulsions.[2]

N-methyl aniline (1.95 g/kg of food) given together with sodium nitrite (1.0 g/l of drinking water) to Swiss mice resulted in a 17% incidence of lung adenomas and a 14% incidence of malignant lymphomas; there were no carcinogenic effects in animals treated with *N*-methyl aniline alone, suggesting that *in vivo* nitrosation is necessary for forming carcinogenic nitrosamines.[3]

In bacterial mutagenicity assays *N*-methyl aniline was negative with or without metabolic activation.[4]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 0.5 ppm (2.2 mg/m^3) with a notation for skin absorption.

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METHYL BROMIDE
CAS: 74-83-9

CH_3Br

Synonyms: Bromomethane; monobromomethane; isobrome

Physical Form. Colorless gas

Uses. Fumigant of soil and stored foods for the control of insects, fungi, and rodents; methylating agent; previously used as a refrigerant and fire-extinguishing agent

Exposure. Inhalation; skin absorption

Toxicology. Methyl bromide is a neurotoxin and causes convulsions; very high concentrations cause pulmonary edema; chronic exposure causes peripheral neuropathy.

There are numerous reports of human intoxication from accidental exposure associated with its use in fire extinguishers and as a fumigant.[1] Estimates of concentrations that have caused human fatalities range from 8000 ppm for a few hours to 60,000 ppm for a brief exposure. The onset of toxic symptoms is usually delayed, and the latent period may be from 30 minutes to several hours. Early symptoms include headache, visual disturbances, nausea, vomiting, and malaise.[2] In some instances there is eye irritation, vertigo, and intention tremor of the hands; the tremor may progress to twitchings and finally to convulsions of the Jacksonian type, being first restricted to one extremity but gradually spreading to the entire body.[1,3] Severe exposure may lead to pulmonary edema.[4] Tubular damage in the kidneys has been observed in fatal cases.[2] Some of those who have recovered from severe intoxication have had persistent central nervous system effects, including vertigo, depression, hallucinations, anxiety, and inability to concentrate.[2]

Eight of 14 workers repeatedly exposed to the vapor (concentration unmeasured) for 3 months developed peripheral neuropathy; all

recovered within 6 months.[5] In two cases of chronic methyl bromide poisoning there were central neurological symptoms (dizziness, unstable gait, and reduced visual acuity) followed by peripheral neuropathy that persisted for at least 2 years.[6]

It is unlikely that bromide ion resulting from metabolic conversion of methyl bromide plays a significant role in the toxicity of methyl bromide.[7] Blood bromide levels after methyl bromide poisoning are much lower than those associated with intoxication by inorganic bromide salts. Concentrations of 100 mg/l have been associated with death following methyl bromide exposure, whereas blood bromide levels of 1000 mg/l or greater have been observed after therapeutic administration of inorganic bromides in the absence of signs of intoxication.[8] A recent report of six methyl bromide poisonings showed serum bromide concentrations at the time of hospital admission to be a poor predictor of survival.[8] One fatal case had an antemortem bromide level of 108 mg/l, whereas a survivor measured 321 mg/l. In another instance, nine workers exposed to 200 ppm or more on two consecutive days had varying symptoms ranging from headache to severe reactive myoclonus and convulsions.[9] A direct association between serum bromide concentrations and neurological symptoms was absent.

Contact with the eye by the gas or liquid resulted in transient irritation and conjunctivitis.[10] Minor skin exposure to the liquid produced erythema and edema.[11] Prolonged or repeated contact resulted in deeper burns with delayed vesiculation.[11] It is doubtful that significant cutaneous absorption occurs. Although victims of skin exposure may show symptoms of neurotoxicity, inhalation is considered the likely cause.[11]

Toxicological studies in animals indicate a steep concentration-response curve for methyl bromide and clear species and sex differences in sensitivity.[12] Inhalation exposure up to 120 ppm 6 hours/day for 13 weeks resulted in 17% mortality in male mice but no mortality in female mice or rats of either sex. No methyl bromide-induced histologic lesions were observed in either species, including mice killed in a moribund state. At 160 ppm for 6 hours/day there was high mortality in rats and mice. Primary target organs were the brain, kidney, nasal cavity, heart, adrenal gland, liver, and testis. Nephrosis was likely a major cause of morbundity and death of mice, whereas neuronal necrosis may have been the principal lesion contributing to the early death of some rats. At 66 ppm, rats and guinea pigs showed no response for up to 6-month exposure but rabbits and monkeys developed paralysis within 3 months; the paralysis was particularly severe in rabbits, which also had pulmonary lesions. No toxic response was observed at 17 ppm.

Repeated exposure at 70 ppm of female rats before and during pregnancy did not cause maternal or embryo toxicity, but severe neurotoxicity and mortality were produced in rabbits.[13] No developmental effects were noted in fetuses of rats or rabbits administered methyl bromide by gavage during gestation despite toxicity to dams at the highest dose.[14] In a two-generation reproduction study of rats fed diets containing 500 ppm total bromine, food consumption was lower in the F_1 parental females and F_2 pups had lowered body weights.[15] No other treatment-related changes were found for clinical signs, estrous cycle, sperm count and morphology, mating, fertility, gestation, litter size, pup viability, and gross or histopathologic examination.

In a 90-day study, 50 mg/kg administered by gavage 5 days per week caused squamous cell carcinomas of the forestomach in 13 of 20 rats; a dose-related incidence of hyperplasia was observed at the 2 and 10 mg/kg levels.[16] A second study using the same experimental design found that the early hyperplastic lesions of the forestomach regressed after discontinuation of treatment and should not be considered neoplasms.[17] Rats fed diets containing 500 ppm total bromine after fumigation with methyl bromide for 2 years showed no evidence of a carcinogenic response.[18] Inhalation of up to 90 ppm, 6 hours/day, 5 days/week for 29 months caused degenerative and hyperplastic changes of the nasal olfactory epithelium, an increased incidence of lesions in the heart, hyperkeratosis in the esophagus and forestom-

ach, but no increase in tumor incidence in rats.[19] In another inhalation study in rats, an increase in the incidence of adenomas of the pituitary gland was observed in high-dose male rats.[20]

The IARC has determined that there is limited evidence in experimental animals and inadequate evidence in humans for the carcinogenicity of methyl bromide.[20]

Methyl bromide is genotoxic in a number of *in vivo* and *in vitro* assays and does not require metabolic activation.[21] This is consistent with the fact that it is a direct-acting alkylating agent that can methylate DNA.

Methyl bromide itself has poor warning properties, but warning agents such as chloropicrin are frequently added.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for methyl bromide is 1 ppm (3.89 mg/m^3) with a notation for skin absorption.

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METHYL BUTYL KETONE

CAS: 591-78-6

$C_6H_{12}O$

Synonyms: 2-Hexanone; *n*-butyl methyl ketone; MBK, MNBK; propylacetone

Physical Form. Colorless liquid

Uses. As industrial solvents for adhesives, lacquers, paint removers, and acrylic coatings

Exposure. Inhalation; skin absorption

Toxicology. Methyl butyl ketone (MBK) at high concentrations may produce ocular and respiratory irritation followed by central nervous system depression and narcosis. Chronic inhalation causes peripheral neuropathy.

Human volunteers exposed to a vapor concentration of 1000 ppm for several minutes developed moderate eye and nasal irritation.[1]

Although MBK is considered to be only a mild sensory irritant with acute exposure, an outbreak of neuropathy among workers in a coated fabrics plant in 1973 revealed the more serious consequences of chronic exposure.[2] Workers exposed to the mixed vapor of MBK (averaging 9.2 ppm in front of printing machines and 36 ppm behind) for 6–12 months with extensive skin exposure developed peripheral neuropathy.[3–6] The neurological pattern was one of a distal motor and sensory disorder, with minimal loss of tendon reflexes.[5] In those with prominent motor involvement, initial symptoms included slowly developing weakness of the hands, with difficulty in pincer movement on the grasping of heavy objects, or weakness of the ankle extensors, resulting in a slapping gait. In other cases, the initial symptoms were intermittent tingling and paresthesias in the hands or feet. Nerves affected could be sensory nerves, motor nerves, or both. Nerve biopsies usually showed enlarged axons, diminished numbers of myelinated nerve fibers, an increased neurofilament accumulation, and increased wallerian degeneration. In some cases, the condition progressed slowly for several months after cessation of exposure; in moderate to severe cases improvement occurred over a period of up to 8 months, although they did not always fully recover.[2–6] Body weight reduction was the only other toxicological effect noted.

The 4-hour LC_{50} for the rat was 8000 ppm.[2] In guinea pigs, exposure to 10,000–20,000 ppm was potentially lethal in 30–60 minutes; concentrations greater than 20,000 ppm killed the animals within a few minutes; at 6000 ppm, there were signs of narcosis after 30 minutes, deep anesthesia after 1 hour, and death after approximately 6.5 hours.[1] A maximum of 3000 ppm for 1 hour did not cause serious disturbances.

Animals continually exposed to concentrations between 100 and 600 ppm developed signs of peripheral neuropathy after 4–8 weeks; in cats, the conduction velocity of the ulnar nerve was less than one-half of normal after exposure for 7–9 weeks.[4] In these animals, histologic examination revealed focal denudation of myelin from nerve fibers with or without axonal swelling. In rats and monkeys, adverse effects on neurophysiological indicators of nervous system integrity were found with 9-month exposures to 100 ppm, 6 hours/day, 5 days/week.[7] MBK neuropathies, however, occurred only after 4-month exposure at 1000 ppm. Four months of intermittent respiratory exposure of rats to 1300 ppm caused severe symmetric weakness in the hind limbs.[8]

Damage caused by hexacarbons such as MBK has also been found in the optic tract and hypothalamus of the cat. These findings are significant, owing to the possibility that

such central nervous system damage is permanent, whereas the peripheral nervous system shows regeneration.[9]

Testicular atrophy of the germinal epithelium was seen in male rats administered 660 mg/kg by gavage for 90 days.[10] A reduction in total circulating white blood cells has also been reported after MBK exposure.[1]

Pregnant rats exposed to 1000 or 2000 ppm MBK during 21 days of gestation had reduced weight gain; a significant decrease in the number and weight of live offspring was also observed in the high-dose group. Behavioral alterations, including deficits in avoidance conditioning and increased activity, occurred in the offspring of both groups.[11]

2,5-Hexanedione was found to be a major metabolite of MBK in several animal species; peripheral neuropathy occurred in rats after daily subcutaneous injection of 2,5-hexanedione at a dose of 340 mg/kg 5 days/week for 19 weeks.[12–14] Nonneurotoxic aliphatic monoketones, such as methyl ethyl ketone, enhance the neurotoxicity of MBK. In one rat study, the longer the carbon chain length of the nonneurotoxic monoketone, the greater the potentiating effect on MBK. It is expected that exposure to a subneurotoxic dose of MBK, plus high doses of some aliphatic monoketones, would also produce neurotoxicity. In addition, MBK itself potentiates the toxicity of other chemicals.[2]

MBK can cause mild eye irritation and minor transient corneal injury. Repeated skin contact may be irritating because of the ability of MBK to defat the skin, resulting in dermatitis.[1]

MBK has an acetone-like odor detectable at 0.076 ppm.[15]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 5 ppm (20 mg/m^3) with a TLV-short-term excursion limit (STEL) of 10 ppm (40 mg/m^3) and a notation for skin absorption.

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METHYL CHLORIDE

CAS: 74-87-3

CH_3Cl

Synonyms: Chloromethane; monochloromethane

Physical Form. Colorless gas

Uses. As a chemical intermediate, especially in industrial methylating reactions; as a blowing agent for plastic foams; rarely as a refrigerant

Exposure. Inhalation

Toxicology. Methyl chloride is a central nervous system depressant; it may cause kidney and liver damage, and it is a reproductive toxin and a teratogen in experimental animals.

Human fatalities have occurred from a single severe exposure or prolonged exposures to lower concentrations.[1] Acute poisoning in humans is characterized by a latent period of several hours, followed by dizziness, drowsiness, staggering gait and slurred speech; nausea, vomiting and diarrhea; double vision; weakness, paralysis, convulsions, cyanosis, and coma.[1–3] Renal or hepatic damage and anemia may also occur. Recovery from an acute exposure usually occurs within 5–6 hours but may take as long as 30 days or more in massive exposures.[1] Recurrence of symptoms after apparent recovery without further exposure has been observed in the immediate postexposure period. Six workers chronically exposed to 200–400 ppm for 2–3 weeks developed symptoms of intoxication including confusion, blurring of vision, slurred speech, and staggering gait; symptoms disappeared over a period of 1–3 months after removal from exposure.[1] In one study, however, 10 of 24 survivors of methyl chloride poisoning experienced mild neurological or psychiatric sequelae 13 years after the incident.[4] Subsequent follow-up of this same small cohort 20 years later also revealed an excess mortality from cardiovascular diseases and an elevated risk for all cancers and lung cancer in particular.[5]

Concentrations ranging from 150,00 to 300,000 ppm are expected to kill most animals in a short time; levels of 20,000–40,000 are considered dangerous within 60 minutes.

Mice exposed continuously to 100 ppm or intermittently to 400 ppm for 11 days had histopathologic evidence of brain lesions characterized by degeneration and atrophy of the granular layer of the cerebellum.[6] Daily exposure of mice to 1000 ppm for 2 years induced a functional limb muscle impairment and atrophy of the spleen.[7] At 2400 ppm administered daily, there were renal and hematopoietic effects and the mice were moribund by day 9.[6] For rats exposed to 3500 ppm 6 hours/day for up to 12 days, clinical signs included severe diarrhea, incoordination of the forelimbs, and, in a few animals, hind limb paralysis and convulsions.[8]

Daily exposure of male rats to 1500 ppm for 10 weeks caused severe testicular degeneration; no males sired litters during a subsequent 2-week breeding period.[9]

An increase in fetal heart defects was observed in mice after 12 days of repeated exposure in utero to 500 ppm.[10]

Rats (F344) and mice (B6C3F1) were exposed at 0, 50, 225, or 1000 ppm 6 hours/day, 5 days/week for 2 years. An excess of tumors was found only in male mice of the highest exposure group; cystadenomas and adenomas of the renal cortex and papillary cystadenomas were reported.[11,12] Subsequent mechanistic studies have shown that methyl chloride does not exhibit direct methylation of DNA *in vivo*.[12] It has been suggested that methyl chloride, at high doses, is metabolically transformed to formaldehyde, which causes DNA-protein cross-links and DNA single-

strand breaks.[13] It has also been noted that such a mechanism is not likely to be operative in humans at low exposure concentrations.[12]

Methyl chloride was mutagenic to bacteria and genotoxic in a number of mammalian cell systems in vitro.[14] It gave positive results in the dominant lethal test in rats *in vivo*.[14]

NIOSH recommends that methyl chloride be considered a potential occupational teratogen and carcinogen.[11]

The IARC states that there is inadequate evidence for the carcinogenicity of methyl chloride to experimental animals and humans.[14]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for methyl chloride is 50 ppm (103 mg/m^3) with a short-term excursion limit (STEL)/ceiling of 100 ppm (207 mg/m^3) and a notation for skin absorption.

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METHYL 2-CYANOACRYLATE
CAS: 137-05-3

$C_5H_5NO_2$

Synonyms: Mecrylate; methyl cyanoacrylate

Physical Form. Colorless liquid

Uses. In high-bond strength, fast-acting glues (e.g., Krazy Glue); surgical use as tissue adhesive

Exposure. Inhalation

Toxicology. Methyl 2-cyanoacrylate is an irritant of the eyes and nose and can induce occupational asthma.

Nose and eye irritation occur at levels of 2–5 ppm; at 20 ppm there is lacrimation and

rhinorrhea, and concentrations greater than 50 ppm produce painful irritation.[1]

A 52-year-old man exposed to undetermined concentrations of methyl cyanoacrylate in an adhesive developed respiratory symptoms after 1 month on the job.[2] Eleven weeks after stopping work, the patient was challenged by working with the adhesive for 25 minutes. This provoked a 42% fall in FEV_1 15 hours after the challenge and symptoms of rhinitis during most of the day. Other studies have linked exposure to methyl 2-cyanoacrylate with occurrences of asthma, but no conclusions can be drawn regarding whether asthma was induced by an allergenic or irritation mechanism because challenge concentrations were directly irritant.[3]

The LC_{50} in rats was 101 ppm for 6 hours.[4] Repeated exposure of rats to 31.3 ppm, 6 hours/day, 5 days/week, for 12 exposures caused no signs of mucous membrane irritation. The acute dermal toxicity is low, with the dermal LD_{50} in guinea pigs being greater than 10 ml/kg.

When methyl 2-cyanoacrylate was applied as an adhesive to rabbit or human eyes, some reports described corneal haze and inflammation; other reports with highly purified material indicated less toxicity.[5] Mistaken use in the eyes as eyedrops has caused immediate brief smarting and firm gluing of the eyelids together.[6] Acetone on a swab can be used to unglue the lids and remove the glue from the cornea with minimal, if any, injury to the corneal epithelium.[5]

Methyl 2-cyanoacrylate was positive in the Ames test with and without activation by metabolic enzymes.[7]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for methyl 2-cyanoacrylate is 2 ppm (9.1 mg/m^3) with a short-term excursion limit (STEL) of 4 ppm (18 mg/m^3).

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METHYLCYCLOHEXANE

CAS: 108-87-2

C_7H_{14}

Synonyms: Cyclohexylmethane; hexahydrotoluene

Physical Form. Colorless liquid

Uses. Solvent; organic synthesis

Exposure. Inhalation

Toxicology. At high concentrations methylcyclohexane causes narcosis in animals, and it is expected that severe exposure will produce the same effect in humans.

No effects have been reported in humans.

Rabbits did not survive exposure for 70 minutes to 15,227 ppm; conjunctival congestion, dyspnea, rapid narcosis, and severe convulsions preceded death.[1] Exposure to 10,000

ppm 6 hours/day for a total of 10 days resulted in convulsions, narcosis, and death.[1] There were no signs of intoxication in rabbits exposed to 2880 ppm for a total of 90 hours, but slight cellular injury was observed in the liver and kidneys.[1]

The only effects seen after chronic exposure of rats, mice, hamsters, and dogs at 400 or 2000 ppm for 1 year were weight depression in hamsters and male rats and progressive renal nephropathy in male rats.[2]

The liquid on the skin of a rabbit caused local irritation, thickening, and ulceration.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 400 ppm (1610 mg/m^3).

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METHYLCYCLOHEXANOL
CAS: 25639-42-3

$CH_3C_6H_{10}OH$

Synonyms: Hexahydrocresol; hexahydromethylphenol; methylhexalin

Physical Form. Colorless viscous liquid that usually exists as a mixture of isomers in which the *meta* and *para* forms predominate.

Uses. Solvent for lacquers; blending agent in textile soaps; antioxidant in lubricants

Exposure. Inhalation; skin absorption

Toxicology. In animals methylcyclohexanol is a mild irritant of the eyes and mucous membranes, and at high concentrations it causes signs of narcosis. It is expected that severe exposure will produce the same effects in humans.

Headache and irritation of the ocular and upper respiratory membranes may result from prolonged exposure to excessive concentrations of the vapor.[1]

Rabbits exposed 6 hours/day to 503 ppm for 10 weeks had conjunctival irritation and slight lethargy.[2] There were no clinical signs of intoxication at 232 ppm for a total exposure of 300 hours.

The minimal lethal dose for rabbits by oral administration was 1.25–2 g/kg; rapid narcosis and convulsive movements preceded death.[3] Sublethal doses caused narcosis with spasmodic head jerking; salivation and lacrimation were also observed; hepatocellular degeneration was apparent at autopsy.

Repeated cutaneous applications to rabbits of large doses of methylcyclohexanol caused skin irritation and thickening, weakness, tremor, narcosis, and death.[3]

Methylcyclohexanol can be detected by its odor at 500 ppm, a concentration capable of causing upper respiratory irritation.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 50 ppm (234 mg/m^3).

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o-METHYLCYCLOHEXANONE

CAS: 583-60-8

$CH_3C_5H_9CO$

Synonyms: 2-Methylcyclohexanone

Physical Form. Clear to pale yellow liquid

Uses. Solvent; rust remover

Exposure. Inhalation; skin absorption

Toxicology. In animals *o*-methylcyclohexanone is an irritant of the eyes and mucous membranes, and at high concentrations it causes narcosis; it is expected that severe exposure would produce the same effects in humans.

Several species of animals exposed to 3500 ppm suffered marked irritation of the mucous membranes and became incoordinated after 15 minutes of exposure and prostrate after 30 minutes.[1] Conjunctival irritation, lacrimation, salivation, and lethargy were observed in rabbits exposed to 1822 ppm 6 hours/day for 3 weeks.[2] Exposure of mice to 450 ppm for an unspecified time period resulted in severe irritation of the eyes and respiratory tract.[3]

Repeated cutaneous application to rabbits of large doses of the liquid caused irritation of the skin, tremor, narcosis, and death; the minimum lethal dose was between 4.9 and 7.2 g/kg.[3]

There are no reports of chronic or systemic effects in humans, probably because of the chemical's irritant properties and warning acetone-like odor at levels below those causing serious effects. Furthermore, lethal concentrations of vapors are not expected at temperatures commonly encountered in the workplace.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 50 ppm (229 mg/m^3) with a short-term excursion limit (STEL)/ceiling level of 75 ppm (344 mg/m^3) and a notation for skin absorption.

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2-METHYLCYCLOPENTADIENYL MANGANESE TRICARBONYL

CAS: 12108-13-3

$C_9H_7MnO_3$

Synonyms: MMT; Combustion Improver-2; CI-2; Antiknock-33

Physical Form. Liquid

Uses. Octane enhancer in gasoline; reduces smoke emissions from home, commercial, industrial, and marine burners

Exposure. Inhalation; skin absorption

Toxicology. 2-Methylcyclopentadienyl manganese tricarbonyl (MMT) causes central nervous system effects and liver, kidney, and pulmonary damage in animals.

Accidental exposure to workers has caused metallic taste in the mouth, headache, nausea, gastrointestinal upset, dyspnea, chest tightness, and paresthesia.[1] A quantity of 5–15 ml spilled on one hand and wrist of a worker caused nausea and headache within 3–5 minutes.[2]

Toxic symptoms in various animal species were similar and consisted of excitement and hyperactivity; tremor; spasms; slow, labored respiration; clonic convulsions; and terminal coma.[1] On histologic examination, there was degeneration and necrosis of liver cells and renal tubules, perivascular edema and swelling of the lungs, and degeneration of the cells of the cerebral cortex.

The oral LD_{50} of MMT in mice, rats, rabbits, and guinea pigs ranged from 58 to 905 mg/kg.[3] The dermal LD_{50} in rabbits was 1.35 g/kg. In rats the 4-hour inhalation LC_{50} was 76 mg/m^3.[4] No deaths occurred in cats, rabbits, guinea pigs, mice, or rats after 150 exposures for 7 hours to 6.4 mg/m^3.[5]

Chronic oral administration of 0.5 g/kg in the diet for 12 months caused suppressed weight gain in mice.[6]

Oxidative metabolism in rats appeared to be an important detoxifying mechanism; the intraperitoneal LD_{50} was 12.1 mg/kg for MMT, but two major metabolites, hydroxymethylcyclopentadienyl manganese tricarbonyl and carboxycyclopentadienyl manganese tricarbonyl, caused no significant toxicity even at doses of 250 mg/kg.[7]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 2-methylcyclopentadienyl manganese tricarbonyl is 0.2 mg/m^3, as Mn, with a notation for skin absorption.

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4,4′-METHYLENE BIS(2-CHLOROANILINE)
CAS: 101-14-4

$CH_2(C_6H_4ClNH_2)_2$

Synonyms: Methylene bis(chloroaniline); DACPM; MBOCA; MOCA

Physical Form. Colorless to tan crystals

Uses. Curing agent for polyurethanes and epoxy resins

Exposure. Inhalation; skin absorption

Toxicology. 4,4′-Methylene bis(2-chloroaniline), or MOCA, is carcinogenic in experimental animals.

MOCA causes low to moderate acute toxicity in animals, with marked species

differences.[1] Dogs showed weakness, cyanosis, and methemoglobinemia after oral dosing. Acute effects have not been reported in humans. Sprayed on the skin the liquid caused a burning sensation of the eyes and skin and nausea.[2]

In chronic studies rats fed 1000 ppm MOCA in a standard diet for 2 years developed lung tumors; there were 25 adenomatoses and 48 adenocarcinomas in 88 rats.[3] Accompanying liver changes included hepatocytomegaly, necrosis, bile duct proliferation, and fibrosis.[2] In 88 control animals, there were two lung adenomatoses. MOCA in a low-protein diet caused lung tumors in rats of both sexes, liver tumors in males, and malignant mammary tumors in females.

Repeated subcutaneous injection of MOCA in 34 rats (total dose 25 g/kg for 620 days) resulted in nine liver cell carcinomas and seven lung carcinomas; 13 of 50 control animals developed tumors, but no malignant tumors of the liver or the lungs were observed.[4]

MOCA was fed to male and female mice for 18 months at a dose of either 1 or 2 g/kg; in female mice, but not in males, a statistically significant incidence of hepatoma was observed.[5] In addition, a higher incidence of hemangiosarcomas and hemangiomas was observed in treated animals compared with controls.[5] Urinary bladder tumors (primarily papillary transitional cell carcinomas) occurred in dogs given 100 mg of MOCA by capsule for up to 9.0 years.[6]

There was no evidence that MOCA was tumorigenic in a study of 31 active workers exposed from 6 months to 16 years.[7] Quantitative analysis of the workers' urine confirmed exposure to the chemical. In addition, the records were reviewed for 178 employees who at one time had worked with MOCA but who thereafter had had no further exposure for at least 10 years. The general health of exposed workers with respect to illness, absenteeism, and medical history was similar to that of the total plant population. Two deaths in this group due to malignancy had been diagnosed before any work with or exposure to MOCA.[7] For the plant population in general, there were 115 cancer deaths/100,000 over a 15-year period compared with the national death rate for cancer of 139/100,000 population.

In another report three noninvasive papillary tumors of the bladder were identified in a screening of 540 MOCA workers; two tumors occurred in men with completely normal urine screening who were under 30, had never smoked, and had no previous occupational exposure to known bladder carcinogens.[8]

Exposure to MOCA was believed to be the cause of urinary frequency and mild hematuria in two of six exposed workers; however, a variety of other materials including toluene diisocyanate, polyester resins, polyether resins, and isocyanate-containing resins also were present.[9]

The IARC has determined that there is inadequate evidence for carcinogenicity to humans and sufficient evidence for carcinogenicity to animals. However, on the basis of animal experiments it was concluded that MOCA probably is carcinogenic to humans, and exposure by all routes should be monitored carefully.[2]

MOCA is genotoxic in a wide variety of assays. It also forms adducts with DNA both *in vivo* and *in vitro*.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 4,4′-methylene bis(2-chloroaniline) is 0.01 ppm (0.11 mg/m^3) with an A2-suspected human carcinogen designation and a notation for skin absorption.

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METHYLENE BIS-(4-HEXYLISOCYANATE)

CAS: 5124-30-1

$C_{15}H_{22}N_2O_2$

Synonyms: HMDI; hydrogenated MDI; dicyclohexylmethane-4,4′-diisocyanate; bis(4-isocyanalocyclohexyl)methane; hydrogenated MDI

Physical Form. Liquid

Uses. In the manufacture of polymers

Exposure. Inhalation

Toxicology. Methylene bis-(4-hexylisocyanate) (HMDI) is an irritant of the eyes, nose, and upper respiratory tract and causes dermal sensitization.

Eleven of 15 workers who were exposed to HMDI showed allergic and nonallergic skin reactions.[1] Six suffered from vertigo with or without headaches, and four showed obstructive ventilatory disorders, tachycardia, and hypotension (ECG normal). All were treated with oral antihistamines and local steroid application. The signs of the intoxication disappeared after 10–14 days of treatment. There was no difference in the clinical syndrome between the atopic and the nonatopic workers.

In another case study, a small polyurethane molding plant employing poor hygienic techniques in which a number of employees developed contact dermatitis was described.[2] Three employees were examined. Patch testing in two of these revealed positive reactions suggesting allergic sensitization to an HMDI and to the catalyst methylenedianiline.

A study in mice examined immune responses following topical exposure to three allergenic diisocyanates: diphenylmethane-4,4′-diisocyanate (MDI), dicyclohexylmethane-4,4′-diisocyanate (HMDI), and isophorone diisocyanate (IPDI).[3] Contact and respiratory sensitizers induce differential immune responses in mice characteristic of Th1 and Th2 T helper cell activation, respectively. All three chemicals are contact allergens. MDI is, in addition, a known human respiratory allergen. HMDI and IPDI did not produce an immunologic response in the mouse similar to MDI. These findings suggest that HMDI has much less potential to cause respiratory sensitization in humans than does MDI.[3]

Rats inhaling a lethal concentration of 20 ppm for 5 hours exhibited marked respiratory irritation, tremors, and convulsions during exposure, and their lungs revealed severe congestion and edema after death.[4] HMDI is a strong eye and skin irritant in animals.[5] A 5% solution applied to the skin of guinea pigs produced erythema and edema, and rabbits treated with 0.1 mg showed severe skin reactions.[4]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 0.005 ppm (0.054 mg/m^3).

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METHYLENE BISPHENYL ISOCYANATE

CAS: 101-68-8

$CH_2(C_6H_4NCO)_2$

Synonyms: Methylenediphenyl diisocyanate; MDI; diphenylmethane diisocyanate

Physical Form. Liquid; aerosol

Uses. Production of polyurethane foams and plastics

Exposure. Inhalation

Toxicology. Methylene bisphenyl isocyanate (MDI) is an irritant of the eyes and mucous membranes and a sensitizer of the respiratory tract.

If the breathing zone concentration reaches 0.5 ppm, the possibility of respiratory response is imminent.[1] Depending on the length of exposure and the level of concentration above 0.5 ppm, respiratory symptoms may develop with a latent period of 4–8 hours. Symptoms include increased secretion, cough, pain on respiration, and, if severe enough, some restriction of air movement due to a combination of secretions, edema, and pain. On removal from exposure, the symptoms may persist for 3–7 days.[1]

A second type of response to isocyanates is allergic sensitization of the respiratory tract. This usually develops after some months of exposure.[1–4] The onset of symptoms may be insidious, becoming progressively more pronounced with continued exposure. Initial symptoms are often nocturnal dyspnea and/or nocturnal cough with progression to asthmatic bronchitis.[3] Asthma characterized by bronchial hyperreactivity, cough, wheeze, chest tightness, and dyspnea was observed in 12 of 78 foundry workers exposed to MDI concentrations greater than 0.02 ppm.[5] Inhalation provocation tests on six of nine of the asthmatics resulted in specific asthmatic reaction to MDI.[5] Persons who are sensitized must not be exposed to any concentration of MDI and must be removed from any work involving potential exposure to MDI. MDI is not a significant eye or skin irritant, but it may produce skin sensitization.[3]

In a 2-year chronic inhalation toxicity/carcinogenicity study, rats that were exposed to polymeric MDI (PMDI) aerosol at concentrations of 0, 0.19, 0.98, or 6.03 mg/m^3 showed changes in the nasal cavity (olfactory degeneration and basal cell hyperplasia), the lungs (fibrosis and interstitial pneumonitis), and the mediastinal lymph nodes.[6] At the high dose there were increases in pulmonary adenomas. Olfactory epithelial degeneration was elevated significantly at the high concentration in both sexes. Basal cell hyperplasia in the olfactory epithelium was elevated significantly in males only at the midlevel and high concentrations.[6] In humans no associations between isocyanates and cancer incidences were demonstrated from cohort or case control studies.[7,8]

The IARC has determined that there is inadequate evidence for the carcinogenicity of MDI or polymeric MDI in humans and that

there is limited evidence in experimental animals for the carcinogenicity of a mixture containing monomeric and polymeric MDI.[8]

MDI forms low-level DNA adducts *in vivo* and induces mutations in bacteria and chromosomal aberrations and sister chromatid exchanges in human lymphocyte cultures.[7]

Exposure of pregnant rats on days 6–15 of gestation at 9 mg/m^3 MDI resulted in a slight but significant increase in fetuses displaying asymmetric sternebrae.[9]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 0.005 ppm (0.051 mg/m^3).

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METHYLENE CHLORIDE
CAS: 75-09-2

CH_2Cl_2

Synonyms: Dichloromethane; methylene dichloride; methylene bichloride

Physical Form. Colorless liquid

Uses. Multipurpose solvent; paint remover; manufacture of photographic film; aerosol propellants; urethane foam

Exposure. Inhalation; skin absorption

Toxicology. Methylene chloride is a central nervous system (CNS) depressant and an eye, skin, and respiratory tract irritant.

Concentrations in excess of 50,000 ppm are thought to be immediately life threatening.[1] Four workers exposed to unmeasured but high levels of methylene chloride for 1–3 hours had eye and respiratory tract irritation and reduced hemoglobin and red blood cell counts; all became comatose, and one died.[2]

A chemist repeatedly exposed to concentrations ranging from 500 to 3600 ppm developed signs of toxic encephalopathy.[3] A healthy young worker engaged in degreasing metal parts had a brief exposure to an undetermined but very high concentration of vapor; he complained of excessive fatigue, weakness, sleepiness, light-headedness, chills, and nausea; pulmonary edema developed after several hours, but all signs and symptoms had cleared within 18 hours of terminating the exposure.[4] In human experiments, inhalation of 500–1000 ppm for 1 or 2 hours resulted in light-headedness.[5]

Volunteers exposed at 300–800 ppm for at least 40 minutes had altered responses to

various sensory and psychomotor tests.[6] No effects were seen in volunteers exposed to 250 ppm for up to 7.5 hours.[6] Although an excess in self-reported neurological symptoms was found in workers repeatedly exposed at 75–100 ppm, no significant deleterious effects were observed on clinical examination, which included measurement of motor conduction velocity, electrocardiogram, and psychological tests.[7]

Limited epidemiological studies initially found no specific cause for excess deaths in workers chronically exposed to methylene chloride.[6] There is no clear evidence of liver or kidney damage in humans despite many reports of fatty degeneration in the liver and tubular degeneration in the kidneys of exposed animals.[8] A recent evaluation of workers exposed to high levels of methylene chloride averaging 475 ppm for 10 years found no adverse health effects as determined by selected liver, cardiac, and neurological tests.[9] In another report, no firm evidence of CNS effects was found in retired mechanics who had had long-term exposure to methylene chloride.[10]

Methylene chloride is metabolized by two pathways.[11] One pathway produces carbon monoxide via mixed-function oxidase enzymes, which results in the subsequent formation of carboxyhemoglobin (COHb). Carbon dioxide is produced from the pathway involving glutathione transferase. The metabolism to COHb is saturable, with disproportionately less carboxyhemoglobin formed and more unchanged methylene chloride expired as exposure increases. CNS effects are thought to be due to methylene chloride itself or in combination with other sources of COHb, but not to the metabolism of methylene chloride to COHb alone. Serious poisonings from methylene chloride have been reported in the absence of significant elevation of COHb levels. Elevated COHb levels may persist for several hours after removal from exposure, as fat and other tissues continue to release accumulated amounts of methylene chloride.[3] Although the elevated COHb levels associated with moderate methylene chloride exposure are not expected to cause adverse effects in healthy individuals, those with a compromised cardiovascular system may not be able to tolerate the added cardiovascular stress.[6]

Contact with the liquid is irritating to the skin, and prolonged contact may cause severe burns.[12] In a thumb immersion experiment, an intense burning sensation was noted within 2 minutes and mild erythema and exfoliation were observed after 30 minutes of immersion; the erythema and paresthesia subsided within an hour after exposure.[13] Marked irritative conjunctivitis and lacrimation were noted at concentrations sufficient to produce unconsciousness.[2] Splashed in the eye, it is painfully irritating but not likely to cause serious injury.[1]

Limited animal studies have suggested that methylene chloride is slightly fetotoxic at doses that also produce maternal toxicity; in rats and mice exposed at 1250 ppm on days 6–15 of gestation, delayed ossification of sternabrae and increased incidence of extra sternabrae were noted, respectively.[14]

A number of long-term animal studies have explored the carcinogenic potential of methylene chloride. A 1986 NTP study with B6C3F1 mice exposed at 2000 or 4000 ppm 6 hours per day, 5 days per week for 2 years showed "clear evidence of carcinogenicity" as indicated by increased incidences of alveolar-bronchiolar and hepatocellular neoplasms.[15] There was also a significant increase in benign mammary gland neoplasms in similarly exposed rats.

In humans methylene chloride exposure has been associated with a wide variety of cancers in a number of cohort and case control studies; pancreatic, prostate, lung, liver, cervical, breast, and astrocytic brain tumors have been reported.[16] Limitations in these studies include small sample size, incomplete exposure information, and concomitant exposure to other carcinogenic substances. The IARC has stated that there is not a sufficiently consistent elevation of risk across studies to make a causal interpretation credible. In a recent study of 1473 workers, followed for nearly 50 years, methylene chloride exposure level was not related to mortality due to all causes, malignant neoplasms, or lung and pancreatic cancers.[17]

Assessment of the carcinogenic risk to humans from a review of animal data is complicated by the results of pharmacokinetic studies that have associated methylene chloride carcinogenicity with a specific metabolic pathway.[18,19] This glutathione *S*-mediated pathway appears to proceed slowly in humans compared with mice and only at high exposure doses. Therefore, extrapolation from high dose to low dose and between species may not provide accurate risk assessment of human exposure.

The IARC has determined that there is sufficient evidence for the carcinogenicity of methylene chloride in experimental animals and inadequate evidence in humans.[16]

Methylene chloride has given positive and negative results in a wide variety of genotoxic assays. It may be a weak mutagen in mammalian systems.[11]

Although a number of methods have been proposed for the biological monitoring of occupational methylene chloride exposure, measurement of urinary methylene chloride levels may be the most suitable. The measurement of urinary methylene chloride is noninvasive, not influenced by smoking as are COHb or carbon monoxide levels in alveolar air, and may reflect cumulative exposures more accurately.[20]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for methylene chloride is 50 ppm (174 mg/m^3) with an A3-confirmed animal carcinogen with unknown relevance to humans designation.

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4,4′-METHYLENE DIANILINE

CAS: 101-77-9

$C_{13}H_{14}N_2$

Synonyms: 4,4′-Diaminodiphenylmethane; DDM; MDA; 4-(4-aminobenzyl)aniline

Physical Form. Light brown crystalline solid

Uses. Production of methylene diphenyl diisocyanate (MDI), which is used to produce polyurethanes; hardening agent for epoxy resins, anticorrosive materials, printed circuit parts, dyestuff intermediates, filament-wound pipe, and wire coatings

Exposure. Skin absorption; inhalation; ingestion

Toxicology. 4,4′-Methylene dianiline (MDA) is a human hepatotoxin; it is carcinogenic in experimental animals and is considered a suspected human carcinogen.

Occupational exposure of 12 male workers, whose hands were in contact with MDA several hours per day, caused toxic hepatitis.[1] The clinical pattern of the cases included right upper quadrant pain, high fever, and chills with subsequent jaundice. A skin rash was seen in five of the cases. Percutaneous absorption was considered to be the major route of exposure because workers in the same occupational setting who did not have direct skin contact with MDA were not affected. All patients recovered within 7 weeks, and follow-up more than 5 years later showed no biochemical or clinical evidence of chronic hepatic disease.

Over a 9-year period (1967–76), 11 cases of jaundice were reported from a company that mixed preground MDA with silicon dioxide.[2] In one instance, transient signs of myocardial damage in addition to transient signs of hepatic damage were observed after MDA exposure from a defective filter system.[3]

The inadvertent ingestion of bread prepared with MDA-contaminated flour led to an outbreak of 84 cases of jaundice in Epping, UK.[4] Liver biopsies from seven of the patients showed partial inflammation, eosinophil infiltration, cholangitis, cholestasis, and varying degrees of hepatocellular damage. All patients made a good clinical recovery with no evidence of progressive liver damage.[5]

In another case, ingestion of MDA in potassium carbonate and γ-butyrolactone resulted in severe systemic toxicity and visual dysfunction.[6] Transient effects included ECG abnormalities, bradycardia, and hypotension—suggesting myocardial involvement—and glycosuria with normoglycemia, which indicated renal tubular dysfunction. Liver effects included slight hepatomegaly 6 weeks after ingestion, which quickly resolved, and disappearance of jaundice 2–3 weeks later. Liver biopsy 1 year after the poisoning showed normal hepatocytes and a preservation of hepatic architecture, but disturbed liver function tests were still evident 18 months after the incident. Most significant, however, was the development of toxic optic neuritis with severe visual dysfunction. Investigation of the retina

revealed gross malfunction of the retinal pigment epithelium, reflected clinically as impaired visual acuity with severe loss of central visual field, color discrimination, and dark adaptation. Eighteen months later there was little improvement, and all visual indices remained subnormal with little likelihood for further recovery.

Support for the role of MDA in causing visual disturbances is found in animal studies.[7] Oral doses of 25–50 mg/kg in cats caused retinal damage. The changes observed in the affected eyes consisted of severe granular degeneration of the rods and cones and proliferation of the pigmented epithelial cells of the retina. The neuronal structures located beyond the pigmented layer remained intact. No visual disturbances were induced by MDA in the rabbit, guinea pig, and rat. In another study, degeneration of the inner and outer segments of the photoreceptor cells and the pigmented epithelial cell layer of the retinas of guinea pigs resulted from a total inhaled dose of 24 mg/kg.

Chronic oral exposure of rats and mice to MDA and its dihydrochloride is carcinogenic.[8] Treatment-related increases in the incidences of thyroid follicular cell adenomas and hepatocellular neoplasms were observed in mice after chronic ingestion of MDA in drinking water.[9] In rats, increases in the incidences of thyroid follicular cell carcinoma and hepatic nodules were observed in males and thyroid follicular cell ademonas occurred in females. Although not statistically significant, certain uncommon tumors such as bile duct adenomas, papillomas of the urinary bladder, and granulosa cell tumors of the ovary also were reported. These tumors are of low incidence in historical controls. In another report, MDA acted as a promoter of thyroid tumors in rats.[10]

An epidemiological study of workers potentially exposed to MDA (and numerous other agents) in the helicopter parts manufacturing industry showed limited evidence of an association between MDA and bladder cancer, colon cancer, lymphosarcoma, and reticulosarcoma.[11] A follow-up of 10 workers who had significant exposure to MDA between 1967 and 1976 revealed one case of a pathologically confirmed bladder cancer.[12] Although not statistically significant, these cases are of interest because of findings of bladder tumors in animals and the structural similarity of MDA to known human bladder carcinogens such as benzene.

MDA is genotoxic *in vitro* and forms DNA adducts *in vivo*.[13]

The IARC has determined that there is sufficient evidence for the carcinogenicity of 4,4′-methylene dianiline and its dihydrochloride to experimental animals and that it is possibly carcinogenic to humans.[8]

Reports of allergic sensitivity to MDA are confounded by mixed exposures to chemicals such as epoxy resins and isocyanates, which make it difficult to relate specific cause with effect. MDA does appear to cause an intense yellow staining reaction involving the skin (especially fingers and palms), nails, and occasionally hair in exposed workers.[14] The staining should serve as a marker for potential systemic exposure.

MDA has a faint amine odor, but the odor is not offensive enough to be useful as a warning property.[7]

Monitoring atmospheric levels of MDA may not be useful, as skin absorption may be a more significant route of exposure. Concentrations of *N*-acetyl MDA, a major metabolite of MDA, in the urine may be used to reflect overall exposure.[15]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for MDA is 0.1 ppm (0.81 mg/m^3) with an A3-confirmed animal carcinogen with unknown relevance to humans designation and a notation for skin absorption.

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METHYL ETHYL KETONE

CAS: 78-93-3

$CH_3COCH_2CH_3$

Synonyms: 2-Butanone; MEK

Physical Form. Colorless liquid

Uses. Solvent

Exposure. Inhalation

Toxicology. Methyl ethyl ketone (MEK) is an irritant of the eyes, mucous membranes, and skin, and at high concentrations it causes nervous system effects; MEK potentiates the toxic effect of other solvents.

In humans, short-term exposure to 300 ppm was "objectionable," causing headache and throat irritation; 200 ppm caused mild irritation of eyes; 100 ppm caused slight nose and throat irritation.[1] No significant neurobehavioral effects (as determined by a series of psychomotor tests) were found in volunteers from 4-hour exposures to methyl ethyl ketone at 200 ppm; significant odor and irritant effects were reported.[2]

Several workers exposed to both the liquid and the vapor at 300–600 ppm for an unspecified time period complained of numbness of the fingers and arms; one worker complained of numbness in the legs and a tendency for them to "give way under him."[3] Many workers in this plant developed dermatitis from contact with the liquid; two workers developed dermatitis of the face from vapor exposure alone. In a case report, a patient developed multifocal myoclonus, ataxia, and postural tremor after exposure through both skin contact and inhala-

tion over a 2-year period to solvents that contained 100% MEK.[4] Symptoms disappeared after 1 month of cessation of exposure.[4]

Compared to controls, 41 MEK workers with an average of 14 years' exposure exhibited significantly lower motor nerve conduction velocities in the median, ulnar, and peroneal nerves; irritation of the eyes and upper respiratory tract and a neurotoxic syndrome characterized by mood disorders, irritability, memory difficulties, sleep disturbances, headache, and numbness were also more prevalent in the exposed workers.[5]

Three cases of polyneuropathy occurred in shoe factory workers exposed to combined MEK and acetone vapors, as well as MEK and toluene vapors at concentrations below 200 ppm.[6] Skin absorption also occurred. Although not highly neurotoxic itself, MEK may potentiate substances known to cause neuropathy.

An historical prospective mortality study of 446 male workers in two MEK dewaxing plants, with an average follow-up of 13.9 years, found no increase in deaths from neoplasms.[7]

In animal studies death of rats and mice occurred within a few hours at concentrations of 90,000 ppm and above.[8] Guinea pigs exposed to 10,000 ppm had signs of eye and nose irritation that developed rapidly, and narcosis occurred after 5 hours.[9] Exposure of rats to 6000 ppm 8 hours/day, 7 days/week, did not result in any obvious motor impairment; all animals died from bronchopneumonia during the seventh week.[10]

Animal studies have shown MEK to enhance the development of or increase the severity of neurotoxic effects due to methyl *n*-butyl ketone, ethyl butyl ketone, *n*-hexane, and 2,5-hexanedione.[11–14] MEK exposure did not, however, potentiate the neurobehavioral test decrements produced by acetone.[15] Exposure to 200 ppm MEK or 100 ppm MEK plus 125 ppm acetone for 4 hours did not produce any significant effects in a variety of behavioral performance tests, whereas exposure to 250 ppm acetone caused some mild decrements. The liver and kidney toxicity of haloalkane solvents may also be potentiated by MEK.[7]

Rats exposed to 3000 ppm during days 6 through 15 of gestation produced litters with an increased incidence of a minor skeletal variation and delay in ossification of fetal bones.[16] Similar effects, including reduced fetal weight and a low incidence of cleft palate, fused ribs, missing vertebrae, and syndactyly, were reported in the offspring of mice exposed at 3000 ppm on days 6–15 of gestation.[17] Slight maternal toxicity in the form of increased relative liver weight was also noted. In a recent human case report, multiple congenital malformations (cleft lip and palate, malformed right ear, cervical meningoencephalocele, horseshoe kidney, and ventricular septum defect) occurred in an infant who did not survive and whose mother had been exposed to MEK during pregnancy.[18]

MEK was not genotoxic in a variety of *in vivo* and *in vitro* assays.[8]

MEK can be recognized at 25 ppm by its odor, which is similar to that of acetone but more irritating; its warning properties should prevent inadvertent exposure to toxic levels.[9] In determining worker exposure to MEK, end of shift urine levels appear to be the most reliable biological indicator of occupational exposure.[19]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for methyl ethyl ketone is 200 ppm (590 mg/m^3) with a short-term excursion limit (STEL) of 300 ppm (885 mg/m^3).

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METHYL ETHYL KETONE PEROXIDE

CAS: 1338-23-4

$C_{18}H_{16}O_4$ *or*
$C_{18}H_{18}O_4$

Synonyms: 2-Butanone peroxide; MEKP; MEK peroxide

Physical Form. Liquid

Uses. Reactive free radical-generating chemical used as a curing agent for unsaturated polyester resins; hardening agent for fiberglass-reinforced plastics; manufacture of acrylic resins

Exposure. Inhalation

Toxicology. Methyl ethyl ketone peroxide (MEKP) is a skin and eye irritant.

MEKP has caused irritant dermatitis with direct contact; only rarely has it caused allergic contact dermatitis from occupational exposure.[1]

Exposure of the eyes has resulted in mild to severe injury.[2] The severity of ocular injury was dependent on the length of time from exposure to adequate lavage. Delayed keratitis has also been reported.

In a case of accidental ingestion massive peripheral zonal hepatic necrosis developed in a 47-year old man.[3] The clinical course was characterized by temporary cardiac arrest,

abdominal burns, severe metabolic acidosis, rapid hepatic failure, rhabdomyolysis, and respiratory insufficiency. The patient died 4 days later from hepatic coma associated with blood coagulation disorders. Microscopic examination showed massive periportal hepatic necrosis. The pathogenic mechanism may involve lipid peroxidation caused by free oxygen radicals derived from the MEKP.[3]

The 4-hour LC_{50} for rats was 200 ppm; the oral LD_{50} was 484 mg/kg.[4] Rats dosed by oral gavage with approximately 96 mg/kg, 3 times a week for 7 weeks, died; histopathologic study revealed liver damage. Two drops of 40% MEKP in dimethyl phthalate in rabbit eyes caused severe damage; at 3%, a moderate reaction occurred lasting for 2 days, followed by rapid improvement. The maximum nonirritating strength on rabbit skin was 1.5%.

In 2-week and 13-week toxicity studies topical administration of MEKP (as a 45% solution in dimethyl phthalate) to both rats and mice resulted in a spectrum of necrotic, inflammatory, and regenerative skin lesions limited to the application site.[5] Lesions considered secondary to the dermal lesions included increased hematopoiesis in the spleen in rats and mice and increased myeloid hyperplasia of the bone marrow in mice.

In a tumor-promoting study using ultraviolet radiation in the UVB region as a tumor initiator, MEKP showed weak promoting activity.[6]

MEKP was not mutagenic in bacterial assays, but it did induce sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells; it was also negative in the *in vivo* mouse micronucleus assay.[5]

The 2003 ACGIH ceiling-threshold limit value (C-TLV) for methyl ethyl ketone peroxide is 0.2 ppm (1.5 mg/m^3).

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METHYL FORMATE
CAS: 107-31-3

$HCOOCH_3$

Synonyms: Methyl methanoate; formic acid, methyl ester

Physical Form. Colorless liquid

Uses. Solvent; chemical intermediate; insecticide, fumigant; refrigerant

Exposure. Inhalation; skin absorption

Toxicology. Methyl formate is an irritant of the eyes and respiratory tract; at high concentrations it causes narcosis in animals, and it is expected that severe exposure will produce the same effect in humans.

Workers exposed to the vapor of a solvent containing 30% methyl formate, in addition to ethyl formate and methyl and ethyl acetate, complained of irritation of mucous mem-

branes, oppression in the chest, dyspnea, symptoms of central nervous system depression, and temporary visual disturbances; air concentrations were not determined.[1] No effects were noted from experimental human exposures to 1500 ppm for 1 minute.[2]

Exposure of guinea pigs to 10,000 ppm for 3 hours was fatal; effects were eye and nose irritation, incoordination, and narcosis; autopsy revealed pulmonary edema.[2] Exposure to 5000 ppm was considered the maximum concentration tolerable for 60 minutes without serious consequences.

Methyl formate was negative in bacterial mutagenicity assays with or without metabolic activation.[3]

Methyl formate has a distinct and pleasant odor, but an odor threshold has not been reported.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 100 ppm (246 mg/m^3) with a short-term excursion limit (STEL)/ceiling of 150 ppm (368 mg/m^3).

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METHYL HYDRAZINE

CAS: 60-34-4

CH_3NHNH_2

Synonyms: Monomethylhydrazine; MMH

Physical Form. Liquid

Uses. Rocket fuel; solvent; chemical intermediate

Exposure. Inhalation; skin absorption

Toxicology. Methyl hydrazine causes respiratory irritation, methemoglobinemia, and convulsions; it is carcinogenic in experimental animals.

Volunteers exposed to 90 ppm for 10 minutes had slight redness in the eyes and experienced a tickling sensation of the nose. The only clinical abnormality found during the 60-day follow-up period was the presence of Heinz bodies in 3–5% of the erythrocytes by the seventh day.

As a reducing agent, methyl hydrazine causes characteristic oxidative damage to human erythrocytes *in vitro*. Effects include formation of Heinz bodies and production of methemoglobin.[1]

Exposure of dogs to 21 ppm for 4 hours resulted in convulsions and some deaths; postmortem examination revealed no lesions attributable primarily to methyl hydrazine, although secondary manifestations, probably due to convulsions, included pulmonary hemorrhage and edema; convulsions but not death occurred at 15 ppm.[2] In the dogs that survived exposure, there was evidence of moderately severe intravascular hemolysis. The hemolytic effect was most pronounced 4–8 days after exposure, and blood values returned to normal within 3 weeks. In another study, additional signs, including eye irritation, tremor, ataxia, diarrhea, and cyanosis, were noted in dogs.[3] Dogs exposed at 5 ppm 6 hours/day for 6 months had at least a twofold increase in methemoglobin and reductions in numbers of erythyrocytes, hemoglobin concentrations, and hematocrit values; the effect was reversible and was not observed at the 1 ppm level.[4]

Applied to the shaved skin of dogs, the liquid was rapidly absorbed, producing toxic signs; at the site of application the skin became red and edematous.[5]

Administered intraperitoneally to rats on days 6 through 15 of pregnancy, 10 mg/kg/day caused slight maternal toxicity in the form of

reduced weight gains but was not selectively embryotoxic or teratogenic.[6]

Mice administered 0.001% methyl hydrazine sulfate in drinking water for life showed an increase in lung tumors, whereas 0.01% methyl hydrazine enhanced the development of lung tumors by shortening latent periods; control incidences were not clearly defined in this study.[7] In two other mice studies that may not have allowed for a sufficient latency period, no evidence of carcinogenicity was found.[8,9]

Chronic inhalation exposure by mice (up to 2 ppm, 6 hours/day, 5 days/week for 1 year) or hamsters (up to 5 ppm, 6 hours/day, 5 days/week for 1 year) caused a significant increase in rare tumors of the upper respiratory system including papillomas, adenomas, and osteomas.[10] These benign tumors were thought to be the result of chronic insult to the system. An increase in liver tumors (hemangioma, hemangiosarcoma, adenoma, and carcinoma) also occurred in mice.

The odor threshold is 1–3 ppm, and the odor is described as ammonia-like or fishy.[1]

The 2003 short-term excursion limit (STEL)/ceiling limit for methyl hydrazine is 0.2 ppm (0.38 mg/m^3) with a notation for skin and an A3-confirmed animal carcinogen designation.

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METHYL IODIDE

CAS: 74-88-4

CH_3I

Synonyms: Iodomethane; monoiodomethane

Physical Form. Colorless liquid

Uses. Chemical intermediate; in microscopy because of its high refractive index

Exposure. Inhalation; skin absorption

Toxicology. Methyl iodide is a neurotoxin and convulsant and has caused pulmonary edema.

The latency period between exposure and onset of symptoms ranges from hours to days.[1] Initial symptoms are lethargy, somnolence, slurred speech, ataxia, dysmetria, and visual disturbances. Neurological dysfunction may progress to convulsions, coma, and death. If

recovery occurs, neurological findings recede over several weeks and are followed by psychiatric disturbances such as paranoia, delusions, and hallucination.

A chemical worker accidentally exposed to an unknown concentration of the vapor developed giddiness, diarrhea, sleepiness, and irritability, with recovery in a week; when reexposed 3 months later, he experienced drowsiness, vomiting, pallor, incoordination, slurred speech, muscular twitching, oliguria, coma, and death.[2] At autopsy there were bronchopneumonia and pulmonary hemorrhages, with accumulation of combined iodine in the brain.

In a recent report, two workers developed symptoms and signs of cerebellar lesions and damage of the third, fourth, or sixth cranial nerve pathways after methyl iodide exposure.[3] Spinal cord lesions producing motor and sensory disturbances were present in one, and late psychiatric disorders were observed in both.

Experimental application of the liquid to human skin produced a stinging sensation and slight reddening in 10 minutes; after 6 hours of contact there was spreading erythema followed by formation of vesicles.[4] Absorption through the skin is said to occur.[5] Splashed in the eye, the liquid causes conjunctivitis.[5]

In rats, reported LC_{50} values are 1750, 900, and 232 ppm for 0.5-, 1-, and 4-hour exposures, respectively.[4–6]

Local sarcomas occurred in rats after subcutaneous injection with 10 mg/kg weekly for 1 year or with a single 50 mg/kg dose.[7] Tumors occurred between 500 and 700 days after the first injection, and, in most cases, pulmonary metastases were observed.[6] Repeated intraperitoneal injection of 44 mg/kg in mice reduced survival and caused an increased incidence of lung tumors.[8]

Methyl iodide is considered a potent methylating agent; it methylates hemoglobin in experimental animals and humans.[9] In DNA binding studies in rats, adducts were found in all organs examined, with the highest levels in the stomach and forestomach, after both oral and inhalation administration.[9] It is mutagenic in short-term genotoxic assays and does not require activation.

NIOSH has determined that there is sufficient evidence of carcinogenicity in animals to indicate a potential for human carcinogencity.[5] The IARC states that there is limited evidence for the carcinogenicity of methyl iodide to experimental animals and it is not classifiable as to its carcinogenicity to humans.[10]

The 2003 ACGIH threshold limit value-time-weighted average for methyl iodide (TLV-TWA) is 2 ppm (12 mg/m^3) with an A2-suspected carcinogen designation and a notation for skin absorption.

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METHYL ISOAMYL KETONE

CAS: 110-12-3

$CH_3COCH(C_2H_5)_2$

Synonyms: MIAK; 5-methyl-2-hexanone; 2-methyl-5-hexanone

Physical Form. Liquid

Uses. Solvent for nitrocellulose, cellulose acetate, butyrate, acrylics, and vinyl polymers

Exposure. Inhalation

Toxicology. Methyl isoamyl ketone (MIAK) is an irritant of the eyes and, at high concentrations, causes narcosis in animals.

Effects in humans have not been reported.

Rats exposed to 2000 ppm 6 hours/day, 5 days/week, for 2 weeks exhibited lethargy and decreased response to noise.[1] When exposed over a period of 90 days to 1000 ppm, there was nose and eye irritation, gel-like casts in seminal fluid of males, and increases in liver and kidney weight. Microscopic examination revealed hepatocyte hypertrophy and renal hyalin droplet formation in males. The toxicity of MIAK after inhalation exposure was not as extensive or severe as that resulting from a prior study in which male rats were dosed orally with 2000 mg/kg/day for 13 weeks.

A single 6-hour exposure of rats to 3207 ppm caused eye irritation, decreased respiratory rate, narcosis, and the death of one of four rats.[2] MIAK produced slight eye irritation in the eyes of rabbits. Repeated daily applications to the backs of guinea pigs resulted in irritation. Slight skin sensitization was observed in one of five guinea pigs injected with MIAK and Freund's complete adjuvant; this is not considered compelling evidence of a sensitization potential.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 50 ppm (234 mg/m^3).

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METHYL ISOBUTYL CARBINOL

CAS: 108-11-2

$C_6H_{14}O$

Synonyms: Methyl amyl alcohol; 4-methyl-2-pentanol

Physical Form. Colorless liquid

Uses. Solvent; organic syntheses; brake fluids

Exposure. Inhalation; skin absorption

Toxicology. Methyl isobutyl carbinol is an eye irritant; at high concentrations it causes narcosis in animals, and it is expected that severe exposure in humans would produce the same effect.

Human subjects exposed to 50 ppm for 15 minutes had eye irritation.[1] No acute, chronic, or systemic effects have been reported in humans.

Five of six rats died after exposure to 2000 ppm for 8 hours; there were no deaths after exposure for 2 hours to the saturated vapor.[2] The

single-dose oral toxicity for rats was 2.6 g/kg; the dermal LD_{50} in rabbits was 3.6 ml/kg.[2]

No mutagenic activity was seen in a variety of in vitro assays.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for methyl isobutyl carbinol is 25 ppm (104 mg/m^3) with a short-term excursion limit (STEL) of 40 ppm (167 mg/m^3) and a notation for skin absorption.

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3. BIBRA working group: *Toxicity Profile of Methyl Isobutyl Carbinol*. Vol 190, pp 1–4. Carshalton, UK, British Industrial Biological Research Association, 1994

METHYL ISOBUTYL KETONE

CAS: 108-10-1

$C_6H_{12}O$

Synonyms: Hexone; MIBK; 4-methyl-2-pentanone

Physical Form. Colorless liquid

Uses. In paints, glues, and cleaning agents; used in the plastic and petrol industries

Exposure. Inhalation

Toxicity. Methyl isobutyl ketone (MIBK) is an irritant of the eyes, mucous membranes, and skin; high concentrations cause narcosis in animals, and it is expected that severe exposure will cause the same effect in humans.

Exposures to 80–500 ppm produced weakness, loss of appetite, headache, eye irritation, sore throat, and nausea.[1] At 200 ppm the eyes of most persons were irritated, and 100 ppm was the highest concentration most volunteers estimated to be acceptable for an 8-hour exposure.[2] Volunteers exposed to 50 ppm for 2 hours showed no significant effects on the performance of reaction time tasks or tests of mental arithmetic; irritation in the nose and throat was reported by three of eight subjects at this level.[3] Eye, throat, and nose irritation and headache occurred in another group of volunteers exposed at 20 or 40 ppm for 7 hours.[4]

Exposure of rats to 4000 ppm for 4 hours caused death; 2000 ppm for 4 hours was not fatal.[5] A 2-week exposure of rats to 200 ppm produced toxic nephrosis of the proximal tubules and increased liver weights.[6] A 90-day continuous exposure at 100 ppm produced no significant changes.[7] In a more recent report of rats and mice exposed 6 hours/day for 2 weeks to 100, 500, or 2000 ppm, the only observed histologic changes were increases in regenerative tubular epithelia and hyalin droplets in kidneys of male rats exposed at the two highest levels.[7] Exposure of both species to MIBK at levels up to 1000 ppm for 14 weeks was without significant toxicological effect, except for an increase in the incidence and extent of hyalin droplets in the kidneys of male rats. The relevance of kidney tubular effects to humans is not known.

Studies in mice have shown that MIBK can enhance the ethanol-induced loss of righting reflex by reducing the elimination rate of ethanol.[8] Human response to ethanol may be affected by MIBK, and simultaneous exposure to alcoholic beverages and MIBK should be avoided.

The liquid splashed in the eyes may cause pain and irritation. Repeated or prolonged skin contact may cause defatting of the skin with primary irritation and desquamation.[9]

Results from a number of genotoxic assays show that MIBK exhibits very little, if any, mutagenic activity.[10] Existing studies also demonstrate that MIBK is not teratogenic. In two-generation reproductive studies, rats exposed at up to 2000 ppm 6 hours/day had some central nervous system effects and

increased liver and kidney weights (males), but reproductive parameters were not adversely affected.[11]

MIBK has a characteristic camphorlike odor detectable at 100 ppm.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for methyl isobutyl ketone is 50 ppm (205 mg/m^3) with a short-term excursion limit (TLV-STEL) of 75 ppm (307 mg/m^3).

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METHYL ISOCYANATE
CAS: 624-83-9

CH_3CNO

Synonyms: Isocyanic acid, methyl ester; MIC

Physical Form. Liquid; aerosol

Uses. Production of polyurethane foams and plastics; chemical intermediate

Exposure. Inhalation; skin absorption

Toxicology. Methyl isocyanate (MIC) is an irritant of the eyes, mucous membranes, and skin; at higher doses it is extremely toxic and can cause death from pulmonary edema.

Isocyanates cause pulmonary sensitization in susceptible individuals; if this occurs, further exposure should be avoided, because extremely low levels of exposure may trigger an asthmatic episode; cross sensitization to unrelated materials probably does not occur.[1]

Experimental exposure of four human subjects to MIC for 1–5 minutes caused the following effects: 0.04 ppm, no effects; 2 ppm, lacrimation, irritation of the nose and throat; 4 ppm, symptoms of irritation more marked; 21 ppm, unbearable irritation of eyes, nose, and throat.[2]

Long-term, low-level exposure [generally below the 0.02 ppm threshold limit value (TLV)] was not associated with any pulmonary impairment in workers at a chemical plant with MIC exposure.[3]

The accidental release of several tons of MIC in 1984 at Bhopal, India, resulted in a very heavy death toll (approximately 1850) and, in survivors, significant impairment of health.[4,5] Immediate symptoms were difficulty in breathing, skin and eye irritation, vomiting, and unconsciousness. Only a few deaths were recorded in the first few hours, with the maximum number of fatalities occurring between 24 and 72 hours. The predominant cause of death was cardiac arrest following severe pulmonary edema. Lung function abnormalities have persisted years after exposure. Ophthalmic effects included lacrimation, lid edema, photophobia, and ulceration of the corneal epithelium. A follow-up study 3 years after exposure showed excess irritation, eyelid infection, cataract, and a decrease in visual acuity, but corneal erosion was resolved.[6]

A case-control study found relative risks of 0.9, 1.4, and 1.2 for lung, oropharynx, and oral cavity cancer, respectively, among men in gas-affected regions in 1992; it was determined that the full potential of excess risk may not manifest for 15–20 years after the accident.[7]

Reproductive effects at the time of the incident included a 44% loss of fetuses in 865 pregnant women (15% expected), and the neonatal death rate increased from 3% to 15%.[4] Reproductive toxicity of MIC has been confirmed in animal studies; exposure has caused increased resorptions, reduced pup weight, and reduced neonatal survival. Teratological anomalies including wrist drop, everted claw, syndactyly, cleft palate formation, and unequal ribs were observed in rats exposed to concentrations of up to 0.353 ppm during gestation.[8]

In genotoxic assays both positive and negative results have been reported.[4] A cytogenic study of 35 patients admitted to the hospital after exposure to MIC at Bhopal found no significant effects on sister chromatid exchanges, chromosomal aberrations, or cell cycle.[9] Other studies have found chromosomal abnormalities (especially translocations) in exposed individuals.[10]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for methyl isocyanate is 0.02 ppm (0.047 mg/m^3) with a notation for skin absorption.

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METHYL ISOPROPYL KETONE
CAS: 563-80-4

$(CH_3)_2CHCOCH_3$

Synonyms: MIPK; 3-methyl-2-butanone

Physical Form. Liquid

Uses. Solvent for nitrocellulose lacquers

Exposure. Inhalation

Toxicology. Methyl isopropyl ketone (MIPK), by analogy to other aliphatic ketones, is expected to be an irritant of the eyes, mucous membranes, and skin; at high concentrations it causes narcosis in animals, and it is expected that severe exposure in humans will produce the same effect.

In a range-finding study, exposure for 4 hours to 5700 ppm was fatal to rats.[1] The oral LD_{50} for male rats and mice was 3200 mg/kg. Signs of intoxication included weakness, prostration, and ataxia.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for methyl isopropyl ketone is 200 ppm (705 mg/m^3).

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METHYL MERCAPTAN

CAS: 74-93-1

CH_3SH

Synonyms: Methanethiol; mercaptomethane; thiomethyl alcohol; methyl sulfhydrate

Physical Form. Flammable gas liquefying at 6°C; odor of rotten cabbage

Uses. Intermediate in manufacturing of jet fuels, pesticides, fungicides, plastics; synthesis of methionine; emission from paper pulp mills, odoriferous additive to natural gas

Exposure. Inhalation

Toxicology. Methyl mercaptan causes coma at high levels; hematologic effects have also been reported.

In a fatal human exposure, a worker engaged in emptying metal gas cylinders of methyl mercaptan was found comatose at the work site; he developed expiratory wheezes, elevated blood pressure, tachycardia, and marked rigidity of extremities.[1] Methemoglobinemia and severe hemolytic anemia developed with hematuria and proteinuria but were brief in duration; deep coma persisted until death due to pulmonary embolus 28 days after exposure. It was determined that the individual was deficient in erythrocyte glucose-6-phosphate dehydrogenase, which was the likely cause of the hemolysis and formation of methemoglobin.

In a nonfatal incident, a worker in a refinery inhaled methyl mercaptan and was comatose for 9 hours. Although not dyspneic, the individual was cyanotic and experienced convulsions; recovery occurred by the fourth day. Ten days later the worker was treated successfully for a lung abscess.

Although details are lacking, one report states that effects in animals exposed to methyl mercaptan were restlessness and muscular weakness, progressing to paralysis, convulsions, respiratory depression, and cyanosis.[1] Rats exposed via inhalation to methyl mercaptan at 1400 ppm, but not 1200 ppm, for 15 minutes became lethargic and comatose.[2] Exposure of rats to various concentrations for 4 hours allowed a determination of an LC_{50} of 675 ppm, making it slightly less acutely toxic than hydrogen sulfide (LC_{50} 444 ppm) A subchronic toxicity study in young male rats exposed at 2, 17, and 57 ppm for 3 months showed a dose-related decreased weight gain (about 15% at 57 ppm) but no clear pathologic or biochemical test alterations. There were some minor microscopic hepatic alterations in the exposed animals, which were of questionable significance.

Irritation of the skin and eyes has been reported by workers exposed to mercaptans in general, although specific information is not available pertaining to methyl mercaptan.[4] There are no reports of developmental, reproductive, or genotoxic effects.[4]

The toxic potential of methyl mercaptan is due to its reversible inhibition of cytochrome *c* oxidase at the end of the respiratory chain of mitochondria.[5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 0.5 ppm (0.98 mg/m^3).

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METHYL METHACRYLATE

CAS: 80-62-6

$C_5H_8O_2$

Synonyms: Methacrylic acid, methyl ester; methyl 2-methylpropenoic acid; methyl α-methyl acrylate; methyl methylacrylate; 2-(methyoxycarbonyl)-1-propene

Physical Form. Colorless liquid; commercial form contains a small amount of hydroquinone or hydroquinone monomethyl ether to inhibit spontaneous polymerization

Uses. Production of polymethyl methacrylate polymers for use in acrylic sheet and acrylic molding, extrusion powder, acrylic surface coatings, printing inks, and adhesives used in surgery and dentistry

Exposure. Inhalation

Toxicology. Methyl methacrylate is an irritant of eyes, skin, and mucous membranes.

The toxic effects are due to the monomer; the polymer appears inert. The severity of effects is believed to be inversely proportional to the degree of polymerization.

Workers exposed to either 11–33 mg/m^3 or 100–200 mg/m^3 had dose-dependent increases in the incidences of neurasthenia, laryngitis, and hypotension.[1] In another study of 91 exposed and 43 nonexposed workers at five plants producing polymethyl methacrylate sheets, exposures ranged from 4 to 49 ppm and there were no detectable clinical signs or symptoms.[2] In a survey of 152 workers exposed to concentrations ranging from 0.5 to 50 ppm, 78% reported a high incidence of headache, 30% pain in the extremities, 10% irritability, 20% loss of memory, and 21% excessive fatigue and sleep disturbances.[3]

Handlers of methyl methacrylate cement have developed paresthesia of the fingers.[4] Dental technicians who use bare hands to mold methyl methacrylate putty had significantly slower distal sensory conduction velocities from the digits, implicating mild axonal degeneration in the area of contact with methyl methacrylate.[5] The toxic effect on the nervous tissues may be due to diffusion into the nerve cells causing lysis of the membrane lipids and destruction of the myelin sheath.

Humans have developed strong skin reactions when rechallenged with the liquid.[6] Allergic contact dermatitis has been reported in workers handling methacrylate sealants, including methyl methacrylate.[7] In another report, five subjects were shown by bronchial provocation tests to have occupational asthma due to methyl methacrylate or cyanoacrylates.[8]

Acute inhalation exposure of dogs to 11,000 ppm led to central nervous system depression, a drop in blood pressure, liver and kidney damage, and death due to respiratory arrest.[9] Mice exposed to 1520 ppm for 2 hours twice daily for 10 days showed no significant histologic changes in heart, liver, kidney, or lungs. In male rats exposed to methyl methacrylate vapor at 116 ppm 7 hours/day, 5 days/week for 5 months, the tracheal mucosa was denuded of cilia and the number of microvilli on the epithelium was reduced.[10]

Exposure of pregnant ICR mice to 1330 ppm for 2 hours twice daily during days 6–15 of pregnancy resulted in no developmental effects.[11] At 2028 ppm for 6 hours/day during days 6–15 of gestation there was decreased maternal food consumption and body weight gain in pregnant rats exposed by vapor inhalation but no embryo or fetal toxicity or malformations.[12]

In a 2-year inhalation study, there was no evidence of carcinogenicity of methyl methacrylate for male rats exposed at 500 or 1000 ppm, for female rats exposed at 250 or 500 ppm, or for male and female mice exposed at 500 or 1000 ppm.[13] There was inflammation of the nasal cavity and degeneration of the olfactory sensory epithelium in rats and mice; epithelial hyperplasia of the nasal cavity was also observed in exposed mice. In another study no exposure-related tumors were seen in rats or hamsters exposed at 100 and 400 ppm for 24 and 18 months, respectively.[14]

A mortality study of three cohorts engaged in the manufacturing and polymerization of acrylate monomers revealed an excess colon cancer rate among men employed extensively during the 1940s in jobs entailing the highest exposures to vapor-phase ethyl acrylate and methyl acrylate monomer.[15] The excess mortality appeared only after the equivalent of 3 years' employment followed by a latency of 20 years. The two cohorts with later dates of hire showed no excess mortality.[15] A mortality study of 2671 men exposed to methyl methacrylate alone found a nonsignificantly increased mortality from all cancers but no significant risk at any particular site with increasing dose.[16]

The IARC has determined that there is inadequate evidence in humans for the carcinogenicity of methyl methacrylate and that there is evidence suggesting the lack of carcinogenicity in experimental animals.[1]

Methyl methacrylate is not genotoxic in bacterial systems, but it has induced mutation and chromosomal aberrations *in vitro*.[17] Increases in chromosomal aberrations in bone marrow cells of rats have been observed after *in vivo* inhalation exposure.[17]

Methanol concentrations in blood and urine have been found to correlate with methyl methacrylate exposure.[18] The lack of specificity of methanol to methyl methacrylate exposure limits its usefulness as a biological indicator.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 50 ppm (205 mg/m^3) and the short-term excursion limit (TLV-STEL) is 100 ppm (410 mg/m^3) with a notation for sensitization.

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METHYL PARATHION

CAS: 298-00-0

$(CH_3O)_2P(S)OC_6H_4NO_2$

Synonyms: *O*, *O*-dimethyl *O*-*p*-nitrophenyl phosphorothioate; Metron; Nitrox; parathion-methyl; Metacide, metaphos

Physical Form. White solid (pure); tan to brown solid (technical)

Uses. Insecticide

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Methyl parathion is an anticholinesterase agent.

Signs and symptoms of overexposure are caused by the inactivation of the enzyme cholinesterase, which results in the accumulation of acetylcholine at synapses in the nervous system, skeletal and smooth muscle, and secretory glands. The sequence of the development of systemic effects varies with the route of entry. The onset of signs and symptoms is usually prompt but may be delayed up to 12 hours.[1–5] After inhalation, respiratory and ocular effects are the first to appear, often within a few minutes of exposure. Respiratory effects include tightness in the chest and wheezing due to bronchoconstriction and excessive bronchial secretion; laryngeal spasms and excessive salivation may add to the respiratory distress; cyanosis may also occur. Ocular effects include miosis, blurring of distant vision, tearing, rhinorrhea, and frontal headache.

After ingestion, gastrointestinal effects, such as anorexia, nausea, vomiting, abdominal

cramps, and diarrhea, appear within 15 minutes to 2 hours. After skin absorption, localized sweating and muscular fasciculations in the immediate area usually occur within 15 minutes to 4 hours; skin absorption is somewhat greater at higher ambient temperatures and is increased by the presence of dermatitis.[1–3]

With severe intoxication by all routes, an excess of acetylcholine at the neuromuscular junctions of skeletal muscle causes weakness aggravated by exertion, involuntary twitchings, fasciculations, and eventually paralysis. The most serious consequence is paralysis of the respiratory muscles. Effects on the central nervous system include giddiness, confusion, ataxia, slurred speech, Cheyne–Stokes respiration, convulsions, coma, and loss of reflexes. The blood pressure may fall to low levels, and cardiac irregularities including complete heart block may occur.[2]

Complete symptomatic recovery usually occurs within a week; increased susceptibility to the effects of anticholinesterase agents persists for up to several weeks after exposure.[4] Daily exposure to concentrations that are insufficient to produce symptoms after a single exposure may result in the onset of symptoms. Continued daily exposure may be followed by increasingly severe effects.

Deaths from occupational exposure have been reported, usually after massive accidental exposures.[1] Data from human poisonings by methyl parathion are not sufficiently detailed to identify the range between the doses producing first symptoms and those producing severe or fatal intoxication.[4] The probable oral lethal dose is 5–50 mg/kg. Most animal data and limited human data indicate that methyl parathion is somewhat less acutely toxic than parathion.[4]

Methyl parathion itself is not a strong cholinesterase inhibitor, but one of its metabolites, methyl paraoxon, is an active inhibitor. Methyl paraoxon inactivates cholinesterase by phosphorylation of the active site of the enzyme to form the "dimethylphosphoryl enzyme." Over the following 24–48 hours there is a process, called aging, of conversion to the "monomethylphosphoryl enzyme." Aging is of clinical interest in the treatment of poisoning because cholinesterase reactivators such as pralidoxime (2-PAM, Protopam) chloride are ineffective after aging has occurred. Measurement of metabolites of methyl parathion, *para*-nitrophenol, and dimethylphosphate in the urine has been used to monitor exposure to workers.[6]

Methyl parathion administered intraperitoneally at maternally lethal doses was teratogenic to mice, producing cleft palate and rib abnormalities. High-dose administration to rats, sometimes producing maternal toxicity, resulted in evidence of embryo-fetotoxicity with increased resorptions and growth retardation.[6]

A 2-year bioassay of methyl parathion in mice and rats did not demonstrate any increased incidence of tumors in dosed animals.[7] The IARC has concluded that there is no evidence that methyl parathion is carcinogenic to experimental animals.[6]

Methyl parathion is not strongly genotoxic; it has produced both positive and negative results in both eukaryotic and prokaryotic assays.[8]

There is no evidence that methyl parathion can induce delayed peripheral neuropathy in humans or experimental animals.[6]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for methyl parathion is 0.2 mg/m^3 with a notation for skin absorption.

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METHYL PROPYL KETONE
CAS: 107-87-9

$CH_3COC_3H_7$

Synonyms: 2-Pentanone; ethyl acetone

Physical Form. Colorless liquid

Uses. Solvent

Exposure. Inhalation

Toxicology. Methyl propyl ketone is an irritant of the eyes and mucous membranes; at high concentrations it causes narcosis in animals, and it is expected that severe exposure will produce the same effect in humans.

At 400 ppm 6 of 10 subjects reported eye irritation; the 4 nonresponders experienced irritation when the concentration was raised to 600 ppm. In other reports, brief exposures of humans to 2000–4000 ppm were very irritating; 1500 ppm had a strong odor and caused irritation of the eyes and nose.[2] There have been no reports of chronic or systemic effects in humans.

In guinea pigs, exposure to 50,000 ppm for 50 minutes or 13,000 ppm for 300 minutes was fatal.[3] Animals survived 810 minutes at 5000 ppm, but narcosis occurred in 460–710 minutes.[2] Although methyl propyl ketone has not been reported to be nephro- or hepatotoxic in rats, it has been shown to potentiate kidney and liver injury produced by chloroform.[4] Applied to the skin of rabbits, the undiluted liquid was only slightly irritating within 24 hours.[5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for methyl propyl ketone is 200 pm (705 mg/m^3) with a short-term excursion limit (STEL) of 250 ppm (881 mg/m^3).

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N-METHYL-2-PYRROLIDONE
CAS: 872-50-4

C_5H_9NO

Synonyms: NMP; M-Pyrol; methylpyrrolidone

Physical Form. Almost colorless liquid with a mild aminelike odor

Uses. Solvent for high-temperature resins; petrochemical processing, in the microelectronics fabrication industry, dyes and pigments, industrial and domestic cleaning compounds; agricultural and pharmaceutical formulations

Toxicology. *N*-methyl-2-pyrrolidone (NMP) is of low systemic toxicity but produces skin and eye irritation with prolonged contact.

NMP produced no skin irritation with patch testing for 24 hours in 50 volunteers.[1] A few mild transient reactions were noted after repeated application. There was no evidence of contact sensitization.

Ten of 12 workers experienced acute irritant contact dermatitis of the hands after 2 days of direct contact.[2] In the most severe case, a woman with no previous skin problems, who wore latex gloves intermittently, had painful swelling of the fingers of both hands with redness and vesicles on the palms. The affected skin later became thickened and showed a brownish discoloration. Another worker noticed small vesicles on the forehead, probably due to scratching with contaminated fingers. All cutaneous reactions cleared within 3 weeks of termination of exposure. Gas chromatograph analysis of the NMP used at the factory did not reveal any contaminating compounds.

In a chamber study, a single exposure of six male volunteers for 8 hours did not cause irritation-related symptoms in the eyes or the respiratory tract at exposures up to 50 mg/m^3 NMP.[3]

In rats, the oral LD_{50} was approximately 4.2 ml/kg. In rabbits, the dermal LD_{50} was between 4 and 8 g/kg.[1] Repeated skin application in lower doses, 0.4 and 0.8 mg/kg/day, resulted in mild skin irritation in rabbits. NMP is a severe eye irritant in rabbits, producing conjunctivitis and corneal opacity after instillation, but did not appear to produce permanent eye damage. Rats exposed to vapor from heated NMP for 6 hours or saturated room temperature air for 6 hours/day for 10 days showed no evidence of toxic effects.[1]

The toxicity profile after exposure to airborne NMP depends strongly on the ratio of vapor to aerosol and on the area of exposure (i.e., head only or whole body).[4] Because of the higher skin absorption for the aerosol, uptake is higher in animals exposed to aerosol than those exposed to vapor at similar concentrations.[4] Rats exposed head only to 1000 mg showed only minor nasal irritation, but massive mortality occurred with whole body exposure to the same concentration of coarse droplets at high humidity.[4]

In 28-day feeding studies in rodents 30,000 ppm in the diet of rats caused significant decreases in feed consumption and body weight gain. In mice swelling of the epithelium in the distal portion of the renal tubules was seen in mice fed 10,000 ppm in the diet.[5] Dietary intake for 90 days caused changes in neurobehavioural parameters in the 18,000 ppm male rats, whereas mice fed 7500 ppm had centrilobular hypertrophy of the liver.[6]

In subchronic inhalation studies, rats exposed to 1.0 mg/l 6 hours/day, 5 days/week for 4 weeks, exhibited lethargy, respiratory difficulty, and excessive mortality.[7] Rats had focal pneumonia, bone marrow hypoplasia, and atrophy of lymphoid tissue in the spleen and thymus. The lesions were reversible in surviving animals after 2 weeks of recovery. No carcinogenic effects were observed in rats exposed to 0.04 or 0.4 mg/l for 2 years; male mice had slightly reduced mean body weight at the higher dose.[7] In general, NMP has been weakly genotoxic in a number of *in vitro* and *in vivo* assays.[4]

Reproductive toxicity studies have shown developmental toxicity at doses causing no or mild maternal toxicity. A transient decrease in pup weight, delayed physical development, and

impaired performance on some neurobehavioral tests were observed in rats exposed to 150 ppm 6 hours/day on gestation days 7–20.[8] Administered by gavage from day 6 to day 20 of gestation, doses of 500 or 750 mg/kg/day, which were maternally toxic, also caused external fetal malformations.[9] Dermal application studies in female rats showed no evidence of teratogenic effects, although lower weight gains in the maternal animals and skeletal variations in the offspring were observed at the highest dose (750 mg/kg/day); the latter effect was thought to be due to maternal toxicity.[1] Pregnant rats exposed to 0.1 or 0.36 mg/l 6 hours/day on days 6–15 of gestation had sporadic lethargy and irregular respiration in the first 3 days but no other clinical signs or pathological lesions.[10] No abnormal development was detected in the offspring.

A 2003 ACGIH threshold limit value (TLV) has not been established.

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METHYL SILICATE

CAS: 681-84-5

$(CHO_3)_4Si$

Synonyms: Tetramethoxysilane; tetramethyl orthosilicate; methyl orthosilicate; tetramethyl silicate

Physical Form. Liquid

Uses. Coating screens of television picture tubes; mold binders; corrosion-resistant coatings; catalyst preparation; silicone intermediate

Exposure. Inhalation

Toxicology. Methyl silicate is a severe eye irritant and is an irritant of the nose and throat.

Application of undiluted methyl silicate to the eyes of rabbits caused marked edema and necrosis of the eyelid.[1] Exposure of rats to 250 ppm for 4 hours caused death in all six animals, whereas none died after exposure to 125 ppm for 4 hours.

Exposure of rats for 6 hours/day, 5 days/week for 4 weeks to 15 ppm caused corneal lesions in some of the rats along with reductions in total serum protein, lactate dehydrogenase, and serum albumin.[2] Rats exposed to

30 ppm exhibited irritation of the upper respiratory tract and bronchiolar inflammation. No adverse effects were noted at 10 ppm.

Human experience indicates that methyl silicate exposure has a delayed action on the eyes, causing slight or no immediate effect that is followed, after a latent period of several hours, by potentially serious injury to the eyes.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for methyl silicate is 1 ppm (6 mg/m^3).

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α-METHYL STYRENE

CAS: 98-83-9

C_9H_{10}

Synonyms: 1-Methyl-1-phenyl ethylene; isopropenylbenzene; β-phenylpropylene

Physical Form. Colorless liquid

Uses. In the formulation of polymers and resins

Exposure. Inhalation

Toxicology. α-Methyl styrene is an irritant of the eyes and mucous membranes; severe exposure may result in central nervous system depression.

Humans briefly exposed to 600 ppm experienced strong eye and nasal irritation; at 200 ppm the odor was objectionable; at 100 ppm the odor was strong but tolerated without excessive discomfort.[1]

Guinea pigs and rats exposed 7 hours/day to 3000 ppm for 3–4 days died; at 800 ppm for 27 days there were slight changes in liver and kidney weight and some reduction in growth.[1] Exposure 7 hours/day to 200 ppm for 139 days caused no adverse effects in several species. In a recent study, concentrations of 600, 800, or 1000 ppm were lethal to some mice after 6 hours; animals surviving 12 exposures had significantly increased liver weights and relative spleen weights were significantly decreased.[2] No microscopic treatment-related lesions were observed. Exposure of male and female F344 rats and male NBR rats to 250 or 500 ppm 6 hours/day for 9 days resulted in increased accumulation of hyalin droplets in the renal tubules of male F344 rats.

The liquid dropped in the eyes of rabbits caused slight conjunctival irritation; applied to rabbit skin, it produced erythema.[1]

α-methyl styrene induced sister chromatid exchanges in human whole blood lymphocyte cultures, but it was not mutagenic in bacterial assays with or without metabolic activation.[3,4]

The odor of α-methyl styrene is detectable at 50 ppm; the odor and irritant properties provide good warning of toxic levels.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 50 ppm (242 mg/m^3) with a short-term excursion level (STEL) of 100 ppm (483 mg/m^3).

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MEVINPHOS
CAS: 7786-34-7

$C_7H_{13}O_6P$

Synonym: 2-Methoxycarbonyl-1-methylvinyl dimethylphosphate

Physical Form. Light yellow to orange liquid

Use. Insecticide

Exposure. Skin absorption; inhalation; ingestion

Toxicology. Mevinphos is an anticholinesterase agent.

Signs and symptoms of overexposure are caused by the inactivation of the enzyme cholinesterase, which results in the accumulation of acetylcholine at synapses in the nervous system, skeletal and smooth muscle, and secretory glands. The sequence of the development of systemic effects varies with the route of entry. The onset of signs and symptoms is usually prompt, but may be delayed up to 12 hours.[1–3] After inhalation, respiratory and ocular effects are the first to appear, often within a few minutes after exposure. Respiratory effects include tightness in the chest and wheezing due to bronchoconstriction and excessive bronchial secretion. Laryngeal spasms and excessive salivation may add to the respiratory distress; cyanosis may also occur. Ocular effects include miosis, blurring of distant vision, tearing, rhinorrhea, and frontal headache.

After ingestion, gastrointestinal effects, such as anorexia, nausea, vomiting, abdominal cramps, and diarrhea appear within 15 minutes to 2 hours. After skin absorption, localized sweating and muscular fasciculations in the immediate area occur usually within 15 minutes to 4 hours; skin absorption is somewhat greater at higher ambient temperatures and is increased by the presence of dermatitis.[1–3]

With severe intoxication by all routes, an excess of acetylcholine at the neuromuscular junctions of skeletal muscle causes weakness, aggravated by exertion, involuntary twitchings, fasciculations, and eventually paralysis. The most serious consequence is paralysis of the respiratory muscles. Effects on the central nervous system include giddiness, confusion, ataxia, slurred speech, Cheyne–Stokes respiration, convulsions, coma, and loss of reflexes. The blood pressure may fall to low levels, and cardiac irregularities, including complete heart block, may occur. Complete symptomatic recovery usually occurs within 1 week; increased susceptibility to the effects of anticholinesterase agents persists for up to several weeks after exposure. Daily exposure to concentrations that are insufficient to produce symptoms after a single exposure may result in the onset of symptoms. Continued daily exposure may be followed by increasingly severe effects.

A group of 31 farm workers who inadvertently entered a field only 2 hours after it was sprayed with mevinphos developed a variety of initial symptoms, including eye irritation, headache, visual disturbances, dizziness, nausea, vomiting, chest pain, shortness of breath, pruritis, eyelid and arm fasciculations, excessive sweating, and diarrhea.[4] Headache, dizziness, visual disturbances, and nausea persisted for 5–8 weeks or more in a significant number of field workers after cessation of exposure. Despite symptoms suggesting moderate organophosphate intoxication, mean plasma and red blood cell cholinesterase depression were only 16%, and 6%, respectively, when compared against a presumed baseline obtained in these workers long after the exposure.[4] Another study of 16 cauliflower workers poisoned by residues of mevinphos and phosphamidon (a less potent organophospate) demonstrated persistent headaches, blurred

vision, and weakness in a number of workers 5–9 weeks or more after the exposure.[5]

In many of these occupational cases, the dermal route of exposure may predominate.[6] In one report, it was found that when greenhouse workers wore long-sleeved shirts, approximately 6% of the pesticide reached the skin, compared with 38% for workers wearing short sleeves.[6]

In two cases of moderate intoxication from mevinphos, urinary excretion of dimethylphosphate (a metabolite of mevinphos) was almost complete 50 hours after exposure.[7] Although a number of other organophosphorus pesticides also yield dimethyl phosphate, the presence of significant amounts of this metabolite in the urine may be useful in estimating the absorption of mevinphos.

Mevinphos inactivates cholinesterase by phosphorylation of the active site of the enzyme to form the "dimethylphosphoryl enzyme." Over the following 24–48 hours, there is a process, called aging, of conversion to the "monomethylphosphoryl enzyme." Aging is of clinical interest in the treatment of poisoning because cholinesterase reactivators such as pralidoxime (2-PAM, Protopam) chloride are ineffective after aging has occurred.

There was no evidence of carcinogenicity in an 18-month feeding study in mice (up to 25 ppm in the diet) or in a 2-year gavage study in rats (0.025, 0.35, or 0.70 mg/kg body weight per day).[8] No fetotoxic or teratogenic effects were observed in rats exposed on days 6 through 15 of gestation at doses of 1.0 mg/kg, which caused maternal toxicity in the form of tremors.[8] There was some evidence of genotoxic potential in vitro but not in vivo.[8]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for mevinphos is 0.01 ppm (0.092 mg/m^3) with a short-term excursion limit (STEL) of 0.03 ppm (0.27 mg/m^3) and a notation for skin absorption.

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MICA
CAS: 12001-26-2

Formula unspecified

Synonyms: Mica is a nonfibrous silicate occurring in plate form and includes nine different species; muscovite is a hydrated aluminum potassium silicate also called white mica; phlogopite is an aluminum potassium magnesium silicate also called amber mica; other forms are biotite, lepidolite, zinnwaldite, and roscoelite

Physical Form. Light gray to dark-colored flakes or particles

Uses. Insulation in electrical equipment; manufacture of roofing shingles and wallpaper; in oil refining; in rubber manufacture

Exposure. Inhalation

Toxicology. Mica dust causes pneumoconiosis.

In a study of 57 workers exposed to mica dust, 5 of six workers exposed to concentrations in excess of 25 million particles per cubic foot (mppcf) for more than 10 years had pneumoconiosis.[1] The most characteristic finding by chest X ray was fine granulation of uneven density; there was a tendency, in some cases, to a coalescence of shadows. The symptoms most frequently reported were chronic cough and dyspnea; complaints of weakness and weight loss were less frequent.[1] Only one of six workers exposed more than 10 years at concentrations in excess of 25 mppcf failed to show evidence of pneumoconiosis.

A group of mica miners were said to show a higher incidence of pneumoconiosis than miners of other minerals, but some quartz was present in the dust to which they were all exposed.[2]

In one case report, a 63-year-old male with a long history of extensive exposure to mica presented (30 years after initial exposure) with complaints of progressive shortness of breath and a chronic nonproductive cough. Pulmonary function tests revealed restrictive lung function and a mild reduction in total lung capacity. Chest radiographs and lung biopsy showed extensive interstitial fibrosis with heavy mica deposition. The presence of mica was confirmed spectroscopically but asbestos and other silicates were not identified, suggesting that mica was the fibrogenic agent in this case. The authors note that the long latency and chronic exposure associated with the disease indicate that mica is not as fibrogenic as other pneumoconiotic agents.

The 2003 threshold limit value (TLV) is 3 mg/m^3, respirable dust.

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MOLYBDENUM (and Compounds)
CAS: 7439-98-7

Mo

Synonyms: Soluble compounds include molybdenum trioxide, ammonium molybdate, and sodium molybdate; insoluble compounds include molybdenum disulfide and molybdenum dioxide

Physical Form. Silverish metal or dark powder

Uses. Manufacture of special-purpose steel; in ceramic glazes, enamels, and pigments; lubricant; corrosion inhibitor; additive to fertilizer

Toxicology. Molybdenum and its compounds are considered to be of relatively low toxicity; chronic inhalation of molybdenum trioxide by animals causes inflammation and neoplastic changes to the lung.

Workers at a molybdenum-roasting plant with time-weighted average (TWA) exposures of approximately 9.5 mg Mo/m^3 to soluble dusts had increased plasma and urine levels of molybdenum; the only adverse biochemical findings were large elevations in serum ceruloplasmin levels and some increase in serum uric acid levels.[1]

No evidence of systemic disease or dermatitis attributable to molybdenum (especially molybdenum disulfide) was seen by a plant physician reporting on 50 years of operation.[1]

In a report from Russia, an increased incidence of nonspecific symptoms, including weakness, fatigue, anorexia, headaches, and joint and muscle pains, was reported among

mining and metallurgy workers exposed to 60–600 mg/m^3 molybdenum.[2] Signs of gout and elevated uric acid concentrations have been observed among inhabitants of areas of Armenia, where the soil is rich in molybdenum. This effect apparently results from the induction of the enzyme xanthine oxidase, for which molybdenum is a cofactor.

Insoluble molybdenite, MoS_2, was practically nontoxic in animal studies; guinea pigs with exposure to 230 mg Mo/m^3 for 25 days only showed increases in respiration rate; rats ingesting as much as 500 mg/day for 44 days showed no toxic signs.

More soluble and more active molybdenum compounds, including calcium molybdate and molybdenum trioxide, were fatal at oral daily doses of over 100 mg/day.[1]

Guinea pigs exposed to molybdenum trioxide dust at a concentration of 200 mg molybdenum/m^3 for 1 hour daily for 5 days developed nasal irritation, diarrhea, weight loss, and incoordination.[3] In 2-year inhalation studies at concentrations of up to 100 mg/m^3 molybdenum trioxide there was no evidence of carcinogenic activity in female rats, but there was equivocal evidence in males based on a marginally significant positive trend of alveolar/bronchiolar adenoma or carcinoma (combined). There was some evidence of carcinogenic activity in mice based on increased incidences of alveolar/bronchiolar adenoma and carcinomas (combined).[4] Other exposure-related effects in exposed animals included alveolar inflammation, squamous metaplasia of the epiglottis and hyaline degeneration of the respiratory and olfactory epithelium. Molybdenum trioxide was not mutagenic in bacterial assays, nor did it induce sister chromatid exchanges or chromosomal aberrations in vitro.[4]

In livestock, chronic molybdenum poisoning, known as "teart disease," is caused by a diet high in molybdenum and low in copper. Symptoms include anemia, gastrointestinal disturbances, bone disorders, and growth retardation.[5]

The metabolism of molybdenum is closely associated with that of copper; molybdenum toxicity in animals can be alleviated by the administration of copper. High intake of molybdenum in rats resulted in a substantial reduction in activity of sulfide oxidase in the liver.[6] The reduced activity of this enzyme leads to accumulation of sulfide in the tissues and subsequent formation of highly undissociated copper sulfide, thus removing copper from metabolic activity. This is a possible explanation for the induction of copper deficiency by molybdate.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 0.5 mg/m^3 respirable particulate for the soluble molybdates; TLV-TWAs of 10 mg/m^3 (inhalable particulate) and 3 mg/m^3 (respirable particulate) are recommended for occupational exposure to elemental molybdenum and its insoluble compounds.

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MORPHOLINE
CAS: 110-91-8

C_4H_9NO

Synonyms: Diethylenimide oxide; diethylene imidoxide; tetrahydro-2*H*-1,4-oxazine

Physical Form. Clear liquid with ammonia-like odor

Uses. Solvent for resins, waxes, casein, dyes; morpholine compounds used as corrosion inhibitors, insecticides, antiseptics, intermediate for rubber-processing chemicals; corrosion inhibitors; waxes and polishes; optical brighteners

Exposure. Inhalation; skin absorption

Toxicology. Morpholine vapor is an irritant of the eyes, nose, and throat.

In industrial use, some instances of skin and respiratory tract irritation have been observed but no chronic effects have been reported.[1] A human exposure to 12,000 ppm for 1.5 minutes in a laboratory produced nose irritation and cough; mouth pipetting of the liquid caused a severe sore throat and reddened mucous membranes.[2] Workers exposed for several hours to low vapor concentrations complained of foggy vision with rings around lights, the results of corneal edema, which cleared within 3–4 hours after cessation of exposure.[1]

Repeated daily exposure of rats to 18,000 ppm for 8 hours was lethal to some animals; those dying had damage to lungs, liver, and kidneys.[2] Rats and guinea pigs survived an 8-hour exposure at 12,000 ppm. Sublethal signs from inhalation include lacrimation, rhinitis, and inactivity.[1] Rats exposed by inhalation to 250 ppm for 6 hours/day, 5 days/week showed signs of irritation after 1 week; animals examined after 7–13 weeks of exposure had focal erosions and squamous metaplasia in the maxilloturbinates.[3]

Oral doses of undiluted unneutralized morpholine caused irritation of the intestinal tract with hemorrhage. Applied to the skin of rabbits, it caused skin burns and systemic injury, including necrosis of the liver and kidney; the dermal LD_{50} was 0.5 ml/kg. The liquid dropped in the eye of a rabbit caused moderate injury, with ulceration of the conjunctiva and corneal clouding.[4] The topical toxicity of morpholine has been attributed to its alkaline properties, and neutralization may significantly reduce its effects.

Rats given 10 g/kg in the diet, plus 0.2% sodium nitrite in the drinking water, had a significantly increased incidence of liver tumors compared with controls.[5] The carcinogenic response is attributed to the *in vitro* production of *N*-nitrosomorpholine. In another study morpholine alone produced a low number of tumors of the liver, lung, and brain, and it was suggested that an unknown nitrate source reacted with the morpholine to form the carcinogenic *N*-nitrosomorpholine.[6]

Morpholine has also been tested for carcinogenicity by inhalation exposure in rats. Exposure to 10, 50, or 150 ppm 6 hours/day, 5 days/week, for up to 104 weeks was associated with dose-related increases in inflammation of the cornea, inflammation and squamous metaplasia of the turbinate epithelium, and necrosis of the turbinate bones in the nasal cavity, but no significant increase in the incidence of tumors.[7]

The IARC has determined that there is inadequate evidence for the carcinogenicity of morpholine in experimental animals and that morpholine is not classifiable as to its carcinogenicity to humans.[8]

In general, morpholine was not genotoxic in a variety of assays.[9]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for morpholine is 20 ppm (71 mg/m^3) with a notation for skin.

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MUSTARD GAS

CAS: 505-60-2

$C_4H_8Cl_2S$

Synonyms: Sulfur mustard; bis-2-chloroethyl sulfide; di-2-chloroethyl sulfide; 1,1-thiobis(2-chloroethane); chemical agent symbol: HD

Physical Form. Colorless, odorless, oily liquid

Uses. As a vesicant in chemical warfare. Although US stockpiles were thought to exist only through the early 1970s, several other countries currently maintain large stockpiles that present an imminent danger from accidental or intentional exposure.[1] Also used in small quantities as a model compound in biological studies on alkylating agents.

Exposure. Inhalation; skin contact

Toxicology. Mustard gas causes skin and eye injury; after inhalation, pulmonary damage may occur. Chronic exposure has been associated with an increased risk of respiratory cancer in humans.

Mustard gas is primarily a vesicant, with blisters being formed by either liquid or vapor contact.[2] It attacks the eyes and lungs and is a systemic poison, so that protection of the entire body must be provided. Insidious in its action, there is no pain at the time of exposure, and the first symptoms typically appear in 4–6 hours. The higher the concentration, the shorter the interval of time between exposure to the agent and the first symptoms. After several hours, the gross biological evidences of injury begin to appear as edema, hyperemia, and irritation. In the eye, the corneal epithelium becomes edematous, the lids and conjunctiva become red and swollen, and the patient experiences burning discomfort and photophobia, including tearing and blepharospasm.[3] Areas of contaminated skin become inflamed and blistered. Burns caused by mustard gas are severe and require long healing periods. After inhalation of the agent, pulmonary edema and long-term dyspnea may occur.[4] Follow-up of 197 Iranians who were exposed to a large single inhalation episode in 1986 revealed chronic destructive pulmonary sequelae including asthma in 21 subjects, chronic bronchitis in 116 and pulmonary fibrosis in 24.[5]

The toxic effects of mustard gas are primarily related to its alkylating ability.[6] In an aqueous environment, mustard gas rearranges and loses one or two molecules of hydrogen chloride; then, mustard gas, minus its chlorides, becomes firmly attached through one or both of its β-carbon atoms to tissue components, altering their functional and physiochemical properties. Cytotoxic effects have

specifically been related to a double alkylation reaction, in which the two reactive ends of the mustard gas molecule attach to strands of DNA, forming cross-links that prevent cell replication.

Exposure to mustard gas was considered to be a possible cause of cancer in humans, in light of its strong alkylating ability. Two types of exposures have been studied in particular: acute exposure resulting from the use of the gas in war and chronic exposure in the course of its manufacture.

The mortality of British and American veterans of World War I (1914–1918) who were acutely exposed to mustard gas has been investigated. British soldiers who received a pension for mustard gas poisoning were found to have a high mortality from chronic bronchitis (217 vs. 21 expected) and increased mortality from cancer of the lung and pleura (29 vs. 14 expected).[7] However, most of the exposed men also had chronic bronchitis, and a similar excess of lung and pleural cancers was found in pensioners with bronchitis who had not been exposed to the gas. US veterans with mustard gas injury had significantly increased mortality from pneumonia and tuberculosis. There was some increased risk of respiratory cancer in the exposed group, but the extent of the increase was not large.[8] A further study involving an additional 10 years of follow-up produced similar results.[9]

Studies of the effects of occupational exposure to mustard gas have provided a stronger association between exposure and respiratory cancer. Among 495 Japanese workers engaged in the manufacture of mustard gas between 1929 and 1945, 33 died from cancers of the respiratory tract, compared to 0.9 expected.[10] In an earlier report of this same cohort, it was stated that the working environment attained mustard gas concentrations of 0.55–0.07 mg/l and that protective measures were neither fully effective nor generally applied.[11] Follow-up of the Japanese factory workers through 1992 found that workers who had engaged in the production of mustard gas for more than 5 years had a standardized mortality ratio (SMR) of 7.35 for lung cancer.[12] Treatment of 146 of these former gas workers with *Nocardia rubra* cell wall skeleton (N-CWS) was found to significantly suppress the development of cancer (7 in treated workers vs. 17 in untreated).

A study of 3354 British workers employed in the manufacture of mustard gas during World War II (1939–1945) and traced for mortality to the end of 1984, found large and highly significant excesses, compared with national death rates, from cancer of the larynx (11 observed vs. 4 expected), pharynx (15 observed vs. 2.73 expected), and all other buccal cavity and upper respiratory sites combined (lip, tongue, salivary gland, mouth, and nose: 12 observed vs. 4.29 expected).[13] For lung cancer deaths, there were 200 observed cases, compared with 138 expected. Significant excesses were also observed for deaths from acute and chronic nonmalignant respiratory disease. The relative risk of both lung cancer and nonmalignant respiratory disease was substantially reduced. However, if comparison rates for the nearest urban area were used rather than national rates, the risk for cancer of the pharynx and lung was significantly related to duration of employment. Furthermore, the risk of respiratory cancer was not localized to individuals employed in process areas where exposures occurred to high levels of short duration, suggesting that the risk of cancer was due more to lower-level ambient exposure of longer duration. Significant excess mortality was also observed for cancers of the esophagus and stomach, but there was no consistent relation with time since first exposure or duration of exposure. The authors conclude that the results provide strong evidence that exposure to mustard gas can cause cancers of the upper respiratory tract and some evidence that it can cause lung cancer and nonmalignant respiratory disease.

Mustard gas has been tested for carcinogenicity in mice, producing lung tumors after inhalation or intravenous injection and local sarcomas after subcutaneous injection.[14]

The IARC has determined that there is sufficient evidence for carcinogenicity to humans and limited evidence in animals.[14]

Mustard gas is highly genotoxic.[15] In vitro assays in both prokaryotic and eukaryotic systems support a mechanism of DNA alkyla-

tion leading to cross-link formation, inhibition of DNA synthesis and repair, point mutation, and chromosome and chromatid aberration formation.

No significant effects on reproductive function or pregnancy outcome were found in two-generation reproduction studies in rats at doses that were toxic, causing hyperkeratosis and benign neoplasms of the forestomach.[16]

The ACGIH has not established a threshold limit value (TLV) for mustard gas.

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NALED
CAS: 300-76-5

$C_4H_7Br_2Cl_2O_4P$

Synonyms: 1,2-Dibromo-2,2-dichloroethyl dimethyl phosphate; Dibrom

Physical Form. Light straw-colored liquid with slightly pungent odor

Uses. Acaricide; insecticide

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Naled is an anticholinesterase agent.

Signs and symptoms of overexposure are caused by the inactivation of the enzyme cholinesterase, which results in the accumulation of acetylcholine in the nervous system, skeletal and smooth muscle, and secretory glands.[1–3] The sequence of the development of systemic effects varies with the route of entry. The onset of signs and symptoms is usually prompt but may be delayed up to 12 hours. After inhalation of the vapor, respiratory and ocular effects are the first to appear, often within a few minutes of exposure. Respiratory effects include tightness in the chest and wheezing due to bronchoconstriction and excessive bronchial secretion; laryngeal spasm and excessive salivation may add to the respiratory distress; cyanosis may also occur. Ocular effects include miosis, blurring of distant vision (due to spasm of accommodation), tearing, rhinorrhea, and frontal headache.

After ingestion of the liquid, gastrointestinal effects such as anorexia, nausea, vomiting, abdominal cramps, and diarrhea appear within 15 minutes to 2 hours. After skin absorption, localized sweating and muscular fasciculations usually occur in the immediate area within 15 minutes to 4 hours; skin absorption is somewhat greater at higher ambient temperatures and is enhanced by the presence of dermatitis.

With severe intoxication, an excess of acetylcholine at the neuromuscular junctions of skeletal muscle causes weakness aggravated by exertion, involuntary twitchings, fasciculations, and eventually paralysis. The most serious consequence is paralysis of the respiratory muscles. Effects on the central nervous system include giddiness, confusion, ataxia, slurred speech, Cheyne–Stokes respiration, convulsions, coma, and loss of reflexes. The blood pressure may fall to low levels, and cardiac irregularities including complete heart block may occur. Complete symptomatic recovery usually occurs within a week; increased susceptibility to the effects of anticholinesterase agents persists for up to several weeks after exposure. Daily exposure to concentrations that are insufficient to produce symptoms after a single exposure may result in the onset of symptoms. Continued daily exposure may be followed by increasingly severe effects.

Dermatitis occurred on the arms, face, neck, and abdomen of 9 of 12 persons working in a field of flowers that had been freshly sprayed with a solution of Naled; 3 of 4 workers patch tested were positive to a 60% solution of Naled in xylene and negative to xylene alone.[4] The liquid may be expected to cause injury in the eye.

In limited gavage studies, Naled was not carcinogenic to rats.[5]

Naled inactivates cholinesterase by phosphorylation of the active site of the enzyme to form the "dimethylphosphoryl enzyme." Over the following 24–48 hours there is a process, called aging, of conversion to the "monomethylphosphoryl enzyme." Aging is of clinical interest in the treatment of poisoning, because cholinesterase reactivators such as pralidoxime (2-PAM, Protopam) chloride are ineffective after aging has occurred.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 3 mg/m^3 with a notation for skin absorption.

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NAPHTHA, COAL TAR
CAS: 64742-95-6

Synonyms: Naphtha solvent, high-flash naphtha, refined naphtha, and heavy naphtha describe various fractions and grades.

Physical Form. Light yellow liquid with boiling ranges between 110°C and 190°C

Use. Solvent

Exposure. Inhalation

Toxicology. Coal tar naphtha is a central nervous system depressant.

Coal tar naphtha is primarily a mixture of toluene, xylene, cumene, benzene, and other aromatic hydrocarbons; it is distinguished from petroleum naphtha, which is comprised mainly of aliphatic hydrocarbons.[1]

There are no well-documented reports of industrial injury resulting from the inhalation of coal tar naphtha.[1] However, severe exposure is expected to cause light-headedness, drowsiness, and possibly irritation of the eye, nose, and throat.

Nephrotoxicity of naphtha, as evidenced by an increased prevalence of albuminuria, erythrocyturia, and leukocyturia, was suggested in one study of newspaper pressroom workers with low levels of exposure.[2] In another report, no evidence of naphtha-associated renal effects were found in 248 workers with exposures ranging from 6 to 790 mg/m^3 and lengths of exposure ranging from 0.8 to 7.3 years.[3] Differences in formulations of naphthas may account for some of the inconsistencies observed between studies. In animal experiments, variations in the proportion of alkanes to alkenes and aromatics and of highly branched and straight-chain paraffins have produced 100-fold changes in the dose of naphtha necessary to cause toxicity.[3]

No signs of neurotoxicity were observed in rats exposed for 90 days to concentrations up to 1500 ppm. Histopathologic examination of peripheral nervous tissue of exposed animals revealed no degenerative changes.[4]

Exposure of pregnant mice to near-lethal levels of 1500 ppm was maternally toxic and caused increased fetal mortality, reduced weight, delayed ossification, and an increased incidence of cleft palate.[5] At 500 ppm there was reduced maternal and fetal weight gain. No developmental or maternal toxicity was seen at 100 ppm. Similar studies in rats reported developmental delays only at doses that were maternally toxic. No significant adverse effects on reproductive parameters were found in rats exposed for three generations at doses that produced severe toxicity.[5]

Naphtha was not genotoxic in a number of *in vivo* and *in vitro* assays.[4]

Skin contact with the liquid may result in drying and cracking due to defatting action.

Coal tar naphtha, a mixture of hydrocarbons, has been deleted from the ACGIH listing of threshold limit values (TLVs) in favor of reference to its chemical components.

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NAPHTHALENE
CAS: 91-20-3

$C_{10}H_8$

Synonyms: Naphthalin; tar camphor; white tar

Physical Form. White crystalline solid with a characteristic "mothball" odor

Uses. Insect repellant; as a feedstock for synthesis of a variety of compounds, especially phthalic anhydride

Exposure. Inhalation; ingestion

Toxicology. Naphthalene is a hemolytic agent and an irritant of the eyes; it may cause cataracts.

Severe intoxication from ingestion results in characteristic manifestations of marked intravascular hemolysis and its consequences, including potentially fatal hyperkalemia.[1,2] Initial symptoms include eye irritation, headache, confusion, excitement, malaise, profuse sweating, nausea, vomiting, abdominal pain, and irritation of the bladder; there may be progression to jaundice, hematuria, hemoglobinuria, renal tubular blockade, and acute renal shutdown.[1,2] Hematologic features include red blood cell fragmentation, icterus, severe anemia with nucleated red blood cells, leukocytosis, and dramatic decreases in hemoglobin, hematocrit, and red blood cell count; sometimes there is formation of Heinz bodies and methemoglobin.[3] Naphthalene itself is nonhemolytic; several metabolites, including α-naphthol, are, however, hemolytic.[3] Individuals with a hereditary deficiency of the enzyme glucose-6-phosphate dehydrogenase in red blood cells (and consequently decreased concentrations of reduced glutathione) are particularly susceptible to the hemolytic properties of naphthalene.[3]

The vapor causes eye irritation at 15 ppm; eye contact with the solid may result in conjunctivitis, superficial injury to the cornea, chorioretinitis, scotoma, and diminished visual acuity. Cataracts and ocular irritation have been produced experimentally in animals and have been described in humans.[4] Of 21 workers exposed to high concentrations of fume or vapor for 5 years, 8 had peripheral lens opacities. In other studies, no abnormalities of the eyes have been detected in workers exposed to naphthalene for several years.[4]

Reportedly, headache, nausea, and confusion may occur after inhalation of vapor. Occupational poisoning from vapor exposure is rare.[3] Naphthalene on the skin may cause hypersensitivity dermatitis.[1]

In acute and subchronic experiments in CD mice, naphthalene failed to induce either hemolytic anemia or cataract formation, even at doses that produced mortality.[5] In chronic studies female B6C3F1 mice had a significantly increased incidence of pulmonary alveolar/bronchiolar adenomas after 2-year exposure at 30 ppm.[6] The increased incidence did not occur in males or in low-dose females. Exposure of rats by inhalation was associated with induction of neuroblastomas of the olfactory epithelium and adenomas of the nasal respiratory epithelium in males and females.[7] It has been suggested that the higher rates of metabolism of napthalene in mice lead to cytotoxic metabolites in the lung, causing increased cell turnover and tumors.[8] The maximal rates of metabolism measured in human lung microsomes are about 10–100 times lower than those in mice.[8] The IARC has determined that there is sufficient evidence in experimental animals for the carcinogenicity of napthalene and inadequate evidence in humans. Overall, napthalene is considered possibly carcinogenic to humans.

Napthalene was not mutagenic in a variety of bacterial assays, but it did cause sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells.[9]

Naphthalene was not teratogenic in a number of developmental studies, although a trend toward dose-related malformations was seen in rats administered up to 450 mg/kg/day on gestation days 6–15.[9,10]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for napthalene is 10 ppm (52 mg/m^3) with a

short-term excursion limit (STEL) of 15 ppm (79 mg/m^3).

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β-NAPHTHYLAMINE

CAS: 91-59-8

$C_{10}H_9N$

Synonyms: 2-Aminonaphthalene; BNA; 2-naphthylamine; 2NA

Physical Form. Colorless crystals that darken on oxidation

Uses. Formerly used in the manufacture of dyes and antioxidants; rarely used for industrial research purposes today

Toxicology. β-Naphthylamine (BNA) is a potent bladder carcinogen.

Acute exposure to BNA causes methemoglobinemia; signs and symptoms include blueish discoloration of the skin, weakness, dizziness, and dyspnea.[1]

Chronic exposures of BNA, either alone or as an impurity in other compounds, are causally associated with the occurrence of bladder cancer.[2] In one early report all 15 workers involved in distilling of BNA in a small plant in England developed bladder cancer.[3] Of 48 BNA workers employed in a coal tar dye plant, 12 developed bladder tumors.[4] The time elapsed from first exposure to first abnormal signs or symptoms (dysuria, frequency, hematuria) ranged from 1 to 35 years, with a mean of 18 years. The time elapsed from first exposure to diagnosis of bladder malignancy ranged from 2 to 42 years, with a mean of 23 years.[4] Workers employed at the last facility in the US that manufactured BNA had a remarkable and significantly increased incidence of bladder cancer (13 observed vs. 3.3 expected).[5] The mortality incidence from bladder cancer in this cohort was not as profound, with two deaths observed while 0.7 such deaths were expected.[6] The authors suggest that an inadequate latency period and/or the high survival rate for bladder cancer could be the reason for the small number of deaths.

In the most recent follow-up of 442 dyestuff workers followed through 1992

(average time since first exposure 39.4 years) revealed a significant increase for bladder carcinoma [standardized mortality ratio (SMR) = 48.4] for BNA manufacturers but not for malignant neoplasms of other organs.[7]

Dyestuff workers exposed to BNA and benzidine before 1972 showed alterations in some T lymphocyte subpopulations some 20 years later.[8] Specifically, there was a decreased number of circulating CD4+ T lymphocytes in exposed workers. Measurement of this T lymphocyte subpopulation may provide a useful biological marker of past exposure to aromatic amines.

Bladder tumors were induced in 24 of 34 dogs that were fed 6.25–50 mg/kg/day for 6–26 months; carcinomas were present in 9 of 11 dogs that received 100–200 g of BNA, whereas 6 of 22 carcinomas occurred in dogs receiving total doses less than 100 g.[9] All dogs treated with the carcinogen had multiple tumors.

In monkeys, intragastric administration of 37–2400 mg/kg/week for up to 250 weeks caused nine transitional cell carcinomas of the bladder and three papillary adenomas.[10]

In genotoxic assays BNA induced unscheduled DNA synthesis in human cells *in vitro* and chromosomal aberrations, sister chromatid exchanges, DNA strand breaks, and unscheduled DNA synthesis in rodent cells *in vitro*; *in vivo* it formed DNA adducts in bladder and liver cells of dogs.[2]

The IARC has determined that there is sufficient evidence of carcinogenicity of BNA in humans and animals.[2] Because of demonstrated high carcinogenicity, exposure by any route should be avoided.

ACGIH classifies β-naphthylamine as A1, a confirmed human carcinogen, and as such, there is no threshold limit value (TLV).

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NICKEL (and Inorganic Compounds)
CAS: 7440-02-0

Ni

Compounds: Nickel carbonate; nickel oxide; nickel subsulfide; nickel sulfate

Physical form. Elemental nickel is a silver-white metal; salts are crystals

Uses/Sources. Corrosion-resistant alloys, electroplating, production of catalysts, nickel-cadmium batteries; nickel subsulfide (Ni_3S_2) is encountered in the smelting and refining of certain nickel ores and may be formed in petroleum refining from the use of nickel catalysts.

Toxicology. Metallic nickel and certain nickel compounds cause sensitization dermatitis. Nickel refining has been associated with an increased risk of nasal and lung cancer.

"Nickel itch" is a dermatitis resulting from sensitization to nickel; the first symptom is usually pruritis, which occurs up to 7 days before skin eruption appears.[1,2] The primary skin eruption is erythematous, or follicular; it may be followed by superficial discrete ulcers that discharge and become crusted or by eczema. The eruptions may spread to areas related to the activity of the primary site such as the elbow flexure, eyelids, or sides of the neck and face.[2] In the chronic stages, pigmented or depigmented plaques may be formed. Nickel sensitivity, once acquired, is apparently not lost; of 100 patients with positive patch tests to nickel, all reacted to the metal when retested 10 years later.[3]

A worker who had developed cutaneous sensitization also developed apparent asthma from inhalation of nickel sulfate; immunologic studies showed circulating antibodies to the salt, and controlled exposure to a solution of nickel sulfate resulted in decreased pulmonary function and progressive dyspnea; the possibility of hypersensitivity pneumonitis could not be excluded.[4]

Pneumoconiosis has been reported among workers exposed to nickel dust, but exposure to known fibrogenic substances could not be excluded.[5] Nasal irritation, damage to the nasal mucosa, perforation of the nasal septum, and loss of smell have only occasionally been reported in workers exposed to nickel aerosols and other contaminants.[6]

The severe acute systemic effects found with nickel carbonyl exposure are not associated with inorganic nickel.[5]

Epidemiological studies have shown an increased incidence of cancers among nickel refinery workers.[6–8] A mortality update of a cohort of 967 Clydach, Wales, refinery workers employed for at least 5 years and followed to 1971 showed significant risks in both lung and nasal cancers among those hired before 1930.[9] The standardized mortality ratio (SMR) was 623 (O/E = 137/21.98) for lung cancer and 28,718 (O/E = 567/0.195) for nasal cancer. Latency was approximately 14 years for nickel-induced lung cancer and 15–24 years for nasal cancer. No case of nasal cancer occurred among those entering employment after 1930, and lung cancer rates dropped steeply after this date. The reduction was attributed to industrial hygiene improvements and process changes made in the 1920s. The respiratory cancers were primarily related to exposure to soluble nickel compounds at >1 mg nickel/m^3 and to exposure to less soluble compounds at >10 mg nickel/m^3.[10]

An excess of sinus cancers occurred in a cohort of 1852 West Virginia nickel alloy workers employed before 1948, when calcining of nickel sulfide matte was done at the plant.[11]

In one of the largest studies, an excess of lung and nasal cancers was found in a cohort of 54,724 Canadian workers.[6–8] The respiratory cancer risk was confined to the sintering, calcining, and leaching occupational group. There was no excess among miners, concentrators, smelters, or other groups.

Other cancers, including prostatic and laryngeal, have been significantly elevated in certain studies but are less convincingly associated with nickel refinery work.[8]

In an evaluation of epidemiological studies to date, it was concluded that most of the respiratory cancer seen among the nickel refinery workers could be attributed to exposure to a mixture of oxidic and sulfidic nickel at very high concentrations.[10] Exposure to large concentrations of oxidic nickel in the absence of sulfidic nickel was also associated with increased lung and nasal cancer risks. There was also evidence that soluble nickel exposure increased the risk of these cancers and that it may enhance risks associated with exposure to less soluble forms of nickel. There was no evi-

dence that metallic nickel was associated with increased lung and nasal cancer risks. The interaction between smoking and nickel exposure appears to be additive rather than multiplicative.[12]

Two-year animal inhalation studies have shown nickel oxide and nickel subsulfide to be carcinogenic in rats, resulting in alveolar/bronchiolar adenomas and tumors of the adrenal medulla; nickel subsulfide was not carcinogenic to mice, whereas nickel oxide caused equivocal evidence of carcinogenicity in mice based on alveolar/bronchiolar adenomas and carcinomas.[13,14] Nickel sulfate was not carcinogenic in rodent assays but did cause an inflammatory response in the lungs of animals.

The IARC has determined that there is sufficient evidence for carcinogenicity to humans for nickel and nickel compounds.[15]

In vitro and *in vivo* studies indicate that nickel is genotoxic.[12] A higher incidence of chromosomal aberrations has been reported in nickel workers compared with controls.[12]

In experimental animals, a range of reproductive effects can be induced by nickel; in male rats, exposure to nickel salts results in degenerative changes in the testes and epididymis and in effects on spermatogenesis.[7] Exposure of pregnant animals has been associated with delayed embryonic development, increased resorptions, and an increase in structural malformations.[12] In one human study an increase in spontaneous abortion rate and an increase in congenital abnormalities were found in women working in a Russian nickel refining plant.[16] The contribution of confounding factors such as heat stress and heavy lifting is not known.

The 2003 ACGIH threshold limit value-time-weighted averages (TLV-TWAs) are as follows: elemental Ni and metal, 1.5 mg/m^3; soluble Ni compounds, 0.1 mg/m^3; insoluble Ni compounds, 0.2 mg/m^3; nickel subsulfide, 0.1 mg/m^3. Insoluble Ni compounds and nickel subsulfide also have an A1-confirmed human carcinogen designation.

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NICKEL CARBONYL

CAS: 13463-39-3

$Ni(CO)_4$

Synonyms: Nickel tetracarbonyl

Physical Form. Colorless liquid

Uses. Purification intermediate in refining nickel; catalyst in the petroleum, plastic, and rubber industries

Exposure. Inhalation

Toxicology. Nickel carbonyl is a severe pulmonary irritant.

The initial effects of acute exposure involve irritation of the respiratory tract and nonspecific symptoms including frontal headache, vertigo, nausea, vomiting, and sometimes substernal and epigastric pain; generally these early effects disappear when the individual is removed to fresh air.[1,2] It is estimated that exposure to 30 ppm for 30 minutes may be lethal to humans.[2]

There may be an asymptomatic interval between recovery from initial symptoms and the onset of delayed symptoms, which tend to develop 12–36 hours after exposure. Constrictive pain in the chest is characteristic of the delayed onset of pulmonary effects, followed by cough, hyperpnea, and cyanosis, leading to profound weakness; gastrointestinal symptoms may also occur. The temperature seldom rises above 101°F, and leukocytosis above 12,000/cm^3 is infrequent. Physical signs are compatible with pneumonitis or bronchopneumonia. Except for the pronounced weakness and hyperpnea, the physical findings and symptoms resemble those of a viral pneumonia.[2,3]

Terminally, delirium and convulsions frequently occur; death has occurred from 3 to 13 days after exposure to nickel carbonyl. In subjects who recover from nickel carbonyl intoxication, convalescence is usually protracted (2–3 months) and is characterized by excessive fatigue on slight exertion.

A close correlation exists between the clinical severity of acute nickel carbonyl intoxication and the urinary concentration of nickel during the first 3 days after exposure; hospitalization should be considered in all cases where the urinary nickel content exceeds 0.5 mg/liter of urine.[2]

Long-term exposure to low levels of nickel carbonyl have been associated with impaired lung function characterized by obstructive pattern and small airway dysfunction.[4]

Controversy as to whether nickel carbonyl causes cancer arose from observation of increased incidence of cancer of the paranasal sinuses and lungs of workers in nickel refineries. Suspicion of carcinogenicity focused primarily on nickel carbonyl vapor, although there were concurrent exposures to respirable particles of nickel, nickel subsulfide, and nickel oxide.[1] Subsequent studies have shown an increased risk of lung and sinus cancer in nickel refineries where nickel carbonyl was not used in the process.[5] Furthermore, the incidence of respiratory cancer decreased greatly by 1930 despite continued exposure of workers to the same levels of nickel carbonyl through 1957.

Administration of nickel carbonyl to rats by repeated intravenous injection was associated with an increased incidence of various malignant tumors.[6] Inhalation exposure of rats was associated with a few pulmonary malignancies not reaching statistical significance.

The IARC has determined that there is limited evidence for the carcinogenicity of

nickel carbonyl in experimental animals and that, overall, nickel compounds are carcinogenic to humans.

Administered by injection or inhalation during gestation nickel carbonyl caused fetal mortality, reduced pup weights, and fetal malformations including anophthalmia, microphthalmia, cystic lungs, and hydronephrosis in rats and hamsters.[7]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for nickel, including nickel carbonyl, is 0.05 ppm (0.12 mg/m^3), measured as nickel.

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NICOTINE
CAS: 54-11-5

$C_{10}H_{14}N_2$

Synonyms: 1-Methyl-2-(3-pyridyl)pyrrolidine; black leaf

Physical Form. Colorless to pale yellow oily liquid; turns brown on exposure to air or light

Uses/Sources. Insecticide; in tanning; present in tobacco

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Nicotine is a potent and rapid-acting poison; it is rapidly absorbed from all routes of entry, including the skin.

Nicotine acts on the central nervous system, the autonomic ganglia, the adrenal medulla, and neuromuscular junctions; initial stimulation is followed by a depressant phase of action.[1,2] The resulting physiological effects are often complex and unpredictable. Small doses of nicotine cause nausea, vomiting, diarrhea, headache, dizziness, and neurological stimulation resulting in tachycardia, hypertension, hyperpnea, tachypnea, sweating, and salivation.[1,2] With severe intoxication, there are convulsions and cardiac arrhythmias. In fatal cases, death nearly always occurs within 1 hour and may occur within a few minutes.[3] Autopsy after fatal nicotine poisoning has shown marked dilation of the right side of the heart, mild pulmonary edema, hemorrhagic gastritis, brain edema, and renal hyperemia.[4]

Many of the acute physiological effects of smoking, chewing, or inhaling tobacco are attributed to nicotine, but the chronic effects of smoking, such as lung cancer, emphysema, and heart disease, are thought to be due to the nitrosamines, polycyclic aromatic hydrocarbons, and carbon monoxide that are also present.[4] Nicotine and its major metabolites were not genotoxic in *Salmonella* assays or in

sister chromatid exchange assays with or without metabolic activation.[5]

Nicotine, absorbed dermally, is probably the cause of "green tobacco sickness," a self-limited illness consisting of pallor, vomiting, and prostration, seen in men handling tobacco leaves in the field.[3]

Nicotine is teratogenic in mice; skeletal system malformations occurred in the offspring of pregnant mice injected subcutaneously with nicotine between days 9 and 11 of gestation.[6] It has also been found to cause behavioral changes in animals after experimental prenatal exposure.[7]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 0.5 mg/m^3 with a notation for skin absorption.

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NITRIC ACID
CAS: 7697-37-2

HNO_3

Synonyms: Aqua fortis; azotic acid; hydrogen nitrate

Physical Form. Colorless or yellowish liquid with a suffocating odor

Uses. Production of fertilizers in the form of ammonium nitrate; photoengraving; steel etching; dye intermediates; explosives

Exposure. Inhalation

Toxicology. Nitric acid causes corrosion of the skin and other tissues from topical contact and acute pulmonary edema or chronic obstructive pulmonary disease from inhalation.

When nitric acid is exposed to air or comes in contact with organic matter, it decomposes to yield a mixture of oxides of nitrogen, including nitric oxide and nitrogen dioxide, the latter being more hazardous than nitric acid.[1] Exposure to high concentrations of nitric acid vapor and nitrogen oxides causes pneumonitis and pulmonary edema, which may be fatal; onset of symptoms, such as dryness of the throat and nose, cough, chest pain, and dyspnea, may or may not be delayed.[2]

Three pulp mill workers died after inhalation of fumes for approximately 10–15 minutes from a nitric acid tank explosion (concentrations not available).[3] No significant respiratory complaints were apparent during initial examination. However, 4–6 hours later they became cyanotic with frothy fluid escaping from the nose and mouth. All died in less than 24 hours. Necropsy showed bronchiolar epithelial necrosis, marked capillary engorgement, and slight interstitial edema of alveoli; the lungs were five times heavier than normal and released abundant frothy fluid from all lobes. The delayed manifestations of lung injury were consistent

with formation of nitrogen dioxide and other nitrous oxides from the nitric acid and subsequent cellular damage from the formation of chemical free radicals and acids from hydration of nitrogen dioxide. Pulmonary edema was a consequence of increased microvascular permeability, initiated by the nitrogen dioxide-mediated capillary injury. Additional findings in this study also implicated neutrophils and serum-derived mediators in the pathogenesis of the pulmonary edema.

Inhalation of 12.2 ml/m^3 heated nitric acid for 1 hour caused irritation of nasal mucous membranes, a feeling of chest pressure, light prickling pain in the trachea and larynx, inclination to cough, and burning sensation in the eyes and in facial skin.[4] Healthy volunteers exposed to 500 µg/m^3 for 4 hours showed no evidence of proximal airway or distal lung injury.[5] However, prolonged exposure to low concentrations of the vapor may lead to chronic bronchitis and/or diminished appetite.[6] The vapor and mist may erode exposed teeth.[1] However, in cases of dental erosion attributed to nitric acid, there was concomitant exposure to sulfuric acid, a potent cause of dental erosion. Ingestion of the liquid will cause immediate pain and burns of the gastrointestinal tract.

In contact with the eyes, the liquid produces severe burns, which may result in permanent damage and visual impairment.[2] On the skin, the liquid or concentrated vapor produces immediate, severe, and penetrating burns; concentrated solutions cause deep ulcers and stain the skin a bright yellow or yellowish-brown color.[1,2] Dilute solutions of nitric acid produce mild irritation of the skin and tend to harden the epithelium without destroying it.

Nitric acid was not mutagenic in limited studies.[4] There is no information regarding the carcinogenic properties of nitric acid, but an association between incidences of laryngeal cancer and exposure to acid mists has been indicated.[4]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 2 ppm (5.2 mg/m^3) with a short-term excursion limit (STEL)/ceiling of 4 ppm (10 mg/m^3).

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NITRIC OXIDE
CAS: 10102-43-9

NO

Synonyms: Nitrogen monoxide; mononitrogen monoxide

Physical Form. Colorless gas

Uses. Manufacture of nitric acid; bleaching of rayon; as a stabilizer

Exposure. Inhalation

Toxicology. Nitric oxide is a vasodilator and at higher concentrations causes methemoglobin.

In human volunteers significant lung vasodilator effects have been observed at 10–40 ppm.[1] Studies indicate that nitric oxide stimulates guanylate cyclase, which leads to smooth muscle relaxation and vasodilation. Because

nitric oxide is rapidly inactivated in hemoglobin, internal organs other than the lungs are unlikely to be affected by vasodilation.[1]

In animals, methemoglobin formation is seen at concentrations above 10 ppm. Exposure of mice to 5000 ppm for 6–8 minutes was lethal, as was 2500 ppm for 12 minutes; cyanosis occurred after a few minutes, the red eye grounds became gray-blue, and then breathlessness appeared with paralysis and convulsions; spectroscopy of the blood showed methemoglobin.[2]

Some recent studies in mice have suggested that concentrations of 2–10 ppm may reduce host resistance to infection.[1]

Nitric oxide is converted spontaneously in air to nitrogen dioxide; hence, some of the latter gas is invariably present whenever nitric oxide is found in the air.[2] At concentrations below 50 ppm, however, this reaction is slow and substantial concentrations of nitric oxide may occur with negligible quantities of nitrogen dioxide.[2] It is likely that the effects of concomitant exposure to nitrogen dioxide will become manifest before the methemoglobin effects due to nitric oxide can occur. Nitrogen dioxide may cause irritation of the eyes, nose, and throat and delayed pulmonary edema.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for nitric oxide is 25 ppm (31 mg/m^3).

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p-NITROANILINE

CAS: 100-01-6

$NH_2C_6H_4NO_2$

Synonyms: PNA; 1-amino-4-nitrobenzene

Physical Form. Yellow crystals

Uses. Chemical intermediate in the manufacture of antioxidants, antiozonants, dyes, colors, and pigments

Exposure. Inhalation; skin absorption

Toxicology. *p*-Nitroaniline (PNA) absorption, whether from inhalation of the vapor or from absorption of the solid through skin, causes anoxia due to the formation of methemoglobin; jaundice and anemia have been reported from chronic exposure.

Signs and symptoms of overexposure are due to the loss of oxygen-carrying capacity of the blood. The onset of symptoms of methemoglobinemia is often insidious and may be delayed for up to 4 hours; headache is commonly the first symptom and may become quite intense as the severity of methemoglobinemia progresses.[1] Cyanosis develops early in the course of intoxication; blueness in the lips, the nose, and the earlobes is usually recognized by fellow workers. Cyanosis occurs when the methemoglobin concentration is 15% or more. The individual usually feels well, has no complaints, and is insistent that nothing is wrong until the methemoglobin concentration approaches approximately 40%. At methemoglobin concentrations of over 40%, there typically is weakness and dizziness; methemoglobin levels above 50% are rarely observed with PNA exposure; however, concentrations up to 70% would be expected to cause ataxia, dyspnea on mild exertion, tachycardia, nausea, vomiting, and drowsiness; methemoglobin levels of about 75% usually result in collapse, coma, and even death.[1,2] There are no reports of chronic effects from single exposures, but prolonged or excessive exposures may cause liver damage.[1,2]

PNA is mildly irritating to the eyes and may cause some corneal damage.[2]

Ingestion of alcohol aggravates the toxic effects of PNA.[2]

In general, higher ambient temperatures increase susceptibility to cyanosis from exposure to methemoglobin-forming agents.[3]

Exposure of rats to aerosol/vapor of PNA at 30 mg/m^3 for 4 weeks produced a significant increase in methemoglobin levels.[4]

In subchronic studies, administration of PNA at 3, 10, or 30 mg/kg/day for 90 days produced a dose-related increase in methemoglobin; decreases in hematocrit, hemoglobin, and/or red blood cell count were indicative of anemia; histopathologic changes in the spleen included congestion, hemosiderosis, and excessive extramedullary hematopoiesis.[5] Chronic studies in male rats administered 0, 0.25, 1.5, or 9.0 mg/kg/day by gavage for a period of 2 years yielded similar results: Blood methemoglobin levels were elevated in the middle- and high-dose groups, and anemia and increased spleen weights were observed in the high-dose groups.[6] No treatment-related increase in tumor incidence occurred at these PNA levels. In contrast to rats, there was equivocal evidence of carcinogenic activity in male mice administered doses of 3, 30, or 100 mg/kg body weight/day 5 days/week for 2 years based on the increased incidences of hemangiosarcoma of the liver and hemangioma or hemangiosarcoma (combined) at all sites.[7] There was no evidence of carcinogenicity in female mice. Methemoglobin concentrations were significantly higher in all 30 or 100 mg/kg mice and erythrocyte counts were significantly lower in the high-dose animals. Treatment-related lesions included increases in the incidence or severity of splenic congestion, hematopoiesis, pigment accumulation, and bone marrow hyperplasia.[7]

PNA was mutagenic *in vitro* in some bacterial strains and in chromosomal aberration studies.[7]

In a reproductive study, doses of up to 9.0 mg/kg/day were administered to male and female rats before and during mating and during gestation and lactation to the F_0 and F_1 generations.[6] No significant effects were seen in mating, pregnancy, or fertility indices.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 3 mg/m^3 with a notation for skin absorption.

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NITROBENZENE
CAS: 98-95-3

$C_6H_5NO_2$

Synonyms: Nitrobenzol; oil of mirbane

Physical Form. Almost water-white oily liquid, turning yellow with exposure to air

Uses. Chemical intermediate for the production of aniline and other products

Exposure. Inhalation; skin absorption

Toxicology. Nitrobenzene causes anoxia due to the formation of methemoglobin; in experimental animals chronic exposure has been associated with lesions of the liver, spleen, and kidney and testicular atrophy; it is carcinogenic to mice and rats.

Exposure of workers to 40 ppm for 6 months resulted in some cases of intoxication and anemia; concentrations ranging from 3 to 6 ppm caused headache and vertigo in 2 of 39 workers; increased methemoglobin and sulfhemoglobin levels and Heinz bodies were observed in the blood.[1]

Signs and symptoms of overexposure are due to the loss of oxygen-carrying capacity of the blood. The onset of symptoms of methemoglobinemia is often insidious and may be delayed up to 4 hours; headache is commonly the first symptom and may become quite intense as the severity of methemoglobinemia progresses.[2] Cyanosis develops early in the course of intoxication, characterized by blueness of the lips, nose, and earlobes, usually recognized first by fellow workers, and occurring when the methemoglobin level is 15% or more. The individual usually feels well, has no complaints, and will insist that nothing is wrong until the methemoglobin concentration approaches 40%. At methemoglobin concentrations ranging from 40% to 70%, there is headache, weakness, dizziness, ataxia, dyspnea on mild exertion, tachycardia, nausea, vomiting, and drowsiness.[2,3] Coma may ensue with methemoglobin levels above 70%, and the lethal level is estimated to be 85–90%.[3]

Hepatotoxicity, manifested by alterations in liver function, including hyperbilirubinemia, and decreased prothrombin activity, is associated with exposure in both animals and humans.[4]

Inhalation exposure of rats and mice (10–25 ppm over 2 weeks or 5–50 ppm over 13 weeks) caused methemoglobinemia, encephalopathy, and lesions in the liver (hepatocyte necrosis and hepatomegaly), kidney (hyalin nephrosis), and spleen (extramedullary hematopoiesis and proliferative capsular lesions).[5,6]

In a 2-year inhalation study, nitrobenzene was carcinogenic in mice and rats with differing target organs based on species, sex, and strain.[7] Male B6C3F1 mice exposed at concentrations up to 50 ppm had increased incidences of pulmonary alveolar/bronchiolar and thyroid follicular cell neoplasms, whereas females had mammary gland neoplasms. In rats, exposures up to 25 ppm resulted in hepatocellular and renal neoplasms (male F344 rats), endometrial stromal neoplasms (female F344), and hepatocellular neoplasms (male CD rats).

Nitrobenzene was not genotoxic in vivo or in bacterial or mammalian assays in vitro.[8] The IARC has determined that there is inadequate evidence in humans and sufficient evidence in experimental animals for the carcinogenicity of nitrobenzene and that, overall, nitrobenzene is possibly carcinogenic to humans.[8]

Nonneoplastic effects in rodents from chronic exposure included methemoglobinemia, anemia, lesions of the olfactory epithelium, and, in the CD males, an increased incidence of testicular atrophy.[7] Degenerative testicular lesions have also occurred in rats exposed to single oral doses of 50–450 mg/kg.[9] Male rats repeatedly administered up to 100 mg/kg body weight by gavage daily showed atrophy of the seminiferous tubules of the testis, but male fertility was not affected.[10]

No evidence of teratogenesis or adverse fetal effects was apparent in the offspring of rats exposed at concentrations of 40 ppm for 6 hours/day from day 6 to day 15 of pregnancy.[9] In a two-generation reproduction study in rats, a decrease in the fertility index of the F_0 and F_1 generations occurred.

Ingestion of alcohol aggravates the toxic effects of nitrobenzene.[3] In general, higher ambient temperatures increase susceptibility to cyanosis from exposure to methemoglobin-forming agents.[11] *p*-Nitrophenol and *p*-aminophenol are metabolites of nitrobenzene, and their presence in the urine is an indication of exposure.[12]

Nitrobenzene is mildly irritating to the eyes; it may produce dermatitis due to primary irritation or sensitization.[3]

The 2003 ACGIH threshold limit value-

time-weighted average (TLV-TWA) for nitrobenzene is 1 ppm (5 mg/m^3) with a notation for skin absorption and an A3-confirmed animal carcinogen with unknown relevance to humans designation.

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p-NITROBIPHENYL

CAS: 92-93-3

$C_{12}H_9NO_2$

Synonyms: 4-Nitrobiphenyl; 4-nitrodiphenyl; PNB

Physical Form. White crystals

Uses. Formerly used as an intermediate for 4-aminobiphenyl

Exposure. Inhalation; skin absorption

Toxicology. *p*-Nitrobiphenyl (PNB) is a urinary bladder carcinogen in dogs.

There are no reports on carcinogenicity of PNB in humans.[1] However, PNB was used as an intermediate in the preparation of 4-aminobiphenyl, a recognized human bladder carcinogen, and bladder tumors found in men exposed to 4-aminobiphenyl may have been partially due to PNB.[2]

Three of four dogs fed 0.3 g of PNB (in capsule) three times/week for up to 33 months developed bladder tumors.[2] The total dose administered ranged from 7 to 10 g/kg in the affected dogs; the animal that did not develop bladder tumors was the largest and therefore had received less of the compound per kilogram of body weight (5.5 g/kg). The tumors produced by PNB were identical histologically with those produced by 4-aminobiphenyl.[2]

The case for the carcinogenicity of PNB is supported by (1) the induction of urinary bladder cancer in dogs after administration of PNB; (2) the evidence that PNB is metabolized in vivo to 4-aminobiphenyl (a potent carcinogen); and (3) the possibility that the cases of human urinary bladder cancer attributed to 4-aminobiphenyl may also have been induced by exposure to PNB.[1]

There is no threshold limit value (TLV) for PNB. It is classified as a confirmed human carcinogen and exposure by any route—respiratory, oral, or skin—should be avoided.

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o-NITROCHLOROBENZENE

CAS: 88-73-3

$NO_2C_6H_4Cl$

Synonyms: 2-chloronitrobenzene; 1-chloro-2-nitrobenzene; 2-CNB; ONCB

Physical Form. Yellow solid

Uses. Chemical intermediate in manufacture of dyes, picric acid, lumber preservatives, and diaminophenol hydrochloride (a photographic developer)

Exposure. Inhalation; skin absorption

Toxicology. *o*-Nitrochlorobenzene (ONCB) absorption causes anoxia owing to formation of methemoglobin.

Numerous cases of cyanosis in workers exposed to ONCB and related compounds occurred in the period 1935–1965.[1]

Signs and symptoms of overexposure are caused by the loss of oxygen-carrying capacity of the blood. The onset of symptoms of methemoglobinemia is often insidious and may be delayed up to 4 hours; headache is commonly the first symptom and may become quite intense as the severity of methemoglobinemia progresses.[1] Cyanosis develops early in the course of intoxication; it is characterized by blueness of the lips, nose, and earlobes, usually recognized first by fellow workers, and occurs when the methemoglobin concentration approaches 40%. At methemoglobin concentrations ranging from 15% to 70%, there is headache, weakness, dizziness, ataxia, dyspnea on mild exertion, tachycardia, nausea, vomiting, and drowsiness. Coma may ensue with methemoglobin levels of about 70%, and the lethal level is estimated to be 85–90%.

In general, higher ambient temperatures increase susceptibility to cyanosis from exposure to methemoglobin-forming agents.[1]

The acute oral LD_{50} of ONCB in rats is 560 mg/kg, whereas the dermal LD_{50} in rabbits is 400 mg/kg.[2] In subchronic inhalation studies, rats were exposed to 10, 30, or 60 mg/m^3 6 hours/day, 5 days/week for 4 weeks. Animals exposed to the midlevel and high concentrations showed a significant increase in blood methemoglobin and a significant decrease in hemoglobin, hematocrit, and red blood cell counts. Spleen and liver weights were also significantly increased for these two groups; microscopic changes, observed only in the spleen, included an increased degree of extramedullary hematopoiesis and hemosiderosis.

Thirteen-week inhalation exposure to ONCB in mice at doses ranging from 1.1 to 18 ppm caused hyperplasia of the forestomach, hepatocellular necrosis, secondary effects of methemoglobin formation on the spleen, liver, and bone marrow, and, at the highest dose, death.[3] Rats similarly exposed had hyperplasia of the nasal cavity and, at the lowest dose tested, methemoglobinemia.

In carcinogenicity bioassays, it was found

that ONCB produced an increase in the incidence of multiple tumors in male rats at the low dose (1000 mg/kg diet for 6 months, followed by 500 mg/kg diet for 12 months and control diets for an additional 6 months) but not at the high dose (2000 mg/kg diet for 6 months, followed by 100 mg/kg diet for 12 months and control diets for 6 months).[4] ONCB produced an increase in hepatocellular carcinomas in female mice at high (6000 mg/kg diet) and low (3000 mg/kg diet) dose levels and in male mice at low but not high dose levels. Because of the inconsistency of the dose-response effects, the high doses used, and the long latent periods before tumor development, ONCB was not regarded as a very potent carcinogen under the conditions of the test. The IARC has determined that the studies were inadequate for an evaluation of the carcinogenicity of ONCB.[5]

In a continuous breeding study in mice reproductive and fertility parameters were not affected by gavage administration of ONCB even in the presence of systemic toxicity (significant methemoglobinemia and increased spleen and liver weights).[5,6] Decreased spermatogenesis has been reported after inhalation exposure in rats and mice.

ONCB has given positive and negative results in a variety of genotoxic assays: In mammalian cells in vitro it has induced sister chromatid exchange and chromosomal aberrations, and *in vivo* it has caused DNA damage in mice; it was not mutagenic in insects in bacterial assays without metabolic activation.[5,6]

There is no threshold limit value (TLV) established for the *ortho* isomer of nitrochlorobenzene.

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p-NITROCHLOROBENZENE

CAS: 100-00-5

$NO_2C_6H_4Cl$

Synonyms: PNCB; *p*-Chloronitrobenzene; 4-CNB

Physical Form. Yellowish crystals

Uses. Manufacture of dyes, rubber, and agricultural chemicals

Exposure. Inhalation; skin absorption

Toxicology. Absorption of *p*-nitrochlorobenzene (PNCB) causes anoxia due to the formation of methemoglobin.

Signs and symptoms of overexposure are due to the loss of oxygen-carrying capacity of the blood. The onset of symptoms of methemoglobinemia is often insidious and may be delayed for up to 4 hours; headache is commonly the first symptom and may become quite intense as the severity of methemoglobinemia progresses.[1] Cyanosis develops early in the course of intoxication; blueness occurs first in

the lips, nose, and earlobes and is usually recognized by fellow workers. Cyanosis occurs when the methemoglobin concentration is 15% or more. The subject usually feels well, has no complaints, and is insistent that nothing is wrong until the methemoglobin concentration approaches approximately 40%. At methemoglobin concentrations over 40%, there is weakness and dizziness; closer to 70% concentration, there may be ataxia, dyspnea on mild exertion, tachycardia, nausea, vomiting, and drowsiness. The ingestion of alcohol aggravates the toxic effects of PNCB. In general, higher ambient temperatures increase susceptibility to cyanosis from exposure to methemoglobin-forming agents.

Four workers exposed to an unmeasured concentration of the vapor for a period of 2–4 days developed methemoglobinemia; in these cases there was an initial collapse, a slate gray appearance, dyspnea, and a mild anemia 1 week after exposure.[2]

The acute oral LD_{50} in rats was 530 mg/kg.[3] In a 4-week inhalation study, exposure to 0.82, 2.5, or 7.5 ppm (5, 15, or 45 mg/m^3) 6 hours/day, 5 days/week caused a dose-related increase in methemoglobin levels and decreases in hemoglobin, hematocrit, and red blood cell counts.[4] Microscopic changes in the spleen included congestion, increased extramedullary hematopoiesis, and hemosiderosis. In more recent 13-week inhalation studies of PNCB in mice and rats 1.5–24 ppm caused methemoglobin formation and oxidative damage to red blood cells and anemia. Male rats also had renal hyalin droplet accumulation and testicular atrophy.[5]

No increase in tumor incidence was seen in rats fed up to 1000 ppm in the diet for 2 years; in mice, results were equivocal, with high-dose animals showing an increase in vascular tumors and low-dose males showing an increase in liver tumors.[6] The IARC has determined that there is inadequate evidence in experimental animals and humans for the carcinogenicity of chlorobenzenes.[7]

When PNCB was administered to pregnant rabbits or rats, fetal effects were observed only at doses that produced severe maternal toxicity.[8] A progressive decrease in fertility was noted in mice in a continuous breeding study.[7]

Applied to the skin or eyes of rabbits, PNCB did not cause irritation; it was absorbed, producing methemoglobinemia, Heinz bodies in erythrocytes, anemia, hematuria, and hemoglobinuria.[3] The acute dermal LD_{50} for rabbits was 3400 mg/kg.

In genotoxic assays PNCB induced reverse mutations but not primary damage in bacteria.[7] At toxic doses, it induced chromosomal aberrations, sister chromatid exchange, and repairable DNA breaks in cultured mammalian cells. In vivo it induced DNA damage in mice.[7]

PNCB has a pleasant, aromatic odor.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 0.1 ppm (0.64 mg/m^3) with a notation for skin absorption.

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NITROETHANE
CAS: 79-24-3

$C_2H_5NO_2$

Synonyms: None

Physical Form. Colorless, oily liquid

Uses. Common industrial solvent; more recently a commercial artificial nail remover

Exposure. Inhalation

Toxicology. In animals, nitroethane is a respiratory irritant and, at high concentrations, it causes narcosis and liver damage; methemoglobin has been reported after ingestion by humans.

Accidental ingestion of less than 1 ounce of an artificial fingernail remover containing 100% nitroethane resulted in life-threatening methemoglobinemia in a 20-month-old child.[1] The child was initially asymptomatic, but on hospital admission 10 hours later, he was short of breath and visibly cyanotic. Methemoglobin concentrations reached 40.1%. The patient received 15 mg of methylene blue intravenously with resolution of cyanosis. One hour later the child's methemoglobin concentration dropped to 5.7% and other laboratory findings and vital signs were within normal limits. He was discharged 1 day later with a methemoglobin concentration of 1.5%. The delayed onset of symptoms (10 hours in this case) suggests a possible metabolism of nitroethane to a more toxic nitrite compound that may in turn be responsible for the induction of methemoglobin.[1]

Rabbits died from exposure to 5000 ppm for 3 hours but survived 3 hours at 2500 ppm.[2,3] Exposure to the higher concentrations caused irritation of mucous membranes, lacrimation, dyspnea, pulmonary rales, and, in a few animals, pulmonary edema; convulsions were rare and of brief duration.[2] Autopsy of animals exposed to lethal concentrations showed mild to severe liver damage and nonspecific changes in the kidneys. Nitroethane was not hepatotoxic after administration of 9 mmol/kg to mice.[4]

Rats exposed to 1000 ppm 6 hours/day, 5 days/week for up to 90 days showed decreased body weight gain, elevated methemoglobin levels with cyanosis, increased reticulocytes, Heinz bodies, and associated splenic congestion and hematopoiesis.[5] Other target organs included olfactory epithelium, liver, renal epithelium, and salivary glands. Similarly exposed mice showed slight effects on methemoglobin, salivary glands, liver, and olfactory epithelium, along with multinucleated spermatids.[5]

Nitromethane was not genotoxic in *Salmonella typhimurium* tester strains.[4]

The liquid is a mild skin irritant due to solvent action.

The odor of nitroethane is detectable at 163 ppm; the odor and irritant properties do not provide sufficient warning of toxic concentrations.[2,3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for nitroethane is 100 ppm (307 mg/m^3).

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NITROGEN DIOXIDE

CAS: 10102-44-0

NO_2

Synonyms: None

Physical Form. Gas

Uses/Sources. Intermediate in nitric and sulfuric acid production; nitration of organic compounds and explosives; found in vehicle emissions and fossil fuel combustion

Exposure. Inhalation

Toxicology. Nitrogen dioxide is a respiratory irritant; at high concentrations it causes pulmonary edema and, rarely among survivors, bronchiolitis obliterans.

Brief exposure of humans to concentrations of about 250 ppm causes cough, production of mucoid or frothy sputum, and increasing dyspnea.[1,2] Within 1–2 hours, the person may develop pulmonary edema with tachypnea, cyanosis, fine crackles and wheezes through the lungs, and tachycardia. Alternatively, there may be only increasing dyspnea and cough over several hours, with symptoms then gradually subsiding over a 2- to 3-week period. The condition may then enter a second stage of abruptly increasing severity; fever and chills precede a relapse, with increasing dyspnea, cyanosis, and recurring pulmonary edema. Death may occur in either the initial or second stage of the disease; a severe second stage may follow a relatively mild initial stage. The subject who survives the second stage usually recovers over 2–3 weeks; however, some cases do not return to normal but experience varying degrees of impaired pulmonary function.

The radiographic features in the acute initial stage vary from normal to those of typical pulmonary edema; most reports mention a pattern of nodular shadows on the chest film at the outset.[1,2] The roentgenogram may then clear, only to show miliary mottling as the second stage commences, progressing to the development of a confluent pattern. Results of pulmonary function tests in the acute stage show reduction in lung volume and diffusing capacity; similar findings are recorded in the second stage.

Pathologic examination of the acute lesion shows extensive mucosal edema and inflammatory cell exudation. The delayed lesion shows the histologic appearance of bronchiolitis obliterans; small bronchi and bronchioles contain an inflammatory exudate that tends to undergo fibrinous organization, eventually obliterating the lumen.

Humans exposed to nitrogen dioxide for 60 minutes can expect the following effects: 100 ppm, pulmonary edema and death; 50 ppm, pulmonary edema with possible subacute or chronic lesions in the lungs; and 25 ppm, respiratory irritation and chest pain.[3] A concentration of 50 ppm is moderately irritating to the eyes and nose; 25 ppm is irritating to some people.[1] Exposure of healthy and asthmatic volunteers at 4 ppm for 75 minutes caused a small but significant decrease in systolic blood pressure; there were no significant effects on airway resistance symptoms, heart rate, skin conductance, or self-reported emotional state.[4] However, in an earlier study, human volunteers exposed to 5 ppm for 15 minutes and 2.5 ppm for 2 hours showed increased airway resistance.[5]

Most reported cases of severe illness from nitrogen dioxide have been accidental exposures to explosion or combustion of nitroexplosives, or from the intermittent process of arc or gas welding (especially in a confined space),

or the entry into an agricultural silo that was not vented.[1,6]

Less severe respiratory complaints have been reported in 116 individuals exposed to nitrogen dioxide during two hockey games in an indoor ice arena.[7] The gas was emitted from the malfunctioning engine of an ice resurfacer. Air concentrations were not recorded, although air sampling under simulated conditions detected 4 ppm nitrogen dioxide; levels were probably higher during the games. Of interest was the occurrence of cough, dyspnea, chest pain, and mild hemoptysis, principally among the hockey players and cheerleaders, who were actively exercising and therefore had a higher minute ventilation and greater lung tissue exposure than spectators.

In experimental animals, nitrogen dioxide induces several types of pulmonary toxicity.[8] Decreased pulmonary function occurs in mice after chronic exposure to 0.2 ppm with daily excursions to 0.8 ppm. Effects on lung morphology were seen in rats exposed to 10 ppm for 36 hours and included cilia loss and hypertrophy of the bronchiolar epithelium. In guinea pigs acute exposure to 4 ppm caused increased airway hyperresponsiveness toward histamine.

Animal experimentation has also indicated that in, addition to irritation and pathologic changes, nitrogen dioxide exposure may decrease host resistance to infection.[8,9] An increased mortality in mice infected with pneumonia-causing organisms was found subsequent to exposure at 0.5 ppm for 7 days and longer.[10] Nitrogen dioxide can adversely effect lung defense mechanisms by reducing the efficacy of mucociliary clearance, the alveolar macrophage, and the immune system.[11]

Individuals with a history of asthma or chronic obstructive airway disease are more susceptible to symptoms arising out of exposure to low levels of nitrogen dioxide.[12,13]

Nitrogen dioxide does not appear to be directly carcinogenic, and evidence regarding its tumor-promoting or -enhancing capabilities is limited and conflicting.[13]

The odor threshold is of the order of 0.12 ppm.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for nitrogen dioxide is 3 ppm (5.6 mg/m3) with a short-term exposure limit (STEL) of 5 ppm (9.4 mg/m^3).

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NITROGEN MUSTARDS (Blister Agents)

CAS: HN-1: 538-07-8
HN-2: 51-75-2
HN-3: 555-77-1

Synonyms: HN-1: $C_6H_{13}Cl_2$; *N*-ethylbis(2-chloroethyl)amine; 2,2′-dichlorotriethylamine; 2-chloro-*N*-(2-chloroethyl)-*N*-ethylethanamine; bis(2-chloroethyl)ethylamine; ethylbis(2-chloroethyl)amine

HN-2: $C_5H_{11}Cl_2N$; Mechlorethanamine; chlormethine; *N*,*N*-bis(2-chloroethyl) methylamine; 2-chloro-*N*-(2-chloroethyl)-*N*-methylethanamine; bis(2-chloroethyl) methylamine; bis(β-chloroethyl) methylamine; Caryolysine; 2,2′-dichloro-*N*-methyldiethylamine; Dichloren; MBA

HN-3; $C_6H_{12}Cl_3N$; tris(2-chloroethyl) amine; 2,2′,2″-trichlorotriethylamine; tris(2-chloroethyl)amine; HN-3; 2-chloro-*N*, *N*-bis(2-chloroethyl)ethanamine; N-methyl lost

Physical Form. Colorless to yellow oily liquids that evaporate very slowly. HN-1 has a faint fishy or musty odor. HN-2 has a soapy odor at low concentrations and a fruity odor at higher concentrations. HN-3 may smell like bitter almond.

Uses. Although nitrogen mustards could be used in chemical warfare, there are presently no records of such use. HN-1 has been used to remove warts in the past, and HN-2 has been used sparingly in chemotherapy.

Exposure. Skin contact and absorption; inhalation

Toxicology. Nitrogen mustards are vesicants and alkylating agents that damage the respiratory airways and cause skin and eye burns.

Because nitrogen mustard agents are alkylating compounds, they destroy individual cells by reaction with cellular proteins, enzymes, RNA, and DNA.[1] Once begun, tissue reaction is irreversible. When nitrogen mustards are absorbed by the body, they cause damage to bone marrow and the immune system. Exposure to high levels causes death. Vesicant agents are also capable of generating delayed effects such as chronic bronchitis, carcinogenesis, or keratitis/keratopathy of the eye under appropriate conditions of exposure and dose. These effects may not become manifest until years after exposure. It is unlikely that the general public or workers will be exposed to nitrogen mustard agents HN-1, HN-2, and HN-3, except in a terrorist attack or during war.

Inhalation will cause nasal and sinus pain or discomfort, pharyngitis, laryngitis, cough, and shortness of breath. Damage to cells lining airways will begin within hours and progress over the next several days. Skin contact with nitrogen mustard vapors or liquid will cause initial swelling and rash followed by blistering. Contact with high levels of nitrogen mustards can result in second- and third-degree burns. If nitrogen mustards contact the eyes there will be inflammation, pain, swelling, corneal damage, burns, and even blindness. In the unlikely event of ingestion, there will be burning of the mouth, esophagus, and stomach.

The IARC has classified nitrogen mustard HN-2 as probably carcinogenic to humans based on evidence that it causes leukemia in humans and cancers of the lung, liver, uterus, and large intestine in animals.[2]

HN-2 nitrogen mustard, administered mainly as the hydrochloride, has been tested for carcinogenicity in mice and rats by subcutaneous, intravenous, and intraperitoneal administration and by skin painting. It produced mainly lung tumors and lymphomas in mice after subcutaneous, intravenous, and intraperitoneal administration. Intravenous injection of nitrogen mustard to rats induced tumors in different organs[3]. Application by skin

painting produced local tumors in mice in a dose-dependent manner.[4,5]

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NITROGEN TRIFLUORIDE

CAS: 7783-54-2

NF_3

Synonyms: Nitrogen fluoride

Physical Form. Colorless gas

Uses. Oxidizing agent in fuel combustion; as a fluorine source in the electronics industry; in high-power chemical lasers

Exposure. Inhalation

Toxicology. Nitrogen trifluoride causes anoxia in animals due to the formation of methemoglobin.

Although there are no reports of human intoxication from nitrogen trifluoride, the initial effects of methemoglobinemia include cyanosis (especially in the lips, nose, and earlobes), weakness, dizziness and severe headache.[1] At higher methemoglobin concentrations up to 70% there may be ataxia, dyspnea on mild exertion, and tachycardia. Coma may ensue with methemoglobin levels of about 70%, and the lethal level in humans is estimated to be 85–90%.

Rats died from exposure to 10,000 ppm for 60–70 minutes; the methemoglobin concentrations at the time of death were equivalent to 60–70% of available hemoglobin.[2] Animals exposed to nearly lethal concentrations suffered severe respiratory distress and cyanosis due to methemoglobinemia; severely affected animals showed incoordination, collapse, and convulsions. Rats repeatedly exposed to 100 ppm for 4.5 months appeared normal, but autopsy findings indicated injury to the liver and kidneys.[3] Dogs surviving exposure to 9600 ppm for 60 minutes exhibited Heinz body anemia, decreased hematocrit levels, decreased hemoglobin levels, reduced red blood cell count, and clinical signs consistent with anoxia from methemoglobin formation; some eye irritation was observed during exposure.[4]

Nitrogen trifluoride provides no odor-warning properties at potentially dangerous levels.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 10 ppm (29 mg/m^3).

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NITROGLYCERIN
CAS: 55-63-0

$CH_2NO_3CHNO_3CH_2NO_3$

Synonyms: 1,2,3-Propanetriol trinitrate; glycerol trinitrate; nitroglycerol; NG; trinitroglycerol; NTG; trinitrin

Physical Form. Oily liquid at room temperature; colorless in pure form and pale yellow or brown in commercial form

Uses. Manufacture of dynamite, gun powder and rocket propellants, and as a therapeutic agent primarily to alleviate angina pectoris. *Note:* Workers engaged in the production or use of dynamite are potentially exposed to mixed vapors of nitroglycerin (NG) and ethylene glycol dinitrate (EGDN).

Exposure. Inhalation; skin absorption

Toxicology. NG is a vasodilator and has been associated with acute episodes of angina pectoris, myocardial infarction, and sudden death.

Initial exposure to NG (or NG:EGDN mixtures where exposures are considered additive) characteristically results in an intense, throbbing headache that begins in the forehead and moves to the occipital region.[1] Volunteers developed mild headaches when exposed to NG:EGDN vapor at concentrations of 0.5 mg/m^3 for 25 minutes.[2] It has been suggested that at least some workers may develop headaches at concentrations as low as 0.1 mg/m^3.[1]

Other signs and symptoms associated with initial exposure include dizziness, nausea, palpitations, and decreases in systolic, diastolic, and pulse pressures.[1] These initial signs and symptoms, including headache, are indicative of a shift in blood volume from the central to the peripheral circulatory system, initiated by dilation of the blood vessels.

After 2–4 days of repeated NG exposure, tolerance to the vasodilatory activity occurs, probably as a result of compensatory vasoconstriction. Tolerance may be lost during periods without NG exposure, such as weekends and holidays.[3] Recent studies have suggested that tolerance may be mediated by a mitochondrial aldehyde dehydrogenase that catalyzes the formation of 1,2-glyceryl dinitrate and nitrite from NG, leading to production of cGMP and relaxation of vascular smooth muscle.[4]

Chronic, repeated exposures to NG and NG mixtures have also been associated with more serious cardiovascular effects, including angina pectoris and sudden death.

Signs and symptoms of ischemic heart disease were observed in nine munitions workers involved in handling a nitroglycerin-cellulose mixture.[5] Within 1–4 years of initial exposure, these workers developed nonexertional chest pain that was relieved either by therapeutic nitroglycerin or by returning to work after the weekend. Coronary angiography performed in five of the patients showed no obstructive lesions. In one patient, observed while in the withdrawal state, coronary artery spasm was demonstrated and readily reversed by sublingual nitroglycerin.

Like the attacks of angina pectoris, sudden deaths occurred most frequently during brief periods away from work and in particular on Sunday nights or Monday mornings.[6] In most cases, there were no premonitory signs or symptoms, although some subjects had anginal episodes during brief periods away from work. Atherosclerotic plaques, with or without thrombosis, have been found in the coronary arteries of workers at autopsy, but their coronary arteries were generally not occluded to the same extent as those of unexposed workers who had died suddenly.[1]

The pathogenesis of the sudden death syndrome has been postulated to be due to withdrawal of coronary vasodilators (e.g., NG), resulting in vasoconstriction with acute hyper-

tension, or with myocardial ischemia in workers adapted to and dependent on NG to maintain a minimum level of coronary flow.[3] A second contributing mechanism for coronary artery toxicity due to NG may relate to the so-called "aging" of the vessels due to repeated dilation.[7] Other theories suggest that sudden deaths may be related to peripheral vasodilation consequent to reexposure to NG.[6]

Estimates of exposure levels associated with sudden death have not been made because workers typically absorb considerable amounts of NG through the skin in addition to inhalation.[1] Skin contact may also cause an irritant dermatitis resembling poison ivy, and, occasionally, allergic contact dermatitis has been reported.[8]

Epidemiological studies have suggested that the effects of long-term workplace exposure to NG may not be completely reversed after exposure is terminated. Former workers may be at increased risk for cardiovascular mortality for months to years after exposure has ceased.

A cohort study of 5668 NG-exposed workers found an increased standardized mortality ratio for deaths from ischemic heart disease.[9] The increase was more pronounced for those with 10 or more years of exposure and was statistically significant for the 40- to 49-year age group, whereas a deficit of cardiovascular mortality had been anticipated because of preplacement and annual medical examinations designed to exclude persons with cardiovascular abnormalities. These results were confirmed in a retrospective cohort mortality study that found a significant excess of ischemic heart disease mortality among workers actively exposed to NG and under the age of 45.[10] (Note: this study failed to detect a chronic cardiovascular effect as excess risk was only associated with workers actively exposed to NG.)

An excess of deaths from acute myocardial infarction was also confirmed in a younger group of workers exposed to NG and EGDN in a Scottish explosives factory and followed for 16 years.[11]

In a case-control study in Sweden, a 2.5 relative risk of cardiocerebrovascular disease was found in explosives workers with over 20 years' experience; most of the deaths occurred months or years after exposure had ceased.[12]

It is generally recognized that workers exposed to either NG or EGDN have reduced tolerance for alcohol.[1] Animal studies suggest that NG may decrease the activity of alcohol dehydrogenase, thereby decreasing the rate of alcohol metabolism.[1]

NIOSH-recommended exposure limits for NG, EGDN, or a mixture of the two were set at a level to prevent significant changes in the diameter of cerebral blood vessels during initial exposure, as indicated by the occurrence of headache or by decrease in blood pressure, thereby preventing the development of compensatory vasoconstrictive mechanisms that may eventually result in more serious effects.[1]

Individuals with preexisting ischemic heart disease should not be assigned to work where significant exposure to NG may occur.[13]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 0.05 ppm (0.46 mg/m^3) with a notation for skin absorption.

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NITROMETHANE

CAS: 75-52-5

CH_3NO_2

Synonyms: Nitrocarbol

Physical Form. Colorless oily liquid

Uses. Solvent; chemical synthesis; fuel for professional and model racing cars; in explosive mixtures

Exposure. Inhalation

Toxicology. Nitromethane, in animals, affects the central nervous system, causing convulsions and narcosis at high doses; it is also a mild pulmonary irritant and may cause liver damage.

The human oral lethal dose is estimated between 0.5 and 5.0 g/kg.[1] Occupational exposure to nitromethane was suspected as the cause of severe peripheral neuropathy in two workers exposed for 1–2 months.[2]

Rabbits died from exposure to 10,000 ppm for 6 hours; initial effects were weakness, ataxia, and muscular incoordination followed by convulsions.[3,4] The same concentration for 3 hours was not fatal. Autopsy of animals exposed to lethal concentrations showed focal necrosis in the liver and moderate kidney damage. Lower concentrations produced slight irritation of the respiratory tract, followed by mild narcosis, weakness, and salivation, but no evidence of eye irritation.

In a subchronic inhalation study, rabbits exposed to 98 ppm 7 hours/day, 5 days/week for 6 months showed hemoglobin depression with some methemoglobin, elevated serum carbamyl transferase, and thyroxin depression.[5] For rats similarly exposed at 745 ppm, there was altered hematocrit, hemoglobin, and erythrocyte counts, altered prothrombin time, and increased thyroid weight.

Findings in rats exposed at 750 or 1500 ppm for 13 weeks included hind limb paralysis, anemia, olfactory epithelial degeneration, and minimal to mild degeneration of the sciatic nerve and the lumbar spinal cord.[6]

Two-year inhalation studies (6 hours/day, 5 days/week for 103 weeks) in rodents showed clear evidence of carcinogenicity. Mice exposed at 375 and 750 ppm had increased incidences of harderian gland adenomas and carcinomas; female mice exposed at 188 and 750 ppm had increased liver neoplasms; female rats in the 188 and 375 ppm-exposed groups had increased incidences of mammary gland fibroadenomas and carcinomas.[6] Other treatment-related effects were an increase in nasal lesions and degeneration of the respiratory epithelium in mice.

Nitromethane was not mutagenic in a variety of *in vitro* and *in vivo* assays.[6]

The IARC has determined that there is sufficient evidence for the carcinogenicity of nitromethane in experimental animals and that it is possibly carcinogenic to humans.[7]

The 2003 ACGIH threshold limit value-

time-weighted average (TLV-TWA) is 20 ppm (50 mg/m^3).

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1-NITROPROPANE
CAS: 108-03-2

$CH_3CH_2CH_2NO_2$

Synonym: 1-NP

Physical Form. Liquid

Uses. Solvent for organic materials; propellant fuel; gasoline additive

Exposure. Inhalation

Toxicology. 1-Nitropropane vapor is an irritant of the eyes; in animals it also causes liver damage and mild respiratory tract irritation.[1] There are no reports of systemic effects from industrial exposures.

Rabbits died from exposure to 5000 ppm for 3 hours, but 10,000 ppm for 1 hour was not lethal.[2] Effects were conjunctival irritation, lacrimation, slow respiration with some rales, incoordination, ataxia, and weakness.[2] Autopsy of animals exposed to lethal concentrations revealed severe fatty infiltration of the liver and moderate kidney damage.[2]

Rats exposed 7 hours/day, 5 days/week at 100 ppm for up to 21 months showed no effects on appearance and behavior, serum chemistry, or hematology, and body and organ weights were unchanged.[3] There were no histopathologic effects on the liver and, in particular, no induction of hepatocarcinomas. This contrasts with similar exposures to 2-nitropropane, which produce severe hepatotoxicity and hepatocellular carcinomas at this level. Further studies have suggested that the lack of a carcinogenic effect of 1-nitropropane may be associated with the fact that it does not induce cell proliferation in the liver, whereas the carcinogenic isomer 2-nitropropane induces marked and rapid induction of cell proliferation in this organ.[4]

1-Nitropropane is mutagenic in V79 cells and can induce unscheduled DNA synthesis in rat hepatocytes, but it was not mutagenic in *Salmonella* assays, nor did it produce sister chromatid exchanges or chromosomal aberrations in vitro.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 1-nitropropane is 25 ppm (91 mg/m^3).

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2-NITROPROPANE

CAS: 79-46-9

$CH_3CHNO_2CH_3$

Synonyms: Isonitropropane; nitroisopropane; dimethylnitromethane; 2-NP; NiPar S-20; NiPar S-30

Physical Form. Liquid

Uses. Industrial solvent; chemical intermediate; component in inks and paints

Exposure. Inhalation

Toxicology. 2-Nitropropane is a pulmonary irritant and hepatotoxin. Inhalation of vapor produces hepatocellular carcinomas in rats, and it is a suspected human carcinogen.

Workers exposed to hot vapor containing an unspecified concentration of xylene and 20–45 ppm of 2-nitropropane developed occipital headache, anorexia, nausea, vomiting, and, in some cases, diarrhea.[1] Substitution of methyl ethyl ketone for 2-nitropropane eliminated the problem. Workers exposed to 30–300 ppm of 2-nitropropane complained of irritation of the respiratory tract.[2] A number of fatalities have been reported in association with 2-nitropropane.[3,4] The deaths all involved application of paint coatings in poorly ventilated areas. In all cases, liver failure was the primary cause of death, and postmortem findings showed massive hepatocellular destruction. Descriptions of prodromal symptoms have included typical central nervous system effects of solvent exposure, including headache, nausea, and vomiting. In the most recently reported cases, two construction workers became ill after applying an epoxy resin coating containing 2-nitropropane in an enclosed area.[4] One man died 10 days later from fulminant hepatic failure; the second man survived but has had persistently elevated serum aminotransferase activity. The serum concentration of 2-nitropropane on admission of the man who died was 13 mg/l vs. 8.5 mg/l for his coworker. Extrapolating from animal pharmacokinetic studies, the serum concentrations would be consistent with 6 hours of inhalation in the 600 ppm range.

Chronic health effects in humans from exposure to 2-nitropropane have not been adequately determined, although a retrospective mortality study of 1481 employees and former employees of a 2-nitropropane production facility with up to 27 years of exposure found no increase in cancer of the liver or other organs and no unusual disease mortality pattern.[5]

Rabbits died from exposure to a concentration near 2400 ppm for 4.5 hours, but 1400 ppm was not lethal.[6] High concentrations caused lethargy, weakness, difficult breathing, cyanosis, prostration, and occasional convulsions; low levels of methemoglobin and the formation of Heinz bodies in erythrocytes were observed. Autopsy of animals exposed to lethal concentrations revealed pulmonary edema and hemorrhage and liver damage.[6] The 6-hour LC_{50} in the male rat is 400 ppm.[7]

Rats exposed to 207 ppm daily for 6 months developed hepatic neoplasms; hepatocellular hyperplasia and necrosis occurred after 3 months of exposure at this concentration.[7] In another series of inhalation experiments on rats, 200 ppm produced hepatocellular carcinomas in both sexes; 100 ppm resulted in liver tumors in males after 12 months of exposure

and in females after 18 months. At 25 ppm for up to 22 months of exposure, no tumors or other hepatic lesions were produced.[8] The authors further suggested that damage to the liver parenchymal cells is an essential precursor to the induction of hepatocarcinoma in the rat. Hepatocellular carcinomas occur only when the degree of exposure is sufficient to cause severe hepatotoxicity followed by hyperregeneration, with some of the newly regenerated cells becoming autonomous, leading to neoplasia.

More recent studies have shown that 10-day gavage treatment of rats with up to 2 mmol/kg 2-nitropropane caused an increased incidence of cell proliferation; similar treatment with the noncarcinogenic isomer 1-nitropropane did not cause an increase in cell proliferation.[9]

The IARC has determined that there is sufficient evidence for carcinogenicity of 2-nitropropane in experimental animals and that it is possibly carcinogenic to humans.[10]

2-Nitropropane is genotoxic in a variety of assays including the Ames/*Salmonella* assay, *in vitro* sister chromatid exchange, and chromosome aberrations and unscheduled DNA synthesis assay.[9]

Although the early literature stated that the odor threshold was above 80 ppm and therefore not capable of providing adequate warning of exposure, a more recent study has determined that a lower threshold of approximately 5 ppm exists that should provide some warning of exposure, especially if workers are familiarized with the odor.[11]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 2-nitropropane is 10 ppm (36 mg/m^3) with an A2-suspected human carcinogen designation.

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N-NITROSODIMETHYLAMINE
CAS: 62-75-9

$(CH_3)N_2O$

Synonyms: Dimethylnitrosamine; DMNA; DMN; NDMA

Physical Form. Yellow liquid

Uses/Sources. No longer used industrially or commercially in the US; may occur as a by-

product from the manufacture of pesticides, rubber tires, alkylamines, and dyes

Exposure. Inhalation; skin absorption

Toxicology. *N*-nitrosodimethylamine (DMN) is a liver toxin and is carcinogenic in many species of test animals.

Two men accidentally exposed to DMN developed toxic hepatitis.[1] There are no reports of chronic effects from human exposure.[2]

The LC_{50} for rats exposed to DMN vapor for 4 hours (and observed for 14 days) was 78 ppm; for similarly exposed mice the LC_{50} was 57 ppm.[3] Dogs exposed for 4 hours to 16–144 ppm developed vomiting, polydipsia, and anorexia; most exposed dogs died, but one survivor showed residual liver damage 7 months after exposure.[3]

DMN is clearly carcinogenic, producing tumors in a number of animal species at relatively low doses. Swiss mice fed a diet containing 0.005% DMN for 1 week developed tumors of the kidney and lung.[4] Hamsters fed a diet containing 0.0025% for 11 weeks developed liver tumors.[5] A consistent observation after oral administration of DMN in rats has been that long-term treatment with doses compatible with a favorable survival rate leads to liver tumors, whereas short-term treatment with high doses produces renal tumors.[2]

Hamsters receiving weekly subcutaneous injections of DMN for life developed tumors; 3 of 10 females receiving weekly injections of 4.3 mg/kg developed liver tumors; at 21.5 mg/kg/week, there were 8 liver tumors and 5 kidney tumors; in 10 male animals receiving 2.8 mg/kg/week, there were 5 liver tumors and 1 kidney tumor.[6]

Intraperitoneal injection of 6 mg/kg once weekly for 10 weeks in mice resulted in a statistically significant increase of vascular tumors, mainly in the retroperitoneum in females. There was a low incidence of hepatic vascular tumors in both sexes.[7] Pregnant mice treated with the maximum nonfetotoxic dose of DMN on gestation day 16 or 19 had significant transplacental carcinogenic effects, causing an increase in hepatocellular carcinomas and sarcomas.[8] One intracranial schwannoma was attributed to DMN because such tumors are extremely rare in mice.[8]

Chronic exposure to hepatotoxic doses of DMN has also been found to suppress humoral and cellular immunity in mice.[9] DMN is genotoxic in a wide variety of assays inducing DNA synthesis, chromosomal aberrations, sister chromatid exchange, and bacterial mutations.[10] The formation of DNA adducts by metabolites of DMN may play a critical role in the carcinogenic process.[11]

The IARC has determined that there is sufficient evidence of carcinogencity to animals and that, although no data are available for humans, the agent is probably carcinogenic to humans.

The ACGIH has classified *N*-nitrosodimethylamine as an A3-confirmed animal carcinogen with unknown relevance to humans; there is a notation for skin absorption and no assigned threshold limit value (TLV).

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N-NITROSODIPHENYLAMINE

CAS: 86-30-6

$(C_6H_5)_2N_2O$

Synonyms: NDPhA; diphenyl nitrosamine

Physical Form. Yellow to brown or orange powder or flakes

Uses. Formerly used as a vulcanization retarder in the rubber industry

Exposure. Inhalation

Toxicology. *N*-nitrosodiphenylamine (NDPhA) is an animal carcinogen and causes bladder tumors in male and female rats.

No acute or chronic effects have been reported from human exposure.[1] Limited animal data suggest that the respiratory system is the target of inhalation exposure.[1] The urinary bladder is considered the target organ after oral administration.

Early carcinogenic studies in rats and mice in which NDPhA was administered orally or by intraperitoneal injection showed no evidence of carcinogenicity.[2–6] However, a more recent study demonstrated carcinogenesis in rats.[7,8] NDPhA was administered in the diet to rats and mice at the maximum tolerated dose for each species and at one-half that amount. A significant incidence of bladder tumors occurred in male (40%) and female (90%) rats at 240 and 320 mg/kg, respectively. Few bladder tumors were seen in the mice.

Primarily negative results have been found in *in vitro* and *in vivo* gene mutation and chromosome assays.[1]

The IARC has determined that there is limited evidence for carcinogenicity in experimental animals and that no evaluation of the carcinogenicity to humans can be made.[9]

ACGIH has not established a threshold limit value (TLV) for *N*-nitrosodiphenylamine.

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N-NITROSODI-*n*-PROPYLAMINE

CAS: 621-64-7

$(NO)N(CH_2CH_2CH_3)_2$

Synonyms: NDPA; Di-*n*-propylnitrosamine; DPNA; dipropylnitrosamine

Physical Form. Liquid

Uses/Sources. Research chemical; impurity in herbicides treflan, isopropalin, and trifluralin; contaminant in wastewater from chemical factories and production of cheese and brandy and other liquors. *N*-nitrosamines are frequently produced during rubber processing and may be airborne in the workplace.

Exposure. Inhalation

Toxicology. *N*-nitrosodi-*n*-propylamine (NDPA) causes hepatic effects in animals and is a carcinogen.

There is no information regarding health effects in humans from NDPA exposure.[1]

Rats that received a single lethal dose of NDPA showed centrilobular necrosis and fatty degeneration of the liver.[2] Specific doses that caused this effect were not listed, but the oral LD_{50} was determined to be 480 mg/kg.

NDPA administered to rats in the drinking water at 2.6 mg/kg/day, 5 days/week for 30 weeks caused liver carcinomas, nasal cavity carcinomas, tongue carcinomas, and esophageal papillomas and carcinomas.[3] Gavage administration produced nasal and liver carcinomas and esophageal tumors, and weekly subcutaneous injections caused a high incidence of malignant tumors at distant sites, primarily nasal cavity, liver, and lungs.[4,5] Similar studies in hamsters reported increases in tumors of the nasal cavities, laryngobronchial tract, and lungs.[6]

Macaque monkeys given weekly intraperitoneal injections of 40 mg NDPA for a total dose of 70 g had a higher incidence of hepatocellular carcinomas (6/6) compared with that of historical controls (7/90).[7]

NDPA has exhibited genotoxicity in bacteria (*Salmonella typhimurium*, *Escherichia coli*) and mammalian cells (mouse lymphoma, Chinese hamster) and caused DNA effects (fragmentation, unscheduled synthesis, repair) in rat hepatocytes and chromosome aberrations in Chinese hamster cells.[1]

The IARC considers that there is "sufficient evidence" that NDPA is carcinogenic to experimental animals and that it is possibly carcinogenic to humans.[8]

A threshold limit value-time-weighted average (TLV-TWA) for NDPA has not been assigned.

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N-NITROSOMORPHOLINE

CAS: 59-89-2

$C_4H_8N_2O_2$

Synonyms: NMOR; NNM; 4-nitrosomorpholine

Physical Form. Yellow crystals

Uses. Solvent for polyacrylonitrile; present during rubber manufacturing

Exposure. Inhalation; skin absorption

Toxicology. *N*-nitrosomorpholine (NMOR) is carcinogenic in animals.

There is no information available concerning toxic effects in humans.

The LD_{50} of NMOR in rats by oral and intraperitoneal routes was 320 mg/kg.

NMOR causes centrilobular hepatic necrosis in rats.[1] Hepatocellular carcinomas were observed in 14 of 16 rats administered NMOR in the drinking water at doses of 8 mg/kg body weight/day for life. Continuous oral exposure of Sprague-Dawley rats to 6, 12, or 24 mg/kg body weight resulted in a dose-dependent increase in the total number of preneoplastic foci of altered hepatocytes and in the incidence of hepatocellular adenomas and carcinomas.[2] The induction of liver tumors by NMOR has been confirmed in several strains of rats.[1] Epithelial kidney tumors were observed in 47 of 69 rats in which NMOR had been administered in the drinking water at 120 or 500 mg/l for 3–14 weeks. NMOR is also carcinogenic in hamsters after subcutaneous injection, producing tumors of the respiratory system (mainly nasal cavity and trachea). The IARC has determined that there is sufficient evidence for carcinogenicity of NMOR to experimental animals.[1]

NMOR is mutagenic in bacterial assays in the presence of activated liver microsomal fractions. However, NMOR did not induce DNA damage in either human or rat kidney cells in vitro as determined by DNA strand breakage.[3]

The ACGIH has not established a threshold limit value (TLV) for *N*-nitrosomorpholine.

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NITROTOLUENE
CAS: 88-72-2: ortho isomer
99-08-1: meta isomer
99-99-0: para isomer

$CH_3C_6H_4NO_2$

Synonyms: Methylnitrobenzene; nitrotoluol, nitrophenylmethane

Physical Form. *Ortho* and *meta* isomers are yellowish liquid; *para* isomer is a yellow solid

Uses. All isomers are used in the synthesis of dyestuffs, explosives, and agricultural chemicals

Exposure. Inhalation; skin absorption

Toxicology. Nitrotoluene has a low potency for producing methemoglobin and subsequent anoxia. Chronic exposure to other aromatic nitro compounds has caused anemia, and it is expected that nitrotoluene may cause the same effect. Animal data suggest a potential for hepatic, renal, and reproductive damage.

Signs and symptoms of overexposure are due to the loss of oxygen-carrying capacity of the blood. The onset of symptoms of methemoglobinemia is often insidious and may be delayed up to 4 hours; headache is commonly the first symptom and may become quite intense as the severity of methemoglobinemia progresses.[1] Cyanosis develops when the methemoglobin concentration is 15% or more; blueness develops first in the lips, nose, and earlobes and is usually recognized by fellow workers. Until the methemoglobin concentration approaches approximately 40%, the individual feels well, has no complaints, and typically may insist that nothing is wrong. At methemoglobin concentrations over 40%, there usually is weakness and dizziness; up to 70% concentration, there may be ataxia, dyspnea on mild exertion, tachycardia, nausea, vomiting, and drowsiness.[1]

In general, higher ambient temperatures increase susceptibility to cyanosis from exposure to methemoglobin-forming agents.[2]

In subchronic animal studies, *o*-, *m*- or *p*-nitrotoluene was administered in the feed to rats and mice at doses ranging from 625 to 10,000 ppm for 13 weeks.[3] Decreased body weights occurred in rats and mice receiving the higher dose levels and were most pronounced in rats receiving the *ortho* isomer. In mice, the only treatment-related lesion was degeneration and metaplasia of the olfactory epithelium in animals receiving *o*-nitrotoluene. All isomers produced kidney toxicity in male rats consisting of hyalin droplet nephropathy and an associated increase in the renal concentration of α_{2u}-globulin. Treatment-related hepatic lesions occurred only in male rats receiving *o*-nitrotoluene and consisted of cytoplasmic vacuolization and oval cell hyperplasia. Elevations in liver weights were observed at the higher dose levels in rats and mice treated with any of the three isomers. Spleens of male and female rats had a mild increase in hematopoiesis, hemosiderin deposition, and/or congestion. All isomers impaired testicular function in the rat, as shown by testicular degeneration and reduction in the density, motility, and number of sperm cells. Mesotheliomas of the epididymis occurred in the *o*-nitrotoluene male rats at 5000 ppm, and mesothelial cell hyperplasia occurred at 10,000 ppm.

Administered by oral gavage to rats for 6 months, all three isomers produced splenic lesions.[4] The *meta* and *para* isomers produced testicular atrophy, whereas *ortho*-nitrotoluene caused renal lesions.[4]

Two-year carcinogenesis studies in rats and mice have recently been reported for the *ortho*and *para* isomers of nitrotoluene.[5,6] There was clear evidence of carcinogenic activity of *o*-nitrotoluene in male rats based on increased incidences of malignant mesothelioma, subcutaneous skin neoplasms, mammary gland adenofibroma, and liver neoplasms. The increased incidences of lung neoplasms in male rats were also considered to be exposure related. There was clear evidence of carcinogenic activity of *o*-nitrotoluene in female rats based on increased incidences of subcutaneous skin neoplasms and mammary gland fibroadenoma. The increased incidence of hepatocellular adenoma in female rats was also considered to be exposure related.

There was equivocal evidence of carcinogenic activity in male and female mice based on increased incidences of hemangiosarcoma, carcinoma of the intestine (cecum), and hepatocellular neoplasms (females only). There was equivocal evidence of carcinogenic activity of *p*-nitrotoluene in male rats based on increased incidences of subcutaneous skin neoplasms, and there was some evidence of carcinogenic activity in females based on increased incidences of clitoral gland neoplasms. There was equivocal evidence of carcinogenic activity in male mice based on increased incidences of alveolar/bronchiolar neoplasms, and there was no evidence of carcinogenic activity in female mice exposed to 1250, 2500, or 5000 ppm in the diet.

Metabolism and genetic toxicity have been reported to differ with the isomer of nitrotoluene. *p*-Nitrotoluene was not mutagenic in bacterial assays, but it did increase sister chromatid exchange frequencies and chromosomal aberrations *in vitro*; *in vivo* it did not increase the frequency of micronuclei in bone marrow of treated rodents.[6] Similar findings were reported for the *ortho* isomer, except that it did not induce chromosomal aberrations *in vitro*.[5] Only the *ortho* isomer induces DNA excision repair in the *in vivo-in vitro* hepatocyte unscheduled DNA synthesis assay.[7] Furthermore, *ortho*-nitrotoluene binds to hepatic DNA to a much greater extent than *meta*- or *para*-nitrotoluene, and investigators suggest that it may act similarly to the rodent hepatocarcinogen 2,6-dinitrotoluene.[8]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for nitrotoluene is 2 ppm (11 mg/m^3) with a notation for skin absorption.

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NITROUS OXIDE

CAS: 10024-97-2

N_2O

Synonyms: Laughing gas; nitrogen oxide; dinitrogen monoxide

Physical Form. Colorless gas with a slightly sweet odor

Uses. As anesthetic agent; as foaming agent for whipped cream; as oxidant for organic compounds; in rocket fuels

Exposure. Inhalation

Toxicology. Nitrous oxide is an asphyxiant at high concentrations; prolonged exposure has been associated with damage to the hematopoietic system, the central nervous system, and the reproductive system.

Until recent times, the only toxicological hazards attributable to nitrous oxide were those common to asphyxiants, with death or permanent brain injury occurring only under conditions of hypoxia.[1] A number of untoward and toxic effects have now been associated with exposure. One of the earliest findings was that patients given 50% nitrous oxide and 50% oxygen for prolonged periods, to induce continuous sedation, developed bone marrow depression and granulocytopenia. The bone marrow usually returned to normal within a matter of days once the nitrous oxide was removed, but several deaths from aplastic anemia have been recorded.[1,2]

Central nervous system toxicity from either social abuse of nitrous oxide or extremely heavy occupational exposure has been characterized by symptoms of numbness, paresthesias, impairment of equilibrium, and difficulty in concentration.[2] In severe cases, the patient becomes incontinent, impotent, and unable to walk. Neurological signs include ataxic gait, muscle weakness, impaired sensation, and diminished reflexes.

Acute exposure to levels of 200,000 ppm and above causes deterioration of performance on tests of reaction time; it has been suggested that the threshold at which nitrous oxide starts to affect performance lies between 80,000 and 120,000 ppm.[3,4] Other studies have examined the effects of trace levels of nitrous oxide on performance tests, with conflicting results. In one unconfirmed study, volunteers exposed to 50 ppm for up to 4 hours showed decrements in audiovisual performance tests.[5] In another report, similar exposures did not produce any changes in a battery of psychomotor tests including an audiovisual task, but there was a nonsignificant trend for mood factors such as tiredness to occur.[6]

A number of epidemiological studies have shown a correlation between occupational exposure to nitrous oxide and adverse reproductive effects. In a survey of female dental assistants, there was a 100% increase in spontaneous abortions among those exposed to nitrous oxide compared with those not exposed; a 52% increase in spontaneous abortions also was observed among wives of dentists.[7] Despite various limitations to the studies including participant bias, inadequate reporting of exposure levels, and possible confounding factors, the ACGIH has determined that there is sufficient evidence that nitrous oxide poses a reproductive hazard to women.[1]

Although a number of animal studies demonstrate that nitrous oxide exposure can cause congenital anomalies, equivocal evidence exists for such effects in humans. In one report, the offspring of chairside female dental assistants exposed to nitrous oxide had a 50% higher incidence of congenital anomalies than the offspring of unexposed assistants.[7] However, the incidence was not related to the extent of nitrous oxide exposure, and the incidence was not greater than that occurring in the wives of dentists (both exposed and unexposed). An increased incidence of reproductive problems also has been reported in the wives of men exposed to nitrous oxide, that is, women who were not directly exposed themselves. A survey of 49,585 anesthesia personnel found a 25% increase in the incidence of congenital abnormalities in the children of male anesthesiologists compared with a control group comprised of the children of male physicians who worked outside the operating room.[8]

In general, numerous animal studies suggest that the production of teratogenic effects requires prolonged exposure to high concentrations during particular times of pregnancy.[9] For example, in rats the exposure threshold for teratogenic effects appears to lie between 350,000 and 500,000 ppm, the former producing no adverse effects and the latter producing cervical rib defects as well as other defects.[10] Groups of rats exposed at 600,000 ppm for 24 hours on each of days 6 through 12 of gestation exhibited an increased incidence of cervical rib defects and an increase incidence of right-sided aortic arch and left-sided umbilical artery (abnormalities indicative of altered

laterality), but only after exposure on day 8 of gestation. Increases in skeletal malformations and hydrocephalus occurred after exposure on day 9 of gestation. An increase in fetal deaths occurred from exposure on days 8 and 11.[9]

There were no significant changes in sperm count or in sperm morphology in a group of male anesthesiologists exposed to nitrous oxide compared with a nonexposed group.[11] Concentrations were estimated to range from 5 to 300 ppm, which is substantially lower than the concentrations that have been shown to have a deleterious effect on sperm in experimental animals.[10]

Nitrous oxide exerts a variety of its adverse effects by oxidizing vitamin B_{12} and rendering it inactive as a coenzyme in many essential metabolic processes.[12] One vitamin B_{12}-dependent enzyme in particular, methionine synthetase, is involved in cell division and is necessary for DNA production. Adverse reproductive and hematologic effects caused by nitrous oxide are thought to be due to inactivation or dysfunction of methionine synthetase resulting in impairment of cell division.

The possible carcinogenicity of nitrous oxide has been studied in dentists and chairside assistants with occupational exposures. No effect was observed in male dentists, but a 2.4-fold increase in cancer of the cervix in heavily exposed female assistants was reported.[7] Other epidemiological reports of workers exposed to waste anesthetic gases have been negative.[1] Carcinogenic bioassays in animals have yielded negative results. Nitrous oxide was not genotoxic in a variety of assays.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for nitrous oxide is 50 ppm (90 mg/m^3).

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NONANE
CAS: 111-84-2

$CH_3(CH_2)_7CH_3$

Synonyms: *n*-Nonane

Physical Form. Liquid

Uses. Solvent; organic synthesis; distillation chaser; major ingredient of such petroleum fractions as VM&P naphtha, 140 flash, Stoddard solvent, and gasoline

Exposure. Inhalation

Toxicology. Nonane is an irritant of the eyes and skin; at extremely high concentrations it causes central nervous system depression.

The 4-hour LC_{50} in rats was 3200 ppm.[1] Rats exposed for 6 hours/day for 7 days to 1500 ppm had mild tremor, slight incoordination, and slight irritation of eyes and extremities. A no-adverse-effect level for 65 days, 6 hours/day, 5 days/week, was 590 ppm in rats.

Nonane could be expected to dry and defat skin, resulting in irritation and dermatitis, by analogy to other liquid paraffin hydrocarbons. Aspiration into the lung could be expected to cause chemical pneumonitis.

Nonane was not mutagenic in bacterial assays with or without metabolic activation.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 200 ppm (1050 mg/m^3).

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NONYLPHENOL
CAS: 25154-52-3 (mixed isomers)
136-83-4 (2-nonylphenol)
104-40-5 (4-nonylphenol)

$C_9H_{19}(C_6H_4)OH$

Synonyms: 2-nonylphenol; *o*-nonylphenol; 4-nonylphenol; *p*-nonylphenol

Physical Form. Clear, straw-colored liquid; technical grade is a mixture of isomers, predominantly *para*-substituted

Uses. Principal use as an intermediate in the production of nonionic ethoxylated surfactants; as an intermediate in the manufacture of phosphite antioxidants used for the plastics and rubber industries

Exposure. Inhalation

Toxicology. Nonylphenol is a severe irritant of the eyes and skin.

Reports of the oral LD_{50} in rats for the mixed isomers have ranged from 580 to 1537 mg/kg; the dermal LD_{50} in rabbits was between 2000 and 3160 mg/kg.[1–4] Nonylphenol is considered to be a corrosive agent that may cause burns and blistering of the skin.[3] When the liquid was applied to the shaved skin of a rabbit and left in place for 4 hours, there was skin necrosis 48 hours after the application.[5] No skin sensitization occurred in tests with guinea pigs.[6] When tested on black guinea pigs and black mice, irritation was observed but nonylphenol did not induce depigmentation.[7]

The liquid in the eye of the rabbit as a 1% solution caused severe corneal damage.[1,2]

Leukoderma was reported in two women engaged in degreasing metal parts with synthetic detergents containing polyoxyethylene (3–16), nonyl- or octylphenylether. Analysis revealed contamination with free alkylphenol, possibly octylphenol, or nonylphenol. Although a relationship between the cases of leukoderma and octyl- and nonylphenol exposure was suggested, it could not be confirmed.[8]

Nonylphenol has recently been shown to have estrogenic properties, triggering mitotic activity in rat endometrium and cell proliferation in estrogen-sensitive tumor cells.[9] Potential toxicity to humans who may be exposed to nonylphenol through leaching of plastics has not been determined.

In a multigenerational study of rats treated at 200, 650, and 2000 ppm 4-nonyklphenol in the diet, there were dose-

related nephrotoxicity and mild reproductive effects.[10]

Nonylphenol was not mutagenic in the Ames *Salmonella typhimurium* assay.[11] A threshold limit value-time weighted average (TLV-TWA) has not been established for nonylphenol.

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NUISANCE PARTICULATES

Containing no asbestos and <1% crystalline silica

Synonyms: Particulates not otherwise classified; PNOC

Physical Form. Total dust as here described includes air-suspended particles of greater than respirable diameter.

Source. Ubiquitous

Exposure. Inhalation

Toxicology. As stated by ACGIH:

"In contrast to fibrogenic dusts which cause scar tissue to be formed in lungs when inhaled in excessive amounts, so-called nuisance dusts have a long history of little adverse effect on lungs and do not produce significant organic disease or toxic effect when exposures are kept under reasonable control. The nuisance dusts have also been called biologically inert dusts, but the latter term is inappropriate to the extent that there is no dust which does not evoke some cellular response in the lung when inhaled in sufficient amount. However, the lung-tissue reaction caused by inhalation of nuisance dusts has the following characteristics: the architecture of the air spaces remains intact; collagen (scar tissue) is not formed to a significant extent; the tissue reaction is potentially reversible."

"Excessive concentrations of nuisance dusts in the workroom air may seriously reduce visibility, may cause unpleasant deposits in the eyes, ears and nasal passages, or cause injury to the skin or mucous membranes by chemical or mechanical action per se or by the rigorous

skin cleansing procedures necessary for their removal."[1]

Animal studies have found that subchronic exposure to nuisance dusts at levels equal to the threshold limit value have induced mild inflammatory response in the lung and sufficient accumulation of particles to slow lung clearance.[2] The investigators suggest that exposure to nuisance dust at a level that will impair pulmonary clearance should be avoided to prevent excessive accumulation of dust in the lung.

The 2003 ACGIH threshold limit value-time weighted average (TLV-TWA) is 10 mg/m^3, total dust, containing no asbestos and <1% crystalline silica.

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OCTACHLORONAPHTHALENE

CAS: 2234-13-1

$C_{10}C1_8$

Synonym: Halowax 1051

Physical Form. Waxy solid

Uses. In electric cable insulation; additive to lubricants

Exposure. Inhalation; skin absorption

Toxicology. The higher-chlorinated naphthalenes may cause severe injury to the liver.

Exposure of workers by inhalation or skin absorption to lower-chlorinated naphthalenes (penta- and hexachloro) causes a severe acneform dermatitis, chloracne.[1–3] Surprisingly, on human volunteers, octachloronaphthalene was entirely nonacneigenic.[2] Octachloronaphthalene (20 mg, 5 times/week for 2 weeks) did not induce gross or histologic changes in skin of hairless mice.[4]

There is no information on systemic effects in humans. In animals, systemic toxicity from chlorinated naphthalenes appears to be limited to liver injury characterized as acute yellow atrophy.[1–3] In general the tri- to hexachlorinated range shows the highest toxicity, with octachlorinated naphthalene significantly less toxic than the others, presumably reflecting poor uptake of octachloronaphthalene by organisms.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for octachloronaphthalene is 0.1 mg/m^3 with a short-term excursion limit (STEL) of 0.3 mg/m^3 and a notation for skin absorption.

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OCTANE
CAS: 111-65-9

$CH_3(CH_2)_6CH_3$

Synonyms: None

Physical Form. Colorless liquid; *n*-octane has 17 isomers with similar properties

Uses. As a constituent in motor and aviation fuels; as an industrial solvent; in organic synthesis

Toxicology. In animals octane is a mucous membrane irritant, and at high concentrations it causes narcosis; it is expected that severe exposure in humans will produce the same effects.

The health effects of octane (both the iso and *n* forms) are thought to be similar to those of *n*-heptane, except that octane is approximately 1.2–2 times more toxic.[1] Octane has not been shown to cause the type of peripheral neuropathy associated with *n*-hexane.

In the only report involving human exposure, the liquid applied to the forearm for 1 hour and the thigh for 5 hours caused erythema, hyperemia, inflammation, and pigmentation. The volunteers experienced burning and itching at the site of application, and some blister formation occurred with the 5-hour exposures.

There was no narcosis in mice exposed to iso-octane at 8000 ppm for 5 minutes; at 16,000 ppm there was sensory irritation throughout the 5-hour exposure, and one of four mice died; at 32,000 ppm effects were irritation and irregular respiration, and all four mice died within 4 minutes of exposure.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 300 ppm (1400 mg/m^3) with a short-term excursion limit (STEL)/ceiling of 375 ppm (1750 mg/m^3).

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OIL MIST (Mineral)
CAS: 8012-95-1

Varying chemical composition

Synonyms: Petrolatum liquid; mineral oil; paraffin oil

Physical Form. Colorless, oily, odorless, and tasteless liquid

Uses. Mineral oil is a lubricant and is used as a solvent for inks in the printing industry.

Exposure. Inhalation

Toxicology. Highly refined mineral oil mist is of low toxicity.

A single case of lipoid pneumonitis suspected to result from repeated exposure to very high concentrations of oil mist was reported in 1950; this occurred in a cash register serviceman whose heavy exposure occurred over 17 years of employment.[1]

A review of exposures to mineral oil mist averaging below 15 mg/m^3 (but higher in some jobs) in several industries disclosed a striking lack of reported cases of illness related to these exposures.[2] A study of oil mist exposures in machine shops, at mean concentrations of 3.7 mg/m^3 and maximum of 110 mg/m^3, showed no increase in respiratory symptoms or decrement in respiratory performance attributable to oil mist inhalation among men

employed for many years.[3] Similar results were found in a 5-year study of 460 printer pressmen exposed to a respirable concentration of less than 5 mg/m^3.[4,5] An increased prevalence of slight basal lung fibrosis was found in oil cable workers in Norway; it is noted that cable oils are only mildly refined and short-term excursion exposures may have approached 4000 mg/m^3.[6,7]

Early epidemiological studies linked cancers of the skin and scrotum with exposure to mineral oils.[8] These effects have been attributed to contaminants such as polycyclic aromatic hydrocarbons (PAH) and/or additives with carcinogenic properties present in the oil. Solvent refining and, to some extent, hydroprocessing selectively extract PAH and reduce carcinogenicity.[9] Later studies, which have also reported excess numbers of scrotal cancer cases, have failed to characterize the composition of the mineral oil and the exposure levels.[10] The IARC has determined that there is inadequate evidence that the fully solvent-refined oils are carcinogenic to experimental animals in feeding or skin painting studies.[11] The IARC's determination that there is sufficient evidence for carcinogenicity in humans is based on epidemiological studies of uncharacterized mineral oils containing additives and impurities; there is inadequate evidence for carcinogenicity to humans for highly refined oils.[11] Most mineral oils in use today present no hazard because of refining techniques; however, because individual oils may vary in composition, an assessment must be made on each product.[12]

More recently there has been some concern about findings of microgranuloma in the liver and histiocytosis in the mesenteric lymph nodes of F344 rats after subchronic oral ingestion of refined white mineral oils.[13,14] The histopathologic changes appear to be species- and strain specific as results have not been replicated in other rat strains or in dogs.[15] The toxicological significance of the histopathologic changes is not known, but the changes do not appear to impact signs of clinical toxicity or animal life span.[16]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for mineral oil mist is 5 mg/m^3 with a short-term excursion level (STEL) of 10 mg/m^3.

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OSMIUM TETROXIDE

CAS: 20816-12-0

OsO_4

Synonym: Osmic acid

Physical Form. Colorless crystals or yellow crystalline mass with acrid chlorine-like odor

Use. Oxidizing agent

Exposure. Inhalation

Toxicology. Osmium tetroxide is an irritant of the eyes, respiratory tract, and skin.

A laboratory investigator briefly exposed to a high concentration of vapor experienced a sensation of chest constriction and difficulty in breathing.[1] Irritation of the eyes is usually the first symptom of exposure to low concentrations of the vapor; lacrimation, a gritty feeling in the eyes, and the appearance of rings around lights are frequently reported. In most cases recovery occurs within a few days.[2] Workers exposed to fume concentrations up to 0.6 mg/m^3 developed lacrimation, visual disturbances, and, in some cases, frontal headache, conjunctivitis, and cough.[1]

Rabbits exposed for 30 minutes to vapor at estimated concentrations of 130 mg/m^3 developed irritation of mucous membranes and labored breathing; at autopsy there was bronchopneumonia, as well as slight kidney damage.[1] A 4-hour exposure at 400 mg/m^3 was lethal to rats.[3]

Application of a drop of 1% solution of osmium tetroxide to a rabbit eye caused severe corneal damage, permanent opacity, and superficial vascularization.[4] Osmium compounds have a caustic action on the skin, resulting in eczema and dermatitis.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 0.0002 ppm (0.0016 mg/m^3) as Os with a short-term excursion limit (STEL)/ceiling of 0.0006 ppm (0.0047 mg/m^3) as Os.

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OXALIC ACID

CAS: 144-62-7

$C_2O_4H_2$

Synonym: Ethanedioic acid

Physical Form. Crystalline solid

Uses. Chemical synthesis; bleaches; metal polish; rust remover

Exposure. Inhalation; ingestion

Toxicology. Oxalic acid is an irritant of the eyes, mucous membranes, and skin; inhalation or ingestion may result in kidney damage, and in severe exposures there may be convulsions and death.

There is little reported information on industrial exposure, although chronic inflammation of the upper respiratory tract has been described in a worker exposed to hot vapor arising from oxalic acid.[1] Ingestion of as little as 5 g has caused fatalities; there is rapid onset of shock, collapse, and convulsions. The convulsions are thought to be the result of hypocalcemia due to the calcium-complexing action of oxalic acid, which depresses the level of ionized calcium in body fluids. Marked renal damage from deposition of calcium oxalate may occur.[1] A study of railroad car cleaners with heavy exposure to oxalic acid solutions found an increased incidence of urinary stones. There was a 53% incidence of urolithiasis in exposed workers compared with a rate of 12% in unexposed workers from the same company.[2]

Gross contact of the hands with solutions of oxalic acid (5.3% and 11.5% in 2 reported cases) used as cleaning solutions caused tingling, burning, soreness, and cyanosis of the fingers.[3]

Splashes of solutions in the eyes have produced epithelial damage from which recovery has been prompt.[4]

The single oral LD_{50} for a 5% by weight oxalic acid solution was 9.5 ml/kg for male rats and 7.5 ml/kg for females.[5] Applied to rabbit skin, a single exposure of 20 g/kg of the solution was not lethal.

Reproductive toxicity has been noted in animal studies.[6] Male mice administered 8400 mg/kg for 7 days before mating had decreased fertility. Female mice given the same dose 7 days before mating and throughout 21 days of gestation showed embryotoxicity and fetotoxicity.[6] Female rats had disrupted estrous cycles when maintained on diets containing 2.5% and 5% oxalic acid.[7]

Oxalic acid was not mutagenic in a number of bacterial strains with or without metabolic activation.[8]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for oxalic acid is 1 mg/m^3 with a short-term exposure limit (STEL) of 2 mg/m^3.

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OXYGEN DIFLUORIDE
CAS: 7783-41-7

OF_2

Synonyms: Fluorine monoxide; oxygen fluoride; fluorine oxide

Physical Form. Colorless gas

Uses. Oxidant in missile propellant systems

Exposure. Inhalation

Toxicology. Oxygen difluoride is a severe pulmonary irritant in animals; exposure is expected to cause the same effect in humans.

In humans, inhalation of the gas at fractions of a part per million produced intractable headache.[1] Although there are no reports of effects on the eyes or skin of humans, it would be expected that the gas under pressure impinging upon the eyes or skin would produce serious burns.[2]

In monkeys and dogs, the LC_{50} was 26 ppm for 1 hour; signs of toxicity were lacrimation, dyspnea, muscular weakness, and vomiting; at autopsy, massive pulmonary edema and hemorrhage were observed.[3] In mice, exposure to a low concentration (1 ppm for 60 minutes) produced tolerance to subsequent exposures 8 days later at levels that would otherwise have been fatal (4.25 ppm for 60 minutes).

The 2003 ACGIH threshold limit value-ceiling limit (TLV-C) for oxygen difluoride is 0.05 ppm (0.11 mg/m^3).

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OZONE

CAS: 10028-15-6

O_3

Synonym: Triatomic oxygen

Physical Form. Blue gas

Uses/Sources. Used as a disinfectant for air and water; for bleaching textiles; in organic synthesis; produced in welding arcs, corona discharges by ultraviolet radiation, and around high-voltage electric equipment

Exposure. Inhalation

Toxicology. Ozone is an irritant of the mucous membranes and the lungs.

The primary target of ozone exposure is the respiratory tract.[1] Symptoms range from nose and throat irritation to cough, dyspnea, and chest pain. By analogy to animal studies, severe exposure may cause pulmonary edema and hemorrhage. Typically, the threshold for effects in humans is reported to be between 0.2 and 0.4 ppm. In one report, a single 2-hour exposure to 0.4 ppm resulted in increased levels of inflammatory cells and soluble factors capable of producing damage in the lower airways of 11 volunteers.[2] Exposure to 0.5 ppm 3 hours/day, 6 days/week for 12 weeks caused a significant reduction in 1-second forced expiratory volume without subject symptoms.[3] Bronchial irritation, slight dry cough, and substernal soreness were reported in subjects exposed to 0.6–0.8 ppm ozone for 2 hours. Marked changes in lung function lasting up to 24 hours were also found.[4] A single 2-hour exposure to 1.5–2 ppm caused impaired lung function, chest pain, loss of coordinating ability, and difficulty in articulation. Cough and fatigue persisted for 2 weeks.[5] No deaths from exposure to ozone have been reported.[6]

Extrapulmonary toxic effects potentially attributable to ozone exposure include hematologic changes, chromosomal effects in circulating lymphocytes, alterations of hepatic

metabolism, reproductive effects, hormonal effects, central nervous system effects, changes in visual acuity, and altered susceptibility to infectious agents.[1,7] Some extrapulmonary effects may be secondary to respiratory system damage.

The toxic effects of ozone can be attributed to its strong oxidative capacity. Specifically, ozone may act by initiating peroxidation of polyunsaturated fatty acids present in the cell membrane and/or by direct oxidation of amino acids and proteins also found in the membranes.[8] If damage is severe, the cell dies; necrosis is commonly reported in the lungs of heavily exposed animals.[1] In animal studies, a characteristic ozone lesion occurs at the junction of the conducting airways and the gas exchange region of the lung after acute ozone exposure. This anatomic site is probably affected in humans as well.[1]

One of the principal modifiers of the magnitude of response to ozone is minute ventilation (V_t), which increases proportionally with increase in exercise workload.[9] Studies show that the heavier the workload the greater is the potentiation of ozone effects on the lung. Surprisingly, patients with mild to moderate respiratory disease do not appear to be more sensitive than normal subjects to threshold ozone concentrations.[10]

The effects of ozone appear to be cumulative for initial exposures followed by adaptation. Five of six subjects exposed to 0.5 ppm ozone 2 hours/day for 4 days showed cumulative effects of symptoms and lung function tests for the first 3 days, followed by a return to near control values on day 4.[11] In animals exposure to 0.3–3 ppm for up to 1 hour permits the animals to withstand multilethal doses for months afterwards.[12] However, repeated exposures impart protection from all forms of lung injury (e.g., susceptibility to infectious agents, enzyme activities, inflammation). Initial ozone exposure may act to reduce cell sensitivity and/or increase mucus thickness, factors which may modify the accessibility and action of the gas.[8] It is not known how variations in the length, frequency, or magnitude of exposure modify the time course for tolerance.

In lifetime inhalation studies there was no evidence of carcinogenicity in rats exposed to 1.0 ppm ozone.[13] There was equivocal evidence of carcinogenic activity in male mice and some evidence in female mice based on increased incidences of alveolar/bronchiolar adenoma or carcinoma. Ozone was mutagenic in bacterial assays with and without metabolic activation.[13]

The ACGIH has recommended different threshold limit values (TLVs) for ozone that incorporate concentration, workload, and cumulative exposure duration.[14] The following TLVs are for durations of 8 hours or for 2 hours or less, depending on the workload: TLV-time-weighted average (TWA) (8 hours), 0.05 ppm (0.1 mg/m^3), heavy work; TLV-TWA (8 hours), 0.08 ppm (0.16 mg/m^3), moderate work; TLV-TWA (8 hours), 0.10 ppm (0.2 mg/m^3), light work; TLV-TWA (2 hours), 0.2 ppm (0.39 mg/m^3), heavy, moderate, or light workloads.

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PARAQUAT
CAS: 4685-14-7

$C_{12}H_{14}N_2$

Synonyms: 1,1′-Dimethyl-4,4′-bipyridinium dichloride; gramoxone; methylviologen

Physical Form. Yellow solid

Uses. Herbicide

Exposure. Inhalation; ingestion

Toxicology. Paraquat is an irritant of the eyes, mucous membranes, and skin; ingestion causes fibroblastic proliferation in the lungs.

In a study of 30 workers engaged in spraying paraquat over a 12-week period, approximately 50% of them had minor irritation of the eyes or nose; one worker had an episode of epistaxis.[1] Of 296 spray operators with skin exposure described as "gross and prolonged," 55 had damaged fingernails. The most common lesion was transverse white bands of discoloration, but other lesions were loss of nail surface, transverse ridging and gross deformity of the nail plate, and, in some cases, loss of the nail.[2]

Paraquat is commonly combined in commercial herbicides with diquat, a related compound; in several instances, the commercial preparations splashed in the eyes have caused serious injury.[3,4] Effects have been loss of corneal and conjunctival epithelium, mild iritis, and residual corneal scarring. In contrast, in the eye of a rabbit, one drop of a 50% aqueous solution of pure paraquat caused slow development of mild conjunctival inflammation and pure diquat proved even less irritating.[5] Presumably, the surfactants present in the commercial preparations are responsible for the severe eye injuries to humans.[4]

In a survey of 36 paraquat formulation workers, acute skin rashes and burns from a delayed caustic effect, eye injuries with conjunctivitis from splash injuries, nail damage, and minor epistaxis were common clinical complaints.[6] Despite a mean exposure period of 5 years, there was no evidence of chronic effects on skin, mucous membranes, or general health. Comparison of a group of 27 Malaysian plantation spray men, with a mean of 5.3 years of heavy paraquat use, to unexposed groups did not demonstrate any significant differences in pulmonary, renal, liver, or hematologic functions.[7] No abnormalities were attributable to paraquat exposure.[7] More recently, farm workers exposed to paraquat have shown some evidence of respiratory disease. South African farm workers had a dose-dependent association with exposure and abnormal exercise physiology based on arterial oxygen desaturation but no effects on chest radiograph or spirometry or self-reported symptoms.[8] Increased wheeze was noted among exposed Nicaraguan banana workers.[9]

In rats exposed to aerosols of paraquat, the LC_{50} for 6 hours was 1 mg/m^3; death was delayed and resulted from pulmonary hemorrhage and edema.[10] In practice, the large particle size of agricultural sprays probably mitigates against this occurring in exposed workers.[11]

The results from ingestion by humans or injection in animals are in marked contrast to the irritant effects usually encountered in industrial exposure. There are numerous reports of fatal accidental and suicidal ingestion by humans.[11–13] In two cases, one person ingested about 114 ml of a 20% solution and the other person was believed to have taken only a mouthful of the liquid, most of which was rejected immediately. The former person died after 7 days; the latter died after 15 days.[12] Initial symptoms included burning in the mouth and throat, nausea, vomiting, and abdominal pain with diarrhea. After 2–3 days, signs of liver and kidney toxicity developed, including jaundice, oliguria, and albuminuria; electrocardiogram changes were suggestive of toxic myocarditis with conduction defects. Shortly before death, respiratory distress occurred; at autopsy, findings in the lung included hemorrhage, edema, and massive solid areas that were airless owing to fibroblastic proliferation in the alveolar walls and elsewhere.[12] Early deaths from massive poisonings usually result from a combination of acute pulmonary edema, acute oliguric renal failure, and hepatic failure. Deaths from less massive poisonings typically result from pulmonary fibrosis, developing 1–3 weeks after ingestion.[11]

Intraperitoneal injection or oral administration to rats at doses that caused delayed death resulted in the same proliferative lesion in the lung; findings were alveolar, perivascular, and peribronchial edema, with cellular proliferation into the alveolar walls resulting in large solid areas of the lung with no air-containing cavities.[5]

There is no evidence that inhalation exposures in occupational settings cause the rapid progressive pulmonary fibrosis and injury to the heart, liver, and kidneys that occur after ingestion. Because of the low vapor pressure, there is little inhalation hazard. Spray droplets are usually too large to reach the alveoli. If exposure is excessive, droplets may be inhaled into the upper respiratory tract and cause nosebleed, sore throat, headache, and coughing from local irritant action. Rarely, dermal exposure to paraquat has resulted in systemic poisonings and deaths with renal and pulmonary damage.[11] Such episodes occurred with prolonged skin contact during spraying and exposure to concentrated solutions or exposure to areas of preexisting dermatitis; all could have been prevented with use of recommended work practices.

Workers involved in the manufacture of paraquat were found to have a high prevalence of hyperpigmented macules and hyperkeratosis, both of which may be premalignant skin lesions. Analysis of the data suggested that exposure to bipyridine precursors along with sunlight, rather than paraquat itself, was responsible.[14]

A mouse bioassay involving dietary exposure to 25, 50, and 75 mg/kg/day for 80 weeks yielded no evidence of carcinogenicity, despite the occurrence of some deaths from respiratory disease.[11] A 2-year bioassay in rats exposed to paraquat in drinking water at 1.3 and 2.6 mg similarly resulted in lung pathology but no increased tumor incidence.[11] In general, paraquat was not genotoxic in a variety of *in vitro* and *in vivo* assays.[15]

Embryotoxicity has only been observed at doses that also cause significant maternal toxicity in rats, mice, and rabbits.[15]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for paraquat is 0.5 mg/m^3 for total dust and 0.1 mg/m^3 for the respirable fraction.

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PARATHION

CAS: 56-38-2

$C_{10}H_{14}NO_5PS$

Synonyms: *O,O*-diethyl *O-p*-nitrophenyl phosphorothioate; Akron; Niran; Amer. Cyan. 3422; BAY E-605; Bladan; Folidol E605

Physical Form. Brown or yellowish liquid

Uses. Acaracide; insecticide

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Parathion is a highly toxic anticholinesterase agent.

Hundreds of deaths associated with parathion exposure have been reported. These deaths have resulted from accidental, suicidal, and homicidal poisonings. It has been the cause of most crop worker poisonings in the United States.[1] Fatal human poisonings have resulted from ingestion, skin exposure, and inhalation (with varying degrees of skin exposure).

Signs and symptoms of overexposure are caused by the inactivation of the enzyme cholinesterase, which results in the accumulation of acetylcholine at synapses in the nervous system, skeletal and smooth muscle, and secretory glands. The sequence of the development of systemic effects varies with the route of entry. The onset of signs and symptoms is usually prompt but may be delayed up to 12 hours.[1–4] After inhalation, respiratory and ocular effects are the first to appear, often within a few minutes after exposure. Respiratory effects include tightness in the chest and wheezing due to bronchoconstriction and excessive bronchial secretion; laryngeal spasms and excessive salivation may add to the respiratory distress; cyanosis may also occur. Ocular effects include miosis, blurring of distant vision, tearing, rhinorrhea, and frontal headache.

After ingestion, gastrointestinal effects such as anorexia, nausea, vomiting, abdominal cramps, and diarrhea appear within 15 minutes to 2 hours. After skin absorption, localized sweating and muscular fasciculations in the immediate area occur usually within 15 minutes to 4 hours; skin absorption is somewhat greater at higher ambient temperatures and is increased by the presence of dermatitis.[3]

With severe intoxication by all routes, an excess of acetylcholine at the neuromuscular junctions of skeletal muscle causes weakness aggravated by exertion, involuntary twitchings,

fasciculations, and eventually paralysis. The most serious consequence is paralysis of the respiratory muscles. Effects on the central nervous system include giddiness, confusion, ataxia, slurred speech, Cheyne–Stokes respiration, convulsions, coma, and loss of reflexes. The blood pressure may fall to low levels, and cardiac irregularities including complete heart block may occur.[2]

Complete symptomatic recovery usually occurs within 1 week; increased susceptibility to the effects of anticholinesterase agents persists for up to several weeks after exposure. Daily exposure to concentrations that are insufficient to produce symptoms after a single exposure may result in the onset of symptoms. Continued daily exposure may be followed by increasingly severe effects.

In humans, an oral dose of 3–5 mg/kg is usually fatal.[6] In a study of 115 workers exposed to parathion under varying conditions, the majority excreted significant amounts of *p*-nitrophenol (a metabolite of parathion) in the urine, whereas only those with heavier exposures had a measurable decrease in blood cholinesterase.[7] Measurement of urinary *p*-nitrophenol can be useful in assessing parathion absorption in occupational or other settings.[1]

Parathion is not irritating to the skin but is rapidly absorbed through the intact skin.[6] With dermal exposure in the occupational setting, onset of symptoms may be delayed for several hours up to as long as 12 hours. This delay in onset, which is unusual for other organophosphate compounds, may occur even with poisonings that prove to be serious.[1]

Parathion itself is not a strong cholinesterase inhibitor, but one of its metabolites, paraoxon, is an active inhibitor. Paraoxon inactivates cholinesterase by phosphorylation of the active site of the enzyme to form the "diethylphosphoryl enzyme." Over the following 24–48 hours there is a process, called aging, of conversion to the "monoethylphosphoryl enzyme." Aging is of clinical interest in the treatment of poisoning, because cholinesterase reactivators such as pralidoxime (2-PAM, Protopam) chloride are ineffective after aging has occurred.

In the field, parathion is converted to varying degrees to paraoxon, which may persist on foliage and in soil. Exposure to paraoxon from weathered parathion residues by the dermal route on reentry by field-workers has resulted in anticholinesterase poisonings.[8]

In an animal bioassay a dose-related increase in the incidence of adrenal cortical adenomas (with a few carcinomas at this site as well) has been observed in one strain of rats in both sexes. The significance of these lesions in aged rats in unclear. Other bioassays in mice and rats had sufficient limitations, such that the IARC deemed them inadequate for evaluation and concluded that there are insufficient data to evaluate the carcinogenicity of parathion for animals and no data for humans.[9]

Parathion was not mutagenic in a wide range of *in vitro* genotoxic assays.[6]

In developmental assays parathion produced embryocidal effects and fetal growth retardation, but no malformations, in mice and rats at doses that were generally below the level that was toxic for the mother.[6]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for parathion is 0.1 mg/m^3 with a notation for skin absorption.

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PARTICULATE MATTER

CAS: None

Synonym: PM

Physical Form. Particulate matter (PM) is not a specific chemical entity but a mixture of particles of different sizes, compositions, and properties. Examples include combustion-generated particles such as diesel soot or fly ash; photochemically produced particles such as those found in urban haze; salt particles formed from sea spray; and soil-like particles from resuspended dust. Some particles are liquid, and some are solid. Others contain a solid core surrounded by liquid. Atmospheric particles contain inorganic ions, metallic compounds, elemental carbon, and organic compounds. The organic fraction is especially complex, containing hundreds of organic compounds. PM is called primary if it exists in the same chemical form in which it was emitted or generated. Secondary particles are formed from gases through chemical reactions in the atmosphere, involving atmospheric oxygen and water vapor; reactive species such as ozone (O_3); radicals such as the hydroxyl ($\cdot OH$) and nitrate ($\cdot NO_3$) radicals; and pollutants such as sulfur dioxide (SO_2) and nitrogen oxides (NO_x).

Particle size of PM is of considerable importance in relating ambient air concentrations to population morbidity and mortality. Routing ambient air monitoring studies before 1999 generally measured "thoracic" PM, namely, PM_{10} (upper size limited by a 50% cut at 10-μm aerodynamic diameter). Research and monitoring studies since 1999 have measured other fractions, but one of considerable significance is termed "fine" PM, namely, $PM_{2.5}$ (upper size limited by a 50% cut point at 2.5-μm aerodynamic diameter.) An emerging measurement of importance is "ultrafine" particles, namely, $PM_{0.1}$ (upper size limited by a 50% cut point at 0.1-μm aerodynamic diameter).

Occurrence. Atmospheric pollutant

Exposure. Inhalation

Toxicology. Epidemiological studies have consistently found an association between small increases in urban PM and health effects, including increased morbidity and mortality in people with respiratory and cardiac disease.[1–5]

Particulate matter air pollution is especially harmful to people with lung disease such as asthma and chronic obstructive pulmonary disease (COPD), which includes chronic bronchitis and emphysema, as well as people with heart disease. Exposure to particulate air pollution can trigger asthma attacks and cause wheezing, coughing, and respiratory irritation in individuals with sensitive airways. It was estimated in one major study that the excess risk of total mortality is 6.2% per each increase in 10 μg $PM_{2.5}/m^3$, and 9.3% for cardiopulmonary mortality.[3]

The elderly are especially susceptible to PM effects, which are associated with fine rather than coarse particles.[6] A recent epidemiological study found that particle number—reflecting ambient ultrafine particles—correlated better than fine particle mass with increased symptoms in asthmatics.[7] Moreover, animal studies have shown that ultrafine particles have a significantly greater pulmonary inflammatory potency than larger submicron particles.[8] Surface properties such as surface chemistry appear to play an important role in

ultrafine particle toxicity, as does their very high size-specific deposition in the lung. It appears also that ultrafine particles, after deposition in the lung, largely escape alveolar macrophage recognition and capture and gain access to the pulmonary interstitium.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for particulate matter containing no asbestos and <1% crystalline silica is 3 mg/m^3 for respirable size fraction and 10 mg/m^3 for inhalable mass fraction. Exposure to any substance in the particulate mass that has a designated TLV should be controlled to that value.

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PENTABORANE
CAS: 19624-22-7

B_5H_9

Synonyms: Dihydropentaborane (9); pentaboron undecahydride

Physical Form. Colorless liquid with a pungent odor

Uses. Reducing agent in propellant fuels

Exposure. Inhalation; skin absorption

Toxicology. Pentaborane is extremely toxic; it affects the nervous system and causes signs of narcosis and hyperexcitation.

In humans, the onset of symptoms may be delayed for up to 24 hours.[1] Minor intoxication causes lethargy, confusion, fatigue, inability to concentrate, headache, and feelings of constriction of the chest. With moderate intoxication, effects are more obvious and include thick speech; confused, sleepy appearance; transient nystagmus and drooping of the eyelids; and euphoria. With severe intoxication, there are signs of muscular incoordination; tremor and tonic spasms of the muscles of the face, neck, abdomen, and extremities; and convulsions and opisthotonos.[1–4]

In a fatal case involving extremely heavy accidental exposure with direct skin contact, there was rapid onset of seizures and opisthotonic spasms accompanied by severe metabolic acidosis without respiratory compensation.[5] The patient expired on day 8, and autopsy revealed severe bilateral necrotizing pneumonia, widespread fatty change of the liver with centrilobular degeneration, widespread degeneration of the brain, and absence of mature spermatozoa in the testes. Another worker who was exposed while in an adjacent building survived but sustained severe neurological damage. After 6 months, he demonstrated marked muscular weakness, incoordination, and spasticity. He could see only shapes and colors. CT scan showed marked cortical

atrophy and ventricular dilation. Institutionalization was required. Eight of 14 individuals with mild exposure to pentaborane from the same accident were judged to have mild cognitive deficits as determined by various neuropsychological tests 2 months after exposure.[6]

The concentrations of vapor and duration of exposures that cause mild, moderate, or severe intoxication are not documented. It has been estimated, on the basis of animal studies, that exposure for 60 minutes will cause slight signs of toxicity at 8 ppm, convulsions at 15 ppm, and death at 30 ppm. It was the clinical impression of one investigator that in humans a transient "wafting" odor did not produce symptoms (median odor threshold is 1 ppm), but a "strong whiff, producing a penetrating feeling in the nose, usually produced symptoms."[1,7] Olfactory fatigue also occurs, and dangerous levels of pentaborane may not be readily detected.[1]

Severe irritation and corneal opacity of the eyes of test animals occurred from exposure to the vapor; the liquid on the skin of animals caused acute inflammation, with the formation of blisters, redness, and swelling.[8] Because the liquid may ignite spontaneously, fire and consequent burn damage may be a greater hazard than toxicity on contact with the liquid.[4]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 0.005 ppm (0.013 mg/m^3) with a short-term excursion limit (STEL)/ceiling of 0.015 ppm (0.039 mg/m^3).

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PENTACHLOROETHANE

CAS: 76-01-7

C_2HCl_5

Synonyms: Ethane pentachloride; pentalin

Physical Form. Dense, colorless liquid with a chloroform-like odor

Uses. May occur as an intermediate in the production of chlorinated ethylenes; formerly used as a solvent for cellulose ethers, resins, and gums, for dry cleaning, coal purification, as a soil sterilizing agent, and as a chemical intermediate in the production of dichloroacetic acid

Exposure. Inhalation

Toxicology. Pentachloroethane is an irritant of the eyes and respiratory tract and may cause mild narcosis; chronic exposure causes hepatocellular carcinomas in mice and inflammation of the kidneys in rats.

No information is available on human exposures to pentachloroethane.

The lowest observed lethal concentrations observed for mice and rats were 35 g/m^3 and 4238 ppm, respectively.[1]

Administration of 1000 mg/kg/day was lethal to 6 of 10 rats between the fourth and tenth days. The only observable clinical signs of toxicity were decreased motor activity and

lethargy and weight gain decrements in the survivors of the 500 mg/kg/day dose group. Neither gross nor histopathologic examinations revealed lesions that could be attributed to the chemical. Mice survived 2 weeks at 1000 mg/kg/day but lost weight during the experiment.[2,3]

Male rats administered 0.62 or 1.24 mmol/kg per day by gavage for 21 days showed hyalin droplet nephropathy.[4]

Dose levels of 75 and 150 mg/kg/day were administered to rats by gavage during chronic (41–103 week) studies.[2,3] A significant dose-related increase in the incidence of chronic renal inflammation and a dose-related trend in the incidence of tubular cell adenomas of the kidneys in males was noted, although the survival of the high-dose group was significantly reduced compared with controls. The kidney lesions were distinguishable from the nephropathy normally seen in aging rats, and some of the dosed animals had both types of changes.

Mice were administered 250 or 500 mg/kg/day pentachloroethane by gavage for life. The hepatic carcinogenicity of pentachloroethane was clearly established despite reduced survival rates. The incidence of hepatocellular carcinomas was significantly increased in low-dose males and in treated females; there also was a significant dose-related increase in the incidence of hepatocellular adenomas in treated females.[2,3]

It has been suggested that the mechanism of action of pentachloroethane may be similar to that of other chlorohydrocarbons that also induce a high incidence of hepatocellular carcinoma in mice and have little or no carcinogenic effect in rats. The carcinogenic potential may be mediated through the active metabolic intermediates trichloroethylene and tetrachloroethylene, which are formed in some species but not in others.

It has also been noted that hexachloroethane is a major contaminant of the pentachloroethane used in the chronic studies. This compound also has been shown to induce hepatocellular carcinoma in mice but not rats, although the low levels of hexachloroethane present in the pentachloroethane samples seem inadequate to produce the high incidence of tumors found in the pentachloroethane studies.

Pentachloroethane was not mutagenic in *Salmonella typhimurium* strains with or without metabolic activation.[1]

The IARC determined that there is limited evidence for the carcinogenicity of pentachloroethane to experimental animals and that it is not classifiable as to its carcinogenicity to humans.[5]

The ACGIH has not established a threshold limit value (TLV) for pentachloroethane exposure.

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PENTACHLORONAPHTHALENE
CAS: 1321-64-8

$C_{10}H_3Cl_5$

Synonyms: Halowax 1013

Physical Form. Waxy white solid

Uses. In electric wire insulation; in lubricants

Exposure. Inhalation; skin absorption

Toxicology. Pentachloronaphthalene is toxic to the liver and skin.

The most striking human response to prolonged skin contact with the solid, or to shorter-term inhalation of hot vapor, is chloracne.[1–3] This is an acneform skin eruption characterized by papules, large comedones, and pustules, chiefly affecting the face, neck, arms, and legs. Pruritic erythematous and vasculoerythematous reactions have also been reported. The reaction is usually slow to appear and may take months to return to normal. Skin lesions are often accompanied by symptoms of systemic effects, including headache, vertigo, and anorexia. (Chloracne has been associated with penta- and hexachloronaphthalene exposure, but not mono-, di-, tri-, tetra-, hepta-, or octachloronaphthalenes.)

Liver damage characterized by toxic jaundice, which may progress to fatal hepatic necrosis, results from the repeated inhalation of higher concentrations of the hot fumes of the molten substance.[4] Concentrations of mixed penta- and hexachloronaph thalene between 1 and 2 mg/m^3 were measured in the air of industrial plants where fatal cases of yellow atrophy of the liver occurred.[5]

An excess mortality of cirrhosis of the liver was observed in 9028 workers employed from 1940 to 1944 at a cable manufacturing plant with chlorinated naphthalene exposure. Cirrhosis deaths were similarly elevated in a subcohort of 460 individuals who had shown symptoms of chloracne.[6] A cancer mortality study of this same subcohort found an excess of two rare causes of death, malignant neoplasm of the esophagus and benign and unspecified neoplasms.[7]

Rats exposed to the vapor of a mixture of hexa- and pentachloronaphthalene at average concentrations of 1.16 mg/m^3 for 16 hours daily up to 4.5 months showed definite liver injury, whereas 8.8 mg/m^3 produced some mortality and severe liver injury.[3]

Much of the past concern over polychlorinated napthalenes was centered on the poisoning of cows, causing a disease called bovine hyperkeratosis or X disease.[5] The main effect of the higher-chlorinated polychlorinated napthalenes in cows appears to be interference with the biotransformation of carotene to vitamin A.[5] As the disease progresses, vitamin A deficiency is followed by inflammation of oral mucosa, lacrimation, excessive salivation, and irregular food consumption. Gross physical effects include thickening of the skin and loss of hair, and the horns may show signs of degeneration or irregular growth. On continued exposure, anemia, dehydration, loss of weight, fever, severe liver damage, and death occur. Experimental studies on cattle have revealed severe systemic disease (bovine hyperkeratosis) at concentrations of 1.7, 1.1, 0.69, and 2.4 mg/kg body weight/day for the congeners penta-, hexa-, hepta-, and octachloronaphthalene, respectively, during 5- to 10-day exposure periods.[5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for pentachloronaphthalene is 0.5 mg/m^3 with a notation for skin absorption.

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PENTACHLOROPHENOL

CAS: 87-86-5

C_6Cl_5OH

Synonyms: Penta; PCP, penchlorol; pentachlorophenate; Santophen 20; Dowicide 7

Physical Form. White to tan needle-like crystals

Uses. Wood preservative; insecticide for termite control; preharvest defoliant; general herbicide; fungicide

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Pentachlorophenol has been reported to have adverse effects on the skin, eyes, respiratory system, nervous system, hematopoietic system, kidney, and liver; at high doses it is fetotoxic to rats and it is carcinogenic to mice.

Deaths from pentachlorophenol have occurred after acute inhalation exposure, dermal exposure, and ingestion.[1,2]

Symptoms of poisoning can include rapid onset of profuse diaphoresis, hyperpyrexia, tachycardia, tachypnea, generalized weakness, nausea, vomiting, abdominal pain, anorexia, headache, intense thirst, pain in the extremities, intermittent delirium, convulsions, progressive coma, and death within hours of the onset of symptoms.[3] The acute toxicity results from the uncoupling of oxidative phosphorylation, causing stimulation of cell metabolism and accompanying hyperthermia.[1–4]

Postmortem examination in fatal cases has shown immediate onset of extreme rigor mortis in the muscles of the thighs and legs, edema and intraalveolar hemorrhage in the lungs, cerebral edema, and liver and kidney damage.[2,5] The risk of serious intoxication is increased during hot weather.[6]

Chronic exposure is associated with an increased prevalence of conjunctivitis, chronic sinusitis, bronchitis, polyneuritis, and dermatitis. Chloracne has been reported and is probably the result of dioxin contaminants in commercial-grade pentachlorophenol.[3] On the skin, solutions of pentachlorophenol as dilute as 1% may cause irritation if contact is repeated or prolonged.

Various hematologic disorders, including aplastic anemia and hemolytic anemia, have been reported in humans after pentachlorophenol exposure. It has been suggested that pentachlorophenol causes blocking of the formation of adenosine triphosphate in red blood cells, leading to premature lysis.[7] In general, adverse hematologic effects have only been observed in animals exposed to the technical-grade pentachlorophenol and not pure pentachlorophenol, suggesting that contaminants may play a role in hematotoxicity.[1]

Hepatic toxicity, as manifested by enlarged liver, fatty infiltration of the liver, centrilobular congestion and degeneration, and elevated serum enzyme levels, has been observed after fatal and nonfatal exposures. Again, animal studies have indicated that purified pentachlorophenol produces much less severe effects than those seen with the technical grade, implicating a role for contaminants in hepatic toxicity.[1] Renal dysfunction, such as reduced glomerular filtration and tubular degeneration, appears to be mild and transient in cases of human exposures.[8]

Animal studies have shown that the immune system is sensitive to exposure.[9] Mice fed diets containing 50 or 500 ppm technical-grade pentachlorophenol showed greatly reduced immunocompetence in the form of increased susceptibility to the growth of transplanted tumors. Oral and intraperitoneal administration to animals causes adverse effects on thyroid homeostasis and on the thyroid gland. Competition for serum protein thyroxine binding sites may account for the antithyroid effects of pentachlorophenol.[1]

Given orally to pregnant rats at doses ranging from 5 to 50 mg/kg body weight/day, purified pentachlorophenol produced dose-related signs of fetotoxicity, including resorptions, subcutaneous edema, dilated ureters, and anomalies of the skull, ribs, and vertebrae.[10]

Although early animal studies found no sufficient evidence of carcinogenicity, a 2-year NTP report found clear evidence of carcinogenicity in mice for two technical-grade pentachlorophenol mixtures.[11,12] Male B6C3F1 mice fed diets containing 100 or 200 ppm technical-grade pentachlorophenol had increased incidences of adrenal medullary and hepatocellular neoplasms; there was some evidence of carcinogenicity in female mice similarly exposed, as shown by increased incidences of hemangiosarcomas and hepatocellular neoplasms. For male and female mice given up to 600 ppm EC-7 pentachlorophenol, there were increased incidences of adrenal medullary and hepatocellular neoplasms (females also had hemangiosarcomas of the liver and spleen). It was concluded that pentachlorophenol was primarily responsible for the carcinogenic response in mice, but that impurities may possibly play a role in the neoplastic process.[12]

A more recent 2-year study found no evidence of carcinogenic activity for pentachlorophenol in male or female F344/N rats fed diets containing 200, 400, or 600 ppm.[13] There was some evidence of carcinogenic activity in male F344/N rats given feed containing 1,000 ppm for 1 year followed by control feed for 1 year (stop-exposure study), based on increased incidences of mesothelioma and nasal squamous cell carcinoma.

Case reports and case control studies in humans have suggested a possible association between cancer, including soft tissue sarcoma, acute leukemia, Hodgkin disease, and non-Hodgkin lymphoma, and occupational exposure to pentachlorophenol. However, in all cases concomitant exposure to other toxic substances may have contributed to the effects seen.[1,11]

The IARC has determined that there is limited evidence for carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals.[11]

Occupational exposure of 20 workers to pentachlorophenol at concentrations that ranged from 1.2 to 180 µg /m^3 for 3–34 years did not result in any increased incidence of sister chromatid exchanges or chromosomal aberrations.[14] In another report, significant increases in the incidence of dicentric chromosomes and acentric fragments were detected in the peripheral lymphocytes of exposed workers; the frequency of sister chromatid exchanges was not increased.[15]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for pentachlorophenol is 0.5 mg/m^3 with a notation for skin absorption.

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PENTAERYTHRITOL

CAS: 115-77-5

$C(CH_2OH)_4$

Synonyms: Tetramethylolmethane; 2,2-bishydroxymethyl-1,3-propanediol

Physical Form. Solid

Uses. In the manufacture of pentaerythritol tetranitrate; alkyd resins in surface-coating compositions; pentaerythritol triacrylate and protective coatings; insecticides; pharmaceuticals

Exposure. Inhalation

Toxicology. Pentaerythritol is of very low toxicity.

Rats, dogs, and guinea pigs exposed for 6 hours/day for 90 days to 11,000 mg/m^3 technical-grade pentaerythritol showed no adverse effects.[1] The oral LD_{50} for guinea pigs was 11.3 g/kg; effects were tremors, ataxia, and loss of righting reflex.

Feeding studies in human subjects indicated that 85% of the pentaerythritol was eliminated unchanged in the urine.[2]

Skin application on rabbits of a saturated aqueous solution daily for 10 days caused no significant irritation; instillation of the same solution into the rabbit eye caused no irritation.[3]

Pentaerythritol was negative in bacterial mutagenicity assays with or without metabolic activation.[4]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for pentaerythritol is 10 mg/m^3.

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PENTANE
CAS: 109-66-0

C_5H_{12}

Synonyms: Amyl hydride

Physical Form. Colorless liquid

Uses. Fuel; solvent; chemical synthesis

Exposure. Inhalation

Toxicology. Pentane causes central nervous system depression at extremely high concentrations.

Pentane is considered nontoxic at concentrations below its lower flammability limits (15,000 ppm). Human subjects exposed to 5000 ppm for 10 minutes did not experience mucous membrane irritation or other symptoms.[1] In early reports topical application of pentane to volunteers caused painful burning sensations accompanied by itching; after 5 hours, blisters formed on the exposed areas.[2] More recent studies showed that 2.0 ml applied to the skin of volunteers for 24 hours was not irritating.[3]

In animal studies, pentane was not irritating to the skin or eyes of rabbits and there was no evidence of sensitizing potential in guinea pigs.[3]

A 5-minute exposure at 128,000 ppm produced deep anesthesia in mice; respiratory arrest occurred in one of four animals during exposure.[4] Mice exposed to 32,000 or 64,000 ppm for 5 minutes showed signs of respiratory irritation and became lightly anesthetized during the recovery period.[4] No effects were observed for 5-minute exposures at 16,000 ppm or below.

There are no studies showing that *n*-pentane alone, without hexane, affects the peripheral nervous system.[5] When tested in a 90-day inhalation toxicity test at levels up to 7000 ppm *n*-pentane did not influence mortality or weight loss, nor did it produce any microscopic effects suggestive of target organ toxicity.[3]

There were no effects in maternal or fetal rats administered up to 10,000 ppm pentane 6 hours/day from gestation day 6 to 15 as determined by body weights, food consumption, clinical signs, and gross external development.

Pentane was not genotoxic in both *in vivo* and *in vitro* assays.[3]

The odor of pentane is readily detectable at 5000 ppm.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for pentane is 600 ppm (1770 mg/m^3) with a short-term excursion limit (STEL)/ceiling of 750 ppm (2210 mg/m^3).

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2,4-PENTANEDIONE

CAS: 123-54-6

$CH_3COCH_2COCH_3$

Synonyms: Acetylacetone, diacetyl methane, acetyl 2-propanone, 2,4-PD

Physical Form. Clear liquid with a rancid odor

Uses. Chemical intermediate, metal chelator, and lubricant additive

Exposure. Inhalation; skin absorption

Toxicology. 2,4-Pentanedione is moderately irritating to the skin and eyes; repeated exposure to high concentrations causes dyspnea, central nervous system damage, and death.

Information on human exposures is limited. Exposure to levels ranging from 2 to 14 ppm have been reported to produce nausea and headache.[1]

For male and female rats the combined LC_{50} for a 4-hour exposure was 1224 ppm.[2] Signs of toxicity before death included periocular, perinasal, and perioral wetness and encrustation, mouth and abdominal breathing, tremors, ataxia, and negative tail and toe pinch reflexes. Necropsy of animals that died showed dark red lungs, mottled livers, and gas-filled gastrointestinal tracts. Survivors did not show any gross pathology. At 919 ppm for 4 hours there was decreased motor activity with recovery by the first postexposure day, and there were no signs of toxicity at 628 ppm.

Repeated exposure of rats to 650 ppm 6 hours/day, 5 days/week for 14 weeks caused hypoactivity, incoordination, ataxia, paresis, and slowed righting reflexes; death occurred in all females and 10 of 30 males between the second and sixth weeks of exposure.[3,4] Death was attributed to brain lesions consisting of degenerative changes in the deep cerebellar and vestibular nuclei and the corpora striata. Gliosis and malacia were observed in the same brain regions in approximately half of the surviving animals. Other changes included minimal squamous metaplasia in the nasal mucosa, decreased body and organ weights, lymphocytosis, and minor alterations in serum and urine chemistries. No spinal cord or peripheral lesions were found in any rats. No clinical signs or neuropathies were seen in rats treated at 101 or 307 ppm for 14 weeks, suggesting a well-defined threshold for effects.

Central neuropathologic lesions have also been described after gavage administration.[1] Rats developed weakness, ataxia, tremors, paresis, and rolling movements of the head after 100–150 mg/kg twice daily for periods from 3 to 61 days. Histologic changes induced by the shorter dosing schedules were perivascular edema, hemorrhage into the Virchow–Robin spaces, and endothelial swelling, all primarily localized in the cerebellum and brain stem. Chronic central nervous system lesions were bilateral, symmetrical areas of malacia and gliosis centered on the cerebellar peduncles, olivary nuclei, and lower brain stem.

The central neuropathologic effects following inhalation exposure in rats appear to require a critical number of repeated exposures to high (>650 ppm) concentrations.[3] Thus central neuropathologic effects did not occur after acute exposure to potentially lethal concentrations or after subchronic exposures at 307 ppm. The steep slope of the concentration-response relationship and the sharply defined exposure conditions for inducing central nervous system damage suggest that the mechanism of neurotoxicity may involve depletion of a biochemical pathway. Specifically, the similarity between the morphologic damage produced by 2,4-pentanedione and acute vitamin B deficiency and the ability of 2,4-pentanedione to inactivate lysyl residues suggest that the toxicity of 2,4-pentanedione is due to its ability to produce deficiencies of thiamine, folic acid, and/or pyridoxine.[1]

Pregnant Fischer 344 rats were exposed to 2,4-pentanedione at 53, 202, or 398 ppm 6 hours/day on gestational days 6–15.[5] At the highest dose there was maternal toxicity in the form of reduced body weight gain and fetotoxicity as reduced fetal body weight and a consistent pattern of reduced skeletal ossification; at 202 ppm there was reduced fetal body weight gain. Embryotoxicity and teratogenicity were not observed at any concentration.

The percutaneous LD_{50} values for 24-hour occluded contact on the skin of rabbits were 1.41 ml/kg for males and 0.81 for females.[2] Times of death ranged from 45 minutes to 1 day. Signs of toxicity were dilated pupils within 15–30 min, convulsions in one animal, and excess, blood-stained saliva. Local signs of inflammation were erythema, edema, and necrosis. In survivors, inflammation persisted for up to 7 days with scab formation by 2 weeks. Instilled in the eye of rabbits, the liquid produced mild conjunctivitis without corneal injury.

Although irritant effects do not appear until high concentrations are reached, it is expected that the low odor threshold (0.01 ppm) could provide adequate warning of exposure to 2,4-pentanedione.[2]

2,4-Pentanedione caused sister chromatid exchange increases in Chinese hamster ovary (CHO) cells and an increase in the incidence of micronuclei in peripheral blood erythrocytes of mice.[6] It was not mutagenic in a *Salmonella typhimurium* assay.

A threshold limit value (TLV) has not been established for 2,4-pentanedione.

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PERCHLOROETHYLENE

CAS: 127-18-4

C_2Cl_4

Synonyms: Tetrachloroethylene; ethylene tetrachloride; tetrachloroethene; 1,1,2,2-tetrachloroethylene; PCE

Physical Form. Colorless liquid

Uses. Solvent for dry cleaning and textile processing; chemical intermediate; metal degreasing

Exposure. Inhalation

Toxicology. Perchloroethylene causes central nervous system depression and liver damage. Chronic exposure has caused peripheral neuropathy, and it is carcinogenic in experimental animals.

Occupational exposure has caused signs and symptoms of central nervous system depression, including dizziness, light-headedness, "inebriation," and difficulty in walking.[1]

Four human subjects exposed to 5000 ppm left a chamber after 6 minutes to avoid being overcome; they experienced vertigo, nausea, and mental confusion during the 10 minutes after cessation of exposure.[2] In an industrial

exposure to an average concentration of 275 ppm for 3 hours, followed by 1100 ppm for 30 minutes, a worker lost consciousness; there was apparent clinical recovery 1 hour after exposure; the monitored concentration of perchloroethylene in the patient's expired air diminished slowly over a 2-week period.[3] During the second and third postexposure weeks, the results of liver function tests became abnormal. Additional instances of liver injury after industrial exposure have been reported.[4]

Other effects on humans from inhalation of various concentrations are as follows: 2000 ppm, mild central nervous system depression within 5 minutes; 600 ppm, sensation of numbness around the mouth, dizziness, and some incoordination after 10 minutes.[5] In human experiments, 7-hour exposures at 100 ppm resulted in mild irritation of the eyes, nose, and throat; flushing of the face and neck; headache; somnolence; and slurred speech.[6] Prolonged exposure has caused impaired memory, numbness of extremities, and peripheral neuropathy, including impaired vision.[1]

Of 40 dry cleaning workers, 16 showed signs of central nervous system depression and, in 21 cases, the autonomic nervous system was also affected.[7] Twenty dry cleaning workers exposed for an average of 7.5 years to concentrations between 1 and 40 ppm had altered electrodiagnostic and neurological rating scores.[7] Abnormal EEG recordings were found in 4 of 16 factory employees exposed to concentrations ranging from 60 to 450 ppm for periods of from 2 years to more than 20 years.[7]

The liquid on the skin for 40 minutes resulted in a progressively severe burning sensation beginning within 5–10 minutes and marked erythema, which subsided after 1–2 hours.[2]

Rats did not survive when exposed for longer than 12–18 minutes to 12,000 ppm. When exposed repeatedly to 470 ppm, they showed liver and kidney injury.[2] Cardiac arrhythmias owing to sensitization of the myocardium to epinephrine have been observed with certain other chlorinated hydrocarbons, but exposure of dogs to perchloroethylene concentrations of 5000 and 10,000 ppm did not produce this phenomenon.[8]

Rats exposed to 300 ppm 7 hours/day on days 6–15 of pregnancy showed reduced body weight and a slightly increased number of resorptions. Among litters of mice similarly exposed, the incidence of delayed ossification of skull bones, subcutaneous edema, and split sternebrae were significantly increased compared with those in controls.[9] In general, perchloroethylene is fetotoxic at concentrations that also produce maternal toxicity. Although a number of case-referent studies have suggested an effect of perchloroethylene on human reproductive parameters, including spontaneous abortions, sperm abnormalities, delayed conception, hormonal disturbances, and idiopathic infertility, the incompleteness of the studies precludes any significant conclusions.[10–13] However, exposure of pregnant women to perchloroethylene should be minimized.

Large gavage doses, approximately 500 and 1000 mg/kg per day for 78 weeks, caused a statistically significant increase in the incidence of hepatocellular carcinomas in mice.[14] Inhalation exposure by rats to 200 or 400 ppm for 2 years caused an increased incidence of mononuclear cell leukemia; a dose-related trend for a rare renal tubular neoplasm was observed in males.[15]

After publication of the rodent carcinogenicity studies, human epidemiological surveys were conducted. From a number of cohort and case control studies there was evidence for positive associations between exposure to perchloroethylene and increased risks for esophageal and cervical cancer and non-Hodgkin lymphoma.[16] The most recent follow-up of a cohort of 1708 US dry-cleaning workers with exposure to perchloroethylene for at least 1 year before 1960 found statistically significant elevated risks for tongue, bladder, esophagus, intestine, lung, and cervical cancer.[17] The large number of target sites, the small numbers of excess cancers, and the multiplicity of chemical exposures limit conclusions about carcinogenicity.[16]

The IARC has determined that there is sufficient evidence in experimental animals and limited evidence in humans for carcinogenicity

and that, overall, perchloroethylene is probably carcinogenic to humans.[16]

Both positive and negative results have been reported in a variety of genotoxic studies. Many studies have been done with commercial grades of perchloroethylene, which suggests that contaminants may be involved when effects are seen. Furthermore, there is evidence that the mutagenic properties may depend on a glutathione-mediated metabolic pathway that is more prominent in rats than in humans.[18]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for perchloroethylene is 25 ppm (170 mg/m^3) with a short-term exposure limit (STEL) of 100 ppm (685 mg/m^3) and an A3-animal carcinogen designation.

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PERCHLOROMETHYL MERCAPTAN

CAS: 594-42-3

CCl_3SCl

Synonyms: PCM; perchloromethanethiol; trichloromethanesulfenyl chloride

Physical Form. Yellow liquid

Uses. Production of fungicides; vulcanizing accelerator in rubber industry

Exposure. Inhalation

Toxicology. Perchloromethyl mercaptan is a severe pulmonary irritant and lacrimating agent; fatal exposure has also caused liver and kidney injury.

Humans can withstand exposures to 70 mg/m^3 (8.8 ppm); eye irritation begins at 10 mg/m^3 (1.3 ppm).[1] Acute exposure to higher concentrations may cause coughing, dyspnea, lacrimation, nausea, cyanosis, convulsions, and death due to lung edema.[2]

Of three chemical workers who were observed after accidental exposures to perchloromethyl mercaptan, two survived episodes of pulmonary edema, and the third died after 36 hours.[1] The fatality resulted from a spill of the liquid on the clothing and floor with exposure to the vapor. At autopsy, there was necrotizing tracheitis, massive hemorrhagic pulmonary edema, marked toxic nephrosis, and vacuolization of centrilobular hepatic cells.

The liquid splashed on the skin may be expected to cause irritation.

Mice and cats exposed for 15 minutes at 45 ppm died within 1–2 days from pulmonary edema; the LC_{50} for mice was 9 ppm for 3 hours; repeated exposures over 3 months at 1 ppm resulted in the death of some of the mice tested.[1,2] Rats exposed at 1 ppm 6 hours/day, 5 days/week for 2 weeks had labored breathing, tremors, and nasal irritation; pulmonary edema was evident at autopsy.[3] No effects were seen at 0.13 ppm for the same exposure period.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for perchloromethyl mercaptan is 0.1 ppm (0.76 mg/m^3).

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PERCHLORYL FLUORIDE

CAS: 7616-94-6

ClO_3F

Synonyms: Chlorine fluoride oxide; chlorine oxyfluoride; trioxychlorofluoride

Physical Form. Gas

Uses. In organic synthesis to introduce F atoms into organic molecules; oxidizing agent in rocket fuels; insulator for high-voltage systems

Exposure. Inhalation

Toxicology. Perchloryl fluoride is an irritant of mucous membranes; in animals it causes methemoglobinemia and pulmonary edema.

One report states that workers suffered symptoms of upper respiratory irritation from brief exposure to unspecified concentrations.[1] There are no reports of methemoglobinemia in humans from exposure to perchloryl fluoride. However, severe exposure may be expected to cause the formation of methemoglobin and resultant anoxia with cyanosis (especially evident in the lips, nose, and earlobes), severe headache, weakness, and dizziness.[2] The liquid is stated to produce moderately severe burns with prolonged contact.[3]

Dogs exposed to 220 ppm for 4 hours or 620 ppm for 2.5 hours developed hyperpnea, cyanosis, incoordination, and convulsions; methemoglobin levels were 29% and 71%, respectively.[4] In dogs that died from exposure, there was lung damage consisting of alveolar collapse and hemorrhage; pigment deposition in the liver, spleen, and bone marrow was observed.[5]

Repeated exposure of three species of animals to 185 ppm for 7 weeks caused the death of more than half of them, guinea pigs being the most susceptible; all of the animals developed dyspnea, cyanosis, methemoglobinemia, alveolar edema, and pneumonitis.[4] With repeated exposure of animals to 104 ppm for 6 weeks, guinea pigs again succumbed and other signs and symptoms were similar to those observed at 185 ppm; the normal fluoride levels were increased by a factor of 20–30 in the blood and 5–8 in the urine.[4]

The 2003 time-weighted average-threshold limit value (TWA-TLV) for perchloryl fluoride is 3 ppm (13 mg/m^3) with a short-term excursion level (STEL/ceiling) of 6 ppm (25 mg/m^3).

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PHENOL
CAS: 108-95-2

C_6H_5OH

Synonyms: Carbolic acid; phenic acid; phenylic acid; phenyl hydroxide; hydroxybenzene; oxybenzene

Physical Form. White crystalline solid

Uses. In the manufacture of phenolic resins, bisphenol A and alkyl phenols, and caprolactam; also used in disinfectants and antiseptics

Exposure. Skin absorption; inhalation; ingestion

Toxicology. Phenol is an irritant of the eyes, mucous membranes, and skin; systemic absorption causes nervous system toxicity as well as liver and kidney damage.

Phenol is not considered a serious respiratory hazard in industry, in large part because of its low volatility.[1] The skin is a primary route of entry for the vapor, liquid, and solid. The

vapor readily penetrates the skin, with an absorption efficiency equal to that for inhalation. Skin absorption can occur at low vapor concentrations, apparently without discomfort. Signs and symptoms can develop rapidly, with serious consequences, including shock, collapse, coma, convulsions, cyanosis, respiratory arrest, and death.

A worker who accidentally fell into a shallow vat containing 40% phenol for a few seconds subsequently collapsed and suffered 50% body surface burns; he developed nausea and vomiting and was diagnosed as suffering from acute renal tubular necrosis.[2] After a number of days, respiratory distress also developed. Kidney function improved after 6 weeks, but the patient still showed marginal polyuria 1 year later.

A laboratory technician repeatedly exposed to the vapor (unknown concentration) and to the liquid spilled on the skin developed anorexia, weight loss, weakness, muscle pain, and dark urine.[3] During several months of nonexposure, there was gradual improvement in his condition, but, after brief reexposure, he suffered an immediate worsening of symptoms, with prompt darkening of the urine and tender enlargement of the liver.

Brief intermittent industrial exposures to vapor concentrations of 48 ppm of phenol (accompanied by 8 ppm of formaldehyde) caused marked irritation of eyes, nose, and throat.[1] Workers at the same plant who were continuously exposed to an average concentration of 4 ppm experienced no respiratory irritation.

Ingestion of lethal amounts causes severe burns of the mouth and throat, marked abdominal pain, cyanosis, muscular weakness, collapse, coma, and death. Tremor, convulsions, and muscle twitching have also occurred.[1,4] The minimal lethal oral dose in humans has been estimated to be approximately 140 mg/kg.[5,6]

Concentrated phenol solutions are severely irritating to the human eye and cause conjunctival swelling; the cornea becomes white and hypesthetic. Loss of vision has occurred in some cases.[7]

In addition to systemic effects, contact with the solid or liquid can produce chemical burns.[1] Erythema, edema, tissue necrosis, and gangrene have been reported, and prolonged contact with dilute solutions may result in deposition of dark pigment in the skin (ochronosis).[1] After severe chemical burns, progressive areas of depigmentation may also develop.

Rats and mice given doses of up to 120 mg/kg and 280 mg/kg, respectively, by gavage on days 6–15 of gestation showed dose-related signs of fetotoxicity with no evidence of teratogenic effects.[4] A Russian study demonstrated increased preimplantation loss and early postnatal death in the offspring of rats exposed to 0.13 and 1.3 ppm throughout pregnancy.[4] In two-generation studies in rats, reduced litter survival was seen at doses of 5000 ppm in the drinking water, which also caused significant reductions in food and water consumption of the parental generation.[8]

Mice were treated twice weekly for 42 weeks by application of one drop of a 10% solution of phenol in benzene to the shaved dorsal skin; after 52 weeks, there were papillomas in 5 of 14 mice, and a single fibrosarcoma appeared at 72 weeks.[9] Phenol, as a nonspecific irritant, may promote development of tumors when applied repeatedly to the skin in large amounts.[1]

Phenol was not considered carcinogenic to rats or mice receiving 2500–5000 ppm in drinking water for 103 weeks, although an increased incidence of leukemia and lymphomas was detected in the low-dose male rats.[10] Two-stage carcinogenicity studies showed that phenol, applied repeatedly to mouse skin, has promoting activity.

In a case-control study of workers in various wood industries, an increased risk for tumors of the mouth and respiratory tract was associated with phenol exposure; however, the small number of cases and confounding exposures were inadequately controlled.[11,12] The IARC has determined that there is inadequate evidence for carcinogenicity of phenol in humans and experimental animals and that it is not classifiable as to its carcinogenicity to humans.[12]

After *in vivo* administration, phenol induced micronuclei in mice and chromosomal

aberrations in rats.[12] *In vitro*, it caused mutations and sister chromatid exchanges in mammalian cells but was not mutagenic in bacteria.[12] Although phenol is a major metabolite of the leukemogen benzene, it does not exhibit any potential for myeloclastogenicity in animal tests.[13]

Phenol is detectable by odor at a threshold of 0.05 ppm.[14]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for phenol is 5 ppm (19 mg/m^3) with a notation for skin absorption.

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p-PHENYLENEDIAMINE

CAS: 106-50-3

$C_6H_4(NH_2)_2$

Synonyms: *p*-Diaminobenzene; 1,4-benzenediamine

Physical Form. Colorless crystalline solid; with exposure to air, it turns red, brown, and finally black

Uses. Dyeing of furs; hair dye formulations; in photographic developers; in antioxidants

Exposure. Inhalation; skin absorption

Toxicology. *p*-Phenylenediamine is a sensitizer of the skin and respiratory tract and may produce bronchial asthma.

Frequent inflammation of the pharynx and larynx has been reported in exposed workers.[1] Very small quantities of the dust have caused asthmatic attacks in workers after periods of exposure ranging from 3 months to 10 years. Sensitization dermatitis has been reported from its use in the fur dyeing industry. In this process, oxidation products of *p*-phenylenediamine are generated that are also strong skin sensitizers. Many instances of inflammation and damage of periocular and ocular tissue have been reported from contact with hair dyes containing *p*-phenylenediamine, presumably in sensitized individuals.[2,3]

Although unlikely in an occupational setting, ingestion of *p*-phenylenediamine (especially hair dyes) has resulted in fatalities.[4] The primary systemic effect is rhabdomyolysis with subsequent renal failure.

Developmental or teratogenic effects were not observed in rats, even at doses that were severely maternally toxic.[5]

p-Phenylenediamine was tested for carcinogenicity in mice by skin application and in rats by oral and subcutaneous administration, however, the IARC has determined that these studies were not adequate to evaluate carcinogenicity.[6] The dihydrochloride was not carcinogenic in 2-year feeding studies with mice and rats.[7]

p-Phenylenediamine was weakly mutagenic in some bacterial strains and caused a dose-dependent increase in chromosomal aberrations in Chinese hamster ovary (CHO) cells *in vitro*.[8]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for *p*-phenylenediamine is 0.1 mg/m^3.

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2-PHENYLETHANOL
CAS: 60-12-8

$C_6H_5CH_2CH_2OH$

Synonyms: Benzyl carbinol; PEA; phenylethyl alcohol

Physical Form. Colorless, viscous liquid

Uses. In fragrance; antimicrobial agent; in organic synthesis; preservative, food additive

Exposure. Inhalation

Toxicology. Phenylethanol is an irritant of the eyes and a teratogen in rats.

An 8-hour exposure of rats to an essentially saturated atmosphere failed to cause any deaths.[1] The acute oral LD_{50} for rats ranged from 2.5 to 3.1 ml/kg.[2] The dermal LD_{50} values for rabbits and guinea pigs were 0.8 and 5 g/kg, respectively.[2]

A solution containing 0.5% phenylethanol and 0.9% sodium chloride caused a sensation of smarting in human test subjects when dropped in the eye.[3] Application of a 1% solution to rabbit eyes caused irritation of the conjunctiva and transient clouding of corneal epithelium.[4]

The liquid on the skin of human test subjects was not irritating or sensitizing.[5]

Daily oral doses of 4.3, 43, or 432 mg/kg to rats on days 6–15 of gestation caused abnormalities in 50%, 93%, and 100% of the animals.[6] Major malformations, including micromelia, vertebral opening, and skull defects, were observed at the highest dose, whereas only skeletal variations occurred at 4.3 mg/kg. Applied to the skin of pregnant rats 1.4 ml/kg caused marked maternal toxicity and morphologic abnormalities in the fetuses; at 0.70 ml/kg/day there was a significant increase in cervical ribs.[2]

Phenylethanol was not mutagenic in bacterial assays, nor did it increase the number of sister chromatid exchanges in human lymphocytes.[2]

A threshold limit value (TLV) has not been established for 2-phenylethanol.

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PHENYL ETHER

CAS: 101-84-8

$(C_6H_5)_2O$

Synonyms: 1,1′-Oxybisbenzene; diphenyl ether; diphenyl oxide

Physical Form. Colorless liquid

Uses. Heat-transfer medium; in perfuming soaps; in organic syntheses

Exposure. Inhalation

Toxicology. Phenyl ether appears to be of relatively low toxicity.

There are no reported effects in humans, although complaints resulting from the disagreeable odor may occur.

Twenty exposures at 10 ppm lasting 7 hours/day caused eye and nose irritation in rats and rabbits but not in dogs.[1] At 4.9 ppm, there were no signs of irritation or toxicity. The acute lethal oral dose for rats and guinea pigs is 4.0 g/kg.[2] Rats receiving 2.0 g/kg and guinea pigs receiving 1.0 g/kg had liver and kidney injury at autopsy.[2] On the rabbit skin, the undiluted liquid is irritating if exposures are prolonged or repeated.[2]

Phenyl ether was not mutagenic in the Ames *Salmonella* assay with or without metabolic activation.[3]

The low vapor pressure of phenyl ether and its easily detectable odor should prevent exposure to hazardous concentrations.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for phenyl ether is 1 ppm (7 mg/m^3) with a short-term excursion limit (STEL)/ceiling of 2 ppm (14 mg/m^3).

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PHENYL GLYCIDYL ETHER

CAS: 122-60-1

$C_6H_5OCH_2CHOCH_2$

Synonyms: PGE; Phenoxypropenoxide; 2,3-epoxypropyl phenyl ether

Physical Form. Colorless liquid

Uses. Chemical intermediate with high solvency for halogenated materials

Exposure. Inhalation

Toxicology. Phenyl glycidyl ether (PGE) is an irritant of mucous membranes and skin and causes sensitization; it has caused nasal tumors in experimental animals.

Of 20 workers exposed to PGE, 13 had acute skin changes, including second-degree burns, vesicular rash, papules, and edema.[1] In another study of 15 workers with PGE-induced dermatitis, there was erythema with papules and vesicles.[2] Of these 15 workers, 8 reacted positively to patch tests. In addition to skin sensitization PGE can also cause cross-sensitization with other glycidyl ethers.

During animal exposure studies, technicians experienced irritation of the eyes, nose, and respiratory tract.[1,2]

There are no reports describing systemic effects in humans, and the low vapor pressure should limit the risk of acute inhalation exposure.[2]

Intragastric LD_{50} values were 1.40 and 3.85 g/kg, respectively, for mice and rats.[1] The predominant effect was central nervous system depression, and death was due to paralysis of the respiratory muscles. Surviving animals exhibited a reversal of the depressant effect, with increased central nervous system activity manifested by hypersensitivity to sound, muscle twitching, and tremor.

No deaths were produced in mice exposed 4 hours, or rats exposed 8 hours, to saturated vapors at room temperature.

Rats exposed for 7 hours/day for 50 days to about 10 ppm showed no overt signs of toxicity and no deaths, although a few animals, when euthanized, had mild pulmonary inflammation and nonspecific cellular changes in the liver.[1,2] Exposure to 5 and 12 ppm PGE 30 hours/week for 13 weeks caused hair loss in rats attributed to direct irritation of the skin rather than to systemic toxicity.[3]

Chronic exposure of rats to 1 or 12 ppm 6 hours/day, 5 days/week for 2 years caused an increased incidence of rhinitis, squamous metaplasia, and epidermal carcinomas of the nasal cavity.[4] The IARC has determined that there is sufficient evidence for the carcinogenicity of PGE in animals and that it is possibly carcinogenic to humans.[5]

Exposure of pregnant rats to 11.5 ppm 6 hours/day on days 4–15 of gestation did not cause effects in mothers or their offspring.[2] Localized degeneration of the seminiferous tubules has been reported in some male rats exposed at this level.[2,6]

Direct application of PGE into rabbit eyes produced irritation ranging from mild to severe without permanent damage.[2]

PGE was mutagenic in *Salmonella typhimurium* assays.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for phenyl glycidyl ether is 0.1 ppm (0.6 mg/m^3) with an A3-animal carcinogen designation.

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PHENYLHYDRAZINE

CAS: 100-63-0

$C_6H_5N_2$

Synonyms: Hydrazinobenzine

Physical Form. Pale-yellow crystal or an oily liquid; becomes reddish-brown when exposed to air and light

Uses. Chemical intermediate; manufacture of dyes

Exposure. Inhalation; skin absorption

Toxicology. Phenylhydrazine causes hemolytic anemia and is a skin sensitizer; in animals it has caused liver and kidney injury secondary to hemolytic anemia and is carcinogenic.

Historically, phenylhydrazine hydrochloride was used to induce hemolysis in the treatment of polycythemia vera (a disease of abnormally high erythrocyte counts).[1] Oral doses totaling 3–4 g were administered; in a few cases, thrombosis occurred during excessive hemolysis, with subsequent liver and spleen damage, but effects cannot be conclusively ascribed to phenylhydrazine hydrochloride alone.[1] Several mild cases of hemolytic anemia from occupational exposure have been reported.[2] Symptoms of intoxication have included fatigue, headache, dizziness, and vertigo.[3]

Phenylhydrazine is a potent skin sensitizer that causes eczematous dermatitis with swelling and vesiculation in a high proportion of individuals who have had repeated skin contact.[1,3] Based on results with other hydrazines, it is expected that phenylhydrazine could also be absorbed through the skin.[1]

The minimal lethal dose in mice by subcutaneous injection was 180 mg/kg; animals developed progressive cyanosis and dyspnea before death; at autopsy, there were degenerative lesions in the liver, kidneys, and other organs, with evidence of vascular damage.[4]

Hemoglobin concentration, hematocrit value, and erythrocyte count were significantly reduced in dogs receiving 20 mg/kg subcutaneously for 2 consecutive days.[5] At necropsy on day 5, the internal organs were dark-brown and the spleen, liver, and kidneys were severely congested. Large amounts of blood pigments were found in these organs, and the spleen was three to five times the normal size.

One milligram of phenylhydrazine hydrochloride administered daily by gavage for 200 days to mice caused adenomas and adenocarcinomas of the lung in 53% of the animals, compared with 13% in the control group.[1] Consumption of 0.6–0.8 mg/day in drinking water for life resulted in an increased incidence of blood vessel tumors.[1] Although other studies have reported negative carcinogenicity results, NIOSH recommends that phenylhydrazine be regulated as a carcinogen.[1]

Phenylhydrazine is mutagenic *in vitro*, and there is some evidence to indicate that it may express genotoxic activity *in vivo*.[6]

Rats injected intraperitoneally (10 or 20 mg/kg) during pregnancy had offspring with severe jaundice, anemia, and reduced performance in certain areas of learning.[1]

Phenylhydrazine has a faint aromatic odor that does not serve as an adequate warning property.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for phenylhydrazine is 0.1 ppm (0.44 mg/m^3) with a notation for skin absorption and an A2-suspected human carcinogen designation.

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PHENYL MERCAPTAN

CAS: 108-98-5

C_6H_6S

Synonyms: Benzenethiol; mercaptobenzene; thiophenol; phenylthiol

Physical Form. Colorless liquid with a penetrating garliclike odor

Uses/Sources. In the production of pesticides, polymers, and pharmaceuticals; as a food additive

Exposure. Inhalation; skin absorption

Toxicology. Phenyl mercaptan is a central nervous system stimulant; the liquid is a severe eye and skin irritant.

In humans phenyl mercaptan may cause headaches.[1] By analogy with effects in animals it is expected that more severe exposures would cause central nervous system effects and other systemic injury.

The 4-hour inhalation LC_{50} was 33 ppm for rats and 28 ppm for mice.[2] The oral LD_{50} for rats was 46 mg/kg, while the dermal LD_{50} was 300 mg/kg. In rabbits the dermal LD_{50} was estimated to be 134 mg/kg. Effects by all exposure routes were consistent with central nervous system stimulation and included restlessness, increased respiration, muscular weakness, paralysis of the hind limbs, and cyanosis followed by coma and death. Subacute inhalation in mice caused some kidney damage, necrosis of the liver, and occasional hemorrhages in the lungs. Effects were less severe in rats.

In a continuous breeding study, F_0 and F_1 rats administered 9, 18, or 35 mg/kg/day phenyl mercaptan by gavage had increased liver and kidney weights (in association with centrilobular hepatocellular hypertrophy and renal tubule degeneration) with increasing dose.[3] At the highest dose decreased sperm motility and inhibited spermiation were observed in males, and females had decreased live pup weight during crossover mating.

Rats administered 20, 35, or 50 mg/kg/day on gestational days 6–15 had increased postimplantation loss and incidence of external malformations and decreased live litter size at the highest dose; maternal toxicity was evidenced by decreased food consumption and body weight gain.[4] Rabbits similarly treated also showed decreased body weight gain and lower food intake at doses of 30 and 40 mg/kg/day, but no developmental toxicity was observed in the offspring.

In rabbits phenyl mercaptan, on direct contact, caused severe erythema and eye injury with edema of the ocular conjunctiva and discharge, but with clearing in 16 days and complete reversal in 2 months.

An odor threshold of 0.00094 ppm has been reported.[5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for phenyl mercaptan is 0.5 ppm (2.3 mg/m^3).

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N-PHENYL-β-NAPHTHYLAMINE

CAS: 135-88-6

$C_{10}H_7NHC_6H_5$

Synonyms: Anilinonaphthalene; 2-naphthylphenylamine; 2-phenylaminonaphthalene; *N*-phenyl-2-naphthylamine; PBNA

Physical Form. Gray to tan flakes or powder

Uses. Formerly as an antioxidant in rubber processing to impart heat, oxidation, and flex-cracking resistance in natural rubber, synthetic rubbers, and latexes; as a stabilizer in electrical-insulating silicone enamels

Exposure. Inhalation

Toxicology. *N*-phenyl-β-naphthylamine (PBNA) is carcinogenic to experimental animals in some studies.

Leukoplakia, acne, and hypersensitivity to sunlight were observed in 36 workers exposed for prolonged periods to PBNA.[1] Dose levels or possible concurrent exposures to other substances were not reported.

The LD_{50} values are 8730 mg/kg for rats and 1450 mg/kg for mice. Acute vascular changes in the liver, lung, and brain as a result of venous congestion were observed. Daily inhalation by rats of 900 mg/m^3 for 14 days caused weight loss, slight erythrocytopenia, and pulmonary emphysema.[1] Intragastric administration of 100 mg/kg/day to rats caused an increase in urinary protein after 1 month, whereas urinary hippuric acid and adrenal ascorbic acid decreased after 6 months and a drop in urinary function occurred after 18 months. Lung and liver weights increased within 1 and 12 months, respectively, and changes were observed in the gastrointestinal tract after 6 months.

Reduced body weight, arched backs, rough coats, and diarrhea were observed in male rats receiving 12,500 ppm in the diet for 2 weeks and in females receiving 25,000 ppm; 50,000 ppm was associated with increased mortality for both sexes.[2] In 13-week studies,

increased mortality, lower weight gain, liver enlargement, and kidney lesions were found in rats and mice receiving up to 40,000 ppm. Other effects in rats included hematopoietic hypoplasia or atrophy of the femoral bone marrow, testicular hypospermatogenesis, lymphoid degeneration of the thymus, and lymphoid depletion of the spleen.

PBNA has been tested for carcinogenicity in a number of species without conclusive results. There was no evidence of carcinogenic activity in male or female rats or in male mice fed 2500 or 5000 ppm in the diet for 2 years.[2] The lack of carcinogenicity in rats may be related to an inability to metabolize PBNA to the known animal and human urinary bladder carcinogen β-naphthylamine. There was equivocal evidence for carcinogenicity in female mice, as indicated by the occurrence of two rare kidney tumors. Chemical-related nonneoplastic lesions, including nephropathy, karyomegaly, and hyperplasia, occurred in the kidneys of both species.

In a limited dog study, no bladder tumors were observed in three animals fed 540 mg 5 days/week for a period of 4.5 years.[3]

An increased incidence of carcinogenicity has been observed in other studies. In one strain of male mice given 464 mg/kg/day by stomach tube for 3 weeks followed by a diet of 1206 mg/kg for 78 weeks, there was an increased frequency of tumor-bearing animals (7/17 vs. 0/16 for controls), with the increase being primarily due to hepatomas (5/17 vs. 0/16 for controls).[4] A single subcutaneous injection of 464 mg/kg PBNA to one strain of female mice on the 28th day of life increased the total tumor incidence (5/18 vs. 9/154 for controls).[4] Repeated subcutaneous injection of 16 mg three times/week for 9 weeks caused an increased incidence of carcinomas of the lungs in treated mice (4/19 vs. 0/18 for controls).[5]

No excess of bladder tumors was found in men with known exposures to PBNA at a rubber tire factory.[6] From 1946 to 1970, there were 9 cases of bladder cancer among 4177 men vs. 10.0 expected; of these 4177 workers, 3301 had known exposures to PBNA. These results contrast with those involving exposures before 1949, when workers at the factory also were exposed to β-naphthylamine (a known carcinogen); 23 bladder tumors were observed vs. 10.3 expected, between 1946 and 1970, among 2081 men exposed to material that contained β-naphthylamine.[1]

An increased risk of death from bladder cancer (33 vs. 22.7 expected) was reported in 40,000 rubber and cable workers who had mixed exposures to many rubber additives, including PBNA, but not to known carcinogens.[6] In contrast to this study, no significant increases in overall or site-specific cancer was detected in a cohort of 2410 rubber chemical manufacturing workers, who were employed at a factory in north Wales, United Kingdom, between 1955 and 1984.[7]

Additional concern has been afforded PBNA because commercial PBNA contains 20–30 ppm of β-naphthylamine.[8] Furthermore, experimental evidence from human volunteers ingesting PBNA and workers inhaling PBNA dust indicates that β-naphthylamine is a metabolite of PBNA. Specifically, 3–4 μg of β-naphthylamine was found in 24-hour samples of urine obtained from two volunteers who ingested 50 mg PBNA containing 0.7 μg of β-naphthylamine.[9]

The IARC has concluded that there is limited evidence for carcinogenicity to animals and inadequate evidence for humans.[10] ACGIH considers PBNA to be a suspected human carcinogen because β-naphthylamine is both an impurity and a human metabolite of PBNA.[8]

A numerical threshold limit value (TLV) is not recommended for occupational exposure to PBNA.

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PHENYLPHOSPHINE

CAS: 638-21-1

$C_6H_5PH_2$

Synonym: PF

Physical Form. Colorless liquid with an objectionable odor

Uses/Sources. Exposure to phenylphosphine may occur when phenylphosphinates (used as catalysts and antioxidants) are heated above 200°C, yielding phenylphosphonic acid derivatives and phenylphosphine.

Exposure. Inhalation

Toxicology. Phenylphosphine is a respiratory and skin irritant; multiple exposures in rodents causes hematologic changes and testicular degeneration in males.

Three volunteers exposed to 0.57 ppm reported an obnoxious odor after one shallow breath.[1]

The 4-hour LC_{50} in rats was 38 ppm.[1] Exposure caused clinical signs typical of respiratory irritation, including red ears, salivation, lacrimation, face pawing, and dyspnea. Exposure at 7.6 ppm 4 hours/day for 10 days caused transient dermatitis around the mouth and feet on conclusion of the exposures in addition to signs of respiratory irritation. Weight loss was noted during the exposure period, but weight gain rate returned to normal during the recovery period. Histopathologic examination showed foci of red blood cell formation in the spleen that were still evident at the end of the recovery period.

In 90-day inhalation studies (6 hours/day, 5 days/week) rats became hypersensitive to sound and touch and had mild hyperemia at 0.6 ppm; at 2.2 ppm there was greater increase in splenic red blood cell formation, mild hemolytic anemia, and dermatitis.[2] Severe testicular degeneration developed in the 2.2 ppm-exposed rats that did not return to normal during a 10-week postexposure observation period. Dogs similarly exposed at 0.6 and 2.2 ppm had some loss of appetite, diarrhea, lacrimation, and hind leg tremor. There was mild, reversible testicular degeneration in the males exposed at 2.2 ppm.

The 2003 ACGIH threshold limit value-ceiling (TLV-C) for phenylphosphine is 0.05 ppm (0.23 mg/m^3).

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PHOSGENE

CAS: 75-44-5

Cl_2CO

Synonyms: Carbonyl chloride; carbon oxychloride

Physical Form. Gas at room temperature; yellowish liquid when compressed or refrigerated

Uses/Sources. Intermediate in organic synthesis, especially production of toluene diisocyanate and polymethylene polyphenylisocyanate; in metallurgy to separate ores by chlorination of the oxides and volatilization; occurs as a product of combustion whenever a volatile chlorine compound comes in contact with a flame or very hot metal; originally manufactured as an agent for chemical warfare during World War I

Exposure. Inhalation

Toxicology. Phosgene gas is a severe respiratory irritant.

Exposure to 3–5 ppm causes immediate irritation of the throat and eyes and cough; exposure above 50 ppm may be rapidly fatal.[1]

The LC_{50} in humans is approximately 500 ppm/min.[2] Prolonged exposure to low concentrations (e.g., 3 ppm for 170 minutes) is equally as fatal as acute exposure to higher concentrations (e.g., 30 ppm for 17 minutes). Exposure to lower concentrations, however, may not lead to noteworthy initial symptoms, whereas higher concentrations cause heavy lacrimation, coughing, nausea, and dyspnea.[2]

The onset of severe respiratory distress may be delayed for 24–48 hours, the latent interval depending on the concentration and duration of exposure.[3,4] The delayed onset of pulmonary edema is characterized by cough, abundant quantities of foamy sputum, progressive dyspnea, and severe cyanosis. Pulmonary edema may progress to pneumonia, and cardiac failure may intervene. During the clinical latent period, phosgene reaches the terminal spaces of the lungs, where hydrolysis occurs, yielding hydrochloric acid. Although hydrochloric acid may cause some of phosgene's toxic effects, acylation of proteins may be the initiating event in phosgene toxicity.[4] Membrane function breaks down, fluid leaks from the capillaries into the interstitial space, and gradually increasing pulmonary edema ensues.[2] In time, air spaces are diminished and the blood is thickened, leading to insufficient oxygen.[3,5] Death is due to asphyxiation or heart failure.[3,5]

Survivors of phosgene-induced pulmonary edema may expect a long recovery period.[6] Exertional dyspnea and reduced physical fitness may be apparent for several months to years after exposure. In exposures involving persons with preexisting lung damage (e.g., chronic bronchitis), there may be severe and progressive deterioration of lung function after toxic pulmonary edema due to phosgene, with no complete recovery.

Mortality experience among men occupationally exposed to phosgene in the years 1943–1945 was evaluated 30 years after exposure.[7] No excess overall mortality, or mortality from diseases of the respiratory tract, was found in a group of chemical workers chronically exposed to levels with daily excursions above 1 ppm. Another group of this cohort, 106 workers acutely exposed at some time to a concentration probably greater than 50 ppm, included one death from pulmonary edema, which occurred within 24 hours of exposure, and three deaths vs. 1.37 expected due to

respiratory disease. No evidence of increased lung cancer mortality was found, but the small sample size was noted.

No chronic lung problems were found in 326 workers exposed to concentrations ranging from nondetectable to greater than 0.13 ppm.[5]

Forty-one percent of animals exposed to 0.2 ppm 5 hours/day for 5 consecutive days developed pulmonary edema.[8] At 1 ppm, lung lesions that would be likely to cause serious clinical symptoms in humans were observed.[8] Splashes of liquefied phosgene in the eye may produce severe irritation.[3] Skin contact with the liquefied material may cause severe burns.[3]

The irritant properties of phosgene are not sufficient to give warning of hazardous concentrations. A trained observer can recognize 0.5 ppm as being "sweet," and, at about 1 ppm, the odor becomes typical of the "musty or new-mown hay" smell usually ascribed to phosgene. Workers exposed to phosgene can lose their ability to detect low concentrations through olfactory fatigue.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for phosgene is 0.1 ppm (0.40 mg/m^3).

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PHOSPHINE
CAS: 7803-51-2

PH_3

Synonyms: Hydrogen phosphide; phosphoretted hydrogen; phosphorus trihydride

Physical Form. Colorless gas

Uses. Insecticide used for fumigation; preparation of phosphonium halides; doping agent in semiconductor manufacture

Exposure. Inhalation

Toxicology. Phosphine is a severe pulmonary irritant.

Workers exposed intermittently to concentrations up to 35 ppm, but averaging below 10 ppm, complained of nausea, vomiting, diarrhea, chest tightness and cough, headache, and dizziness; no evidence of cumulative effects was noted.[1] Single severe exposures cause similar signs and symptoms, as well as excessive thirst, muscle pain, chills, sensation of pressure in the chest, dyspnea, syncope, and stupor.[2] In a few cases of exposure, dizziness and staggering gait have also occurred.[1] From 1900 to 1958 there were 59 reported cases of phosphine poisoning with 26 deaths; the effect most frequently reported was marked pulmonary edema.[2] The acute lethal effects of phosphine are associated with its ability to inhibit electron transport and combine with heme iron in the presence of oxygen.[3]

Inhalation of phosphine released after fumigation with aluminum phosphide on a grain freighter resulted in acute illnesses

among 29 of 31 crew members and two children, one of whom died.[4] Air concentrations measured 2 days after illness onset ranged from 0.5 ppm in some of the living quarters to 12 ppm at an air intake. The most common symptoms were headache, fatigue, nausea, vomiting, cough, and shortness of breath. Congestive heart failure with pulmonary edema and myocardial necrosis with inflammation were noted in the child who died. The other child had echocardiographic evidence of poor left ventricular function, an elevated MB (cardiac) isoenzyme fraction of creatine kinase, and an abnormal ECG, with resolution of abnormalities within 72 hours. No long-term clinical or laboratory abnormalities were observed in the survivors.

The long-term health sequelae of lower-level exposures have been examined. Fumigant applicators who were exposed to phosphine or to phosphine plus other pesticides 6 weeks to 3 months earlier had significantly increased stable chromosome rearrangement, primarily translocations in G-banded lymphocytes.[3] Less stable aberrations, including chromatid deletions and gaps, were significantly increased at the time of exposure, but not at later time points. In a more recent study of fumigators, occupational exposures up to 2.4 ppm/hour were not associated with genotoxic effects including micronuclei in peripheral blood lymphocytes and urine mutagenicity.[5]

Animals survived exposure to 5 ppm 4 hours/day for 2 months, but seven similar exposures at 10 ppm were fatal.[6] No treatment-related changes suggestive of toxic or carcinogenic effect were seen in rats exposed to 0.3, 1, or 3 ppm for up to 104 weeks.[7] Exposure of pregnant CDR rats to 0.03, 0.33, 2.8, or 4.9 ppm 6 hours/day during gestation days 6–15 was not maternally or developmentally toxic.[8]

Phosphine has a fishy or garliclike odor detectable at 2 ppm; the odor threshold does not provide sufficient warning of dangerous concentrations.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for phosphine is 0.3 ppm (0.42 mg/m^3) with a short-term excursion limit (STEL) of 1 ppm (1.4 mg/m^3).

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3. Garry VF, Griffith J, Danzl TJ, et al: Human genotoxicity: Pesticide applicators and phosphine. *Science* 246:251–255, 1989
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PHOSPHORIC ACID
CAS: 7664-38-2

H_3PO_4

Synonyms: Orthophosphoric acid; white phosphoric acid

Physical Form. Crystals or colorless liquid

Uses. Manufacture of fertilizers, detergents, dental cements, pharmaceuticals, foods, and beverages; also found in electropolishing, engraving, sugar refining, and water treatment industries

Exposure. Inhalation

Toxicology. Phosphoric acid mist is a mild irritant of the eyes, upper respiratory tract, and

skin; the dust is especially irritating to skin in the presence of moisture.[1]

The hazards associated with occupational exposure to phosphoric acid depend on its acidic nature.[2] Concentrated phosphoric acid is corrosive to exposed tissue, and lower concentrations are irritating to the skin, eyes, and mucous membranes. Phosphoric acid has a low vapor pressure at room temperature and is unlikely to present an inhalation hazard unless introduced into the atmosphere as a spray or mist.[2] Unacclimated workers could not endure exposure to fumes of phosphorus pentoxide (the anhydride of phosphoric acid) at a concentration of 100 mg/m^3; exposure to concentrations between 3.6 and 11.3 mg/m^3 produced cough, whereas concentrations of 0.8–5.4 mg/m^3 were noticeable but not uncomfortable.[3]

It has been noted that phosphorus pentoxide is a powerful dehydrating agent that combines with moisture in the respiratory tract to produce phosphoric acid in an exothermic reaction; because this reaction generates heat and desiccates tissues it contacts, it is likely to cause more tissue damage than preformed phosphoric acid.[2] There is no evidence that phosphorus poisoning can result from contact with phosphoric acid.[4] The risk of pulmonary edema resulting from the inhalation of mist or spray is remote.[4] A subcohort of workers from 16 phosphate companies who were occupationally exposed to unspecified amounts of phosphoric acid had no significant increase in cause-specific mortality.[5]

Ingestion of concentrated solutions can produce nausea, vomiting, abdominal pain, hematemesis, bloody diarrhea, and burns of the mouth, esophagus, and stomach.[6] In one case, death occurred 19 days after ingestion as a result of recurrent internal hemorrhage; at autopsy there was necrosis of the upper and lower digestive tract and of the pancreas.[3] In some cases signs of obstruction and scarring may occur weeks to months after initial exposure.[6]

A dilute solution buffered to pH 2.5 caused a moderate brief stinging sensation but no injury when dropped in the human eye.[7] A 75% solution will cause severe skin burns.[1]

Phosphoric acid was not mutagenic in bacterial assays.[2]

The 2003 threshold limit value-time-weighted average (TLV-TWA) for phosphoric acid is 1 mg/m^3 with a short-term excursion limit (STEL) of 3 mg/m^3.

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PHOSPHORUS (Yellow)
CAS: 7723-14-0

P_4

Synonyms: Phosphorus (white)

Physical Form. Yellowish or colorless transparent crystals that darken on exposure to light

Uses/Sources. Manufacture of rat poisons; for smoke screens; gas analysis; fireworks; in ammunitions such as mortar, artillery shells, and grenades; the elemental material is produced as a by-product in the production of phosphate fertilizer; it does not occur in the elemental state in nature

Exposure. Inhalation

Toxicology. Yellow phosphorus fume is an irritant of the respiratory tract and eyes; the solid in contact with the skin produces deep thermal burns. Prolonged absorption of phosphorus causes necrosis of facial bones.

Yellow phosphorus burns spontaneously in air, and the vapor released is irritating to the respiratory tract. The early signs of systemic intoxication by phosphorus are abdominal pain, jaundice, and a garlic odor of the breath; prolonged intake may cause anemia, as well as cachexia and necrosis of bone, involving typically the maxilla and mandible (phossy jaw).[1–4] In chronic phosphorus intoxication, lowered potassium blood levels or increased chloride concentrations along with leukopenia have also been reported.[5]

The presenting complaints of overexposed workers may be toothache and excessive salivation. There may be a dull red appearance of the oral mucosa. One or more teeth may loosen, followed by pain and swelling of the jaw; healing may be delayed after dental procedures such as extractions; with necrosis of bone, a sequestrum may develop with sinus tract formation.[2] In a series of 10 cases, the shortest period of exposure to phosphorus fume (concentrations not measured) that led to bone necrosis was 10 months (2 cases), and the longest period of exposure was 18 years.[2]

Although ingestion would not be expected in an occupational setting, the human lethal oral dose is about 1 mg/kg body weight.[5]

Acute oral intoxication is characterized by an initial phase in which gastrointestinal effects such as nausea and vomiting predominate, followed by an apparent recovery period lasting up to 2 days, which in turn is followed by the return of gastrointestinal symptoms plus signs of hepatic renal and cardiovascular involvement.

Yellow phosphorus fume causes severe eye irritation with blepharospasm, photophobia, and lacrimation; the solid in the eye produces severe injury.[6] Phosphorus burns on the skin are deep and painful; a firm eschar is produced and is surrounded by vesiculation.[7]

In limited testing phosphorus was not mutagenic in bacterial assays.[8] There is no information in humans or animals regarding the carcinogenicity of phosphorus.[8]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for yellow phosphorus is 0.02 ppm (0.1 mg/m^3).

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8. Agency for Toxic Substances and Disease Registry (ASTDR): *Toxicological Profile for White Phosphorus*, 208pp. US Department of Health and Human Services, Public Health Service, 1997

PHOSPHORUS OXYCHLORIDE

CAS: 10025-87-3

$POCl_3$

Synonyms: Phosphoryl chloride; phosphoryl trichloride

Physical Form. Colorless liquid

Uses/Sources. In the manufacture of pesticides, pharmaceuticals, plasticizers, gasoline additives, and hydraulic fluid

Exposure. Inhalation

Toxicology. Phosphorus oxychloride is strongly irritating to the skin, eyes, and respiratory tract.

Exposure to the vapors can cause cough, painful inflammation of the eyes, burning in the nose and throat, shortness of breath, and, in severe exposures, death.[1] Both chronic and acute cases of occupational exposures have been reported in the foreign literature.[2]

Single exposure of humans to airborne material has been reported to cause conjunctivitis, pharyngitis, and respiratory tract irritation, including pulmonary edema.[3] No reliable threshold concentration for these effects is available. Similar effects were seen after repeated exposure including asthmatic bronchitis and, in severe cases, emphysema. Exposure levels were 10–20 mg/m^3, rising to 70 mg/m^3 and sometimes to higher levels.[3] The 4-hour LC_{50} values for rats and guinea pigs were 48 and 53 ppm, respectively.[1] During exposure the animals were restless and showed signs of irritation such as pawing and scratching of the nose and head. Gasping and convulsions preceded death, which occurred within 48 hours of exposure. Signs of toxicity gradually abated in surviving animals and were not evident at the end of the 14-day observation period. Microscopic examination of tissues from animals that died showed desquamation of the tracheal and bronchial epithelium resulting in plugging of the lumen of the bronchioles. The alveolar spaces surrounding these lumen plugs became edematous and hemorrhagic. Surviving animals had no lesions attributable to phosphorus oxychloride when autopsied 14 days after exposure.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for phosphorus oxychloride is 0.1 ppm (0.63 mg/m^3).

REFERENCES

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PHOSPHORUS PENTACHLORIDE

CAS: 10026-13-8

PCl_5

Synonyms: Phosphoric chloride; phosphorus perchloride

Physical Form. White to pale yellow fuming crystalline mass with pungent, unpleasant odor

Uses. Catalyst in manufacture of acetylcellulose; chlorinating and dehydrating agent

Exposure. Inhalation

Toxicology. Phosphorus pentachloride fume is a severe irritant of the eyes and mucous membranes.

In humans, the fume causes irritation of the eyes and respiratory tract; cases of bronchitis have resulted from exposure.[1] Although not reported, delayed onset of pulmonary edema may occur. The material on the skin

would be expected to cause dermatitis or ulceration.

Exposure of mice to 120 ppm for 10 minutes was fatal.[2]

The oral LD_{50} in rats is 660 mg/kg, and the inhalation LC_{50} for 4 hours is 205 mg/m^3.[3]

Phosphorus pentachloride is expected to produce 67% more hydrogen chloride than an equimolar amount of phosphorus trichloride.[2] Accordingly, the ACGIH threshold limit value-time-weighted average (TLV-TWA) for phosphorus pentachloride is 0.1 ppm (0.85 mg/m^3) (half that of phosphorus trichloride).

REFERENCES

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PHOSPHORUS PENTASULFIDE

CAS: 1314-80-3

P_2S_5

Synonyms: Phosphorus sulfide; phosphorus persulfide; phosphorus sulfide, thiophosphoric anhydride

Physical Form. Light yellow to greenish crystals

Uses. Intermediate in the manufacture of safety matches, ignition compounds, and lubricant additives

Exposure. Inhalation

Toxicology. Phosphorus pentasulfide is an irritant of the eyes, skin, and respiratory tract.

There is very little information on the toxicity of phosphorus pentasulfide.[1] Irritancy of the respiratory tract would be expected because the substance is rapidly hydrolyzed to phosphoric acid and hydrogen sulfide; pulmonary irritation is expected at concentrations of 10 mg/m^3.[2]

The oral LD_{50} in rats was 389 mg/kg; 500 mg applied to rabbit skin for 24 hours was moderately irritating, and 20 mg instilled in rabbit eyes for 24 hours was severely irritating.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for phosphorus pentasulfide is 1 mg/m^3 with a short-term excursion limit (STEL)/ceiling of 3 mg/m^3.

REFERENCES

1. Payne MP, Shillaker RO, Wilson AJ: Phosphoric acid, phosphorus pentoxide, phosphorus oxychloride, phosphorus pentachloride, phosphorus pentasulfide. *HSE Toxicity Rev* 30: 1–22, 1993
2. Smyth HF Jr: Improved communication—hygienic standards for daily inhalation. *Am Ind Hyg Assoc J* 17:129–185, 1956
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PHOSPHORUS TRICHLORIDE

CAS: 7719-12-2

PCl_3

Synonym: Phosphorus chloride

Physical Form. Colorless, clear, fuming liquid

Uses. As chlorinating agent; manufacture of other phosphorus chloride compounds; producing iridescent metallic deposits

Exposure. Inhalation

Toxicology. Phosphorus trichloride vapor is a severe irritant of the eyes, mucous membranes, and skin.

The irritant effects of phosphorus trichloride result primarily from the action of the strong acids (hydrochloric acid and acids of phosphorus) formed on contact with water.[1]

Inhalation by humans could be expected to cause injury ranging from mild bronchial spasm to severe pulmonary edema; the onset of severe respiratory symptoms may be delayed for 2–6 hours, and, after moderate exposure, the onset may not occur until 12–24 hours later.[1] Prolonged or repeated exposure to low concentrations may induce chronic cough and wheezing; pulmonary changes are nonfibrotic and nonprogressive.

Phosphorus trichloride causes severe burns in contact with the eyes, skin, or mucous membranes.[1] Although ingestion is unlikely to occur in industrial use, it will cause burns of the mouth, throat, esophagus, and stomach.[2]

Seventeen people exposed to phosphorus trichloride liquid and its hydration products after a tanker accident were evaluated.[3] Those closest to the spill experienced burning of the eyes, lacrimation, nausea, vomiting, dyspnea, and cough. Six patients had transient elevation of lactic dehydrogenase. Chest roentgenograms were normal. Pulmonary function tests showed statistically significant decreases in vital capacity and FEV_1 in direct correlation with distance from the accident and duration of exposure. Of the 17 patients examined 1 month later, pulmonary function tests showed improvement, suggesting that acute effects were due to phosphorus trichloride toxicity.[3]

In rats, the LC_{50} was 104 ppm for 4 hours; at autopsy, the chief finding was nephrosis; pulmonary damage was negligible.[2]

The 2003 ACGIH threshold limit value-time-weighted average TLV-TWA for phosphorus trichloride is 0.2 ppm (1.1 mg/m^3) with a short-term excursion limit (STEL)/ceiling of 0.5 ppm (2.8 mg/m^3).

REFERENCES

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PHTHALIC ANHYDRIDE

CAS: 85-44-9

$C_6H_4(CO)_2O$

Synonyms: Phthalic acid anhydride; phthalandione; 1,3-isobenzofurandione

Physical Form. White crystalline solid

Uses. Production of plasticizers for vinyl, epoxy, and acetate resins; in alkyd resins; manufacture of dyes

Exposure. Inhalation

Toxicology. Phthalic anhydride is an irritant of the eyes, skin, and respiratory tract; it may also act as a sensitizer.

In workers, air concentrations of 30 mg/m^3 (5 ppm) caused conjunctivitis; at 25 mg/m^3 (4 ppm), there were signs of mucous membrane irritation.[1] Workers exposed to undetermined concentrations of mixed vapors of phthalic acid and phthalic anhydride developed, in addition to conjunctivitis, bloody nasal discharge, atrophy of the nasal mucosa, hoarseness, cough, occasional bloody sputum, bronchitis, and emphysema.[2] Several cases of bronchial

asthma resulted; there was also skin sensitization with occasional urticaria and eczematous response.

Phthalic anhydride is a direct but delayed irritant of the skin; it is more severely irritating after contact with water, because of the pronounced effects of the phthalic acid that is formed.[1] Prolonged or repeated exposure also may cause an allergic type of skin rash. Because phthalic anhydride is a known pulmonary and skin irritant, it is often difficult to differentiate between sensitization and irritation by clinical history.[3]

A group of 23 phthalic anhydride-exposed workers (air levels up to 17 mg/m^3) had more work-related symptoms in their eyes and nose than 18 unexposed controls.[4] The exposed workers also had significantly higher levels of total IgE than controls, although values for specific IgE against phthalic anhydride did not differ. The investigators suggested that the irritant effect of phthalic anhydride on the mucous membranes facilitated the entry of other allergens, causing an increase in serum IgE levels. Lung function tests did not reveal any significant impairment of large or small airways.

In another report, a worker who developed symptoms of rhinorrhea, lacrimation, and wheezing from exposure to phthalic anhydride over a period of a year was shown to have a positive patch test to the chemical and a high serum titer of specific IgE.[5]

A case of asthma was attributed to the release of phthalic anhydride during the grinding of cured moldings.[6] Unreacted phthalic anhydride may be trapped within cured resin and released during grinding, or, alternatively, heat generated during grinding may lead to disruption of bonds between the resin and the hardener and cause release of phthalic anhydride vapor.[6]

In 2-year feeding studies, phthalic anhydride was not carcinogenic to rats or mice.[7]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for phthalic anhydride is 1 ppm (6.1 mg/m^3).

REFERENCES

1. Hygienic Guide Series: Phthalic anhydride. *Am Ind Hyg Assoc J* 28:395–398, 1967
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m-PHTHALODINITRILE

CAS: 626-17-5

$C_8H_4N_2$

Synonyms: 1,3-Benzenedicarbonitrile; 1,3-dicyanobenzene; isophthalonitrile

Physical Form. Light tan powder

Uses. An intermediate in the manufacture of paints, varnishes, and agricultural chemicals

Exposure. Inhalation

Toxicology. *m*-Phthalodinitrile is a skin irritant in animals.

In humans there have been no reports of adverse effects. The probable reason for lack of systemic effects is that aromatic, unlike aliphatic, nitriles do not liberate cyanide in the body.

The oral LD_{50} values for rats, cats, and rabbits was 5000, 500, and 250 mg/kg, respectively.[1] Rats exposed to 190 or 1250 mg/m^3 6 hours/day for 2 weeks had decreased food consumption and reduced body weight.[2] Alopecia was observed in the low-dose group and rhinorrhea occurred in the high-dose animals. Pathologic examination did not reveal any treatment related effects. Slight skin reactions were observed after topical application to rabbits.

The 2003 ACGIH threshold limit value-time weighted average(TLV-TWA) for *m*-phthalodinitrile is 5 mg/m^3.

REFERENCES

1. Zeller H, Hofmann HTH, Thiess AM, et al: Toxicity of nitriles: Results of experiments carried out on animals as well as occupational health experiences made during 15 years. *Zentralbl Arbeitsmed Arbeitschtz* 19:226–238, 1969
2. ACGIH: *m*-Phthalodinitrile. *Documentation of the TLVs and BEIs*, 6th ed, pp 1266–67. Cincinnati, OH, American Conference of Governmental Industrial Hygienists, 1991

PICRIC ACID
CAS: 88-89-1

$C_6H_2(NO_2)_3OH$

Synonyms: 2,4,6-Trinitrophenol; carbazotic acid; picronitric acid

Physical Form. Yellow crystalline solid

Uses. High explosive; oxidant in rocket fuels; processing of leather; metal etching

Exposure. Inhalation

Toxicology. Picric acid causes sensitization dermatitis; absorption of large amounts causes liver and kidney damage.

Dermatitis from skin contact with the chemical usually occurs on the face, especially around the mouth and the sides of the nose; the condition progresses from edema, through the formation of papules and vesicles, to ultimate desquamation.[1,2] The skin and hair of workers handling picric acid may be stained yellow.[1]

Inhalation of high concentrations of the dust by one worker caused temporary coma followed by weakness, myalgia, anuria, and later polyuria.[3] After ingestion of 2–5 g of picric acid, which has a bitter taste, there may be headache, vertigo, nausea, vomiting, diarrhea, yellow coloration of the skin, hematuria, and albuminuria; high doses cause destruction of erythrocytes, hemorrhagic nephritis, and hepatitis.[3,4]

High doses that cause systemic intoxication will color all tissues yellow, including the conjunctiva and aqueous humor, and cause apparent yellow vision.[5] Corneal injury is stated to have resulted from a splash of a solution of picric acid in the eyes; dust or fume may cause eye irritation, which may be aggravated by sensitization.[5]

The LD_{50} values for picric acid after oral dosing of male and female rats were 290 and 200 mg/kg, respectively.[6] Death was due to severe acidosis, with toxic doses of picric acid exceeding the buffering capacity of the blood. In rats, metabolism of picric acid is primarily limited to reduction of nitro groups of the aromatic ring and subsequent conjugation by acetate.

Picric acid was mutagenic in the Ames *Salmonella* assay in the presence of metabolic activation.[7]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for picric acid is 0.1 mg/m^3.

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PINDONE
CAS: 83-26-1

$C_{14}H_{14}O_3$

Synonyms: Pival; Pivalyl Valone; Tri-Ban; 2-pivaloyl-1,3-indanedione

Physical Form. Yellow powder

Uses. Rodenticide

Exposure. Inhalation; ingestion

Toxicology. Pindone is a vitamin K antagonist and causes inhibition of prothrombin formation, which results in hemorrhage.

There are no reports of effects in humans.

In rats, the ingestion of a single large dose of pindone causes rapid death due to pulmonary and visceral congestion without hemorrhage and may not be related to vitamin K antagonism.[1] Death in animals from chronic exposure is due to multiple internal hemorrhage.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for pindone is 0.1 mg/m^3.

REFERENCE

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PIPERAZINE DIHYDROCHLORIDE
CAS: 142-64-3

$C_4H_{12}N_2Cl_2$

Synonyms: Dihydrochloride salt of diethylenediamine; piperazidine hydrochloride

Physical Form. White crystalline solid

Uses. In the manufacture of fibers, pharmaceuticals, and insecticides

Exposure. Inhalation

Toxicology. Piperazine dihydrochloride is an irritant and sensitizer.

Little information exists on the toxicology of piperazine dihydrochloride in humans or in animals. Acute human exposures to the dust have reportedly resulted in irritation to the eyes, mild to moderate skin burns, and sensitization.[1] Exposure levels and duration were not available. Occupational exposures have been associated with occasional cases of asthma. In one factory, several cases of asthma were precipitated by a time-weighted average (TWA) exposure of 1.2 mg/m^3, although there were brief exposure peaks of 100 mg/m^3 or higher.[2] There were no new cases noted in a workplace

where the average concentration was 0.3 mg/m^3. It is unclear whether the total dose or the brief high exposure was critical to asthma induction.

The systemic toxicity appears to be low; the oral LD_{50} for rats was approximately 4.9 g/kg.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for piperazine dihydrochloride is 5 mg/m^3.

REFERENCES

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PLATINUM (and Soluble Salts)
CAS: 7440-06-4

Pt

Compounds: Ammonium chloroplatinate; sodium chloroplatinate; platinic chloride; platinum chloride; sodium tetrachloroplatinate; potassium tetrachloroplatinate; ammonium tetrachloroplatinate; sodium hexachloroplatinate; potassium hexachloroplatinate; ammonium hexachloroplatinate

Physical Form. Crystalline solids

Uses. Jewelry; oxygen sensor in internal combustion engines; chemical and electrical industries; dentistry; windings of high-temperature furnaces; electroplating; photography; cancer chemotherapeutic agents

Exposure. Inhalation

Toxicology. Exposure to the complex salts of platinum, especially ammonium hexachloroplatinate and ammonium tetrachloroplatinate, but not elemental platinum, may cause skin sensitization and a progressive allergic reaction that may lead to pronounced asthmatic symptoms.

The signs and symptoms of hypersensitivity include urticaria, contact dermatitis of the skin, and respiratory disorders ranging from sneezing, shortness of breath, and cyanosis to severe asthma.[1] The latency period from the first contact with platinum to the occurrence of the first symptoms varies from a few weeks to several years.[1]

A syndrome characterized by runny nose, sneezing, tightness of the chest, shortness of breath, cyanosis, wheezing, and cough has been described after exposure to soluble complex platinum salts and is referred to variously as platinum allergy, platinum asthma, and platinosis.[2,3] Of 91 men employed in four platinum refineries and exposed to the dust or spray of the complex platinum salts, 52 experienced these symptoms.[2] The severity of response was greatest in workers crushing platinum salts, where airborne levels reached 1.7 mg/m^3. Thirteen of the men also complained of dermatitis. Contact dermatitis has also been said to occur from exposure to platinum oxides and chlorides.[4] Removal from platinum salt exposure results in almost immediate relief of asthma; the dermatitis usually clears in 1–2 days but may be persistent.[4] However, if long-duration exposure occurs after sensitization, individuals may never become completely free of symptoms.[1]

Smokers have been found to be at increased risk of sensitization by platinum salts.[5] An historical perspective cohort study of 91 platinum refinery workers showed a four- to fivefold risk of developing a positive skin test to platinum salts in smokers. The risk of smokers developing symptoms was approximately twofold, and, among recent employees, the rate of development of a positive skin test result was faster in smokers versus nonsmokers. Smoking is thought to act by increasing the serum levels of IgE. In another report, 78 newly hired refinery workers were followed for 24 months; platinum salt sensitivity developed in 41% of the new hires.[6] Smoking was found to increase the risk of platinum salt sensitivity

eightfold compared with not smoking and being exposed to platinum salts above the threshold limit value (TLV) increased the risk by sixfold compared with exposures below the TLV.

The assumption that platinosis is due to an allergic response rather than to toxic or irritant effects is suggested by the following: (1) the appearance of sensitivity after previous exposure without apparent effect; (2) only a fraction of exposed persons exhibit a response; and (3) affected subjects show increasingly high degrees of sensitivity to small amounts.[7] The potent allergenicity of the divalent and tetravalent platinum compounds is thought to occur by conjugation with sulfhydryl-containing groups within proteins, thus forming immunogenic complexes.[8] Complexes where there are no halogen ligands coordinated to platinum ("nonhalogenated complexes"), such as $K_2[Pt(NO_2)_4]$, $[Pt(NH_3)_4]C_{12}$, and $[Pt(NH_2)_2CS_4]C_{12}$, and neutral complexes such as *cis*-$[PtC_{12}(NH_3)_2]$, are not allergenic, because they probably do not react with proteins to form a complete antigen.[1]

Solid platinum wire or foil is considered to be biologically inert.[1]

In the eyes, the dusts cause a burning sensation, lacrimation, and conjunctival hyperemia, sometimes associated with photophobia.[9]

Several platinum compounds have been found to be mutagenic in bacterial assays.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 1.0 mg/m^3 for the metal dust and 0.002 mg/m^3 for the soluble salts as Pt.

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POLYBROMINATED BIPHENYLS

Hexabromobiphenyl: $C_{12}H_4Br_6$
Technical grades:
FireMaster BP-6 (CAS: 59536-65-1)
FireMaster FF-1 (CAS: 67774-32-7)

Octabromobiphenyl $C_{12}H_2Br_8$
Technical grade:
Bromkal 80 (CAS: 61288-13-9)

Decabromobiphenyl $C_{12}Br_{10}$
Technical grade:
Flammex B-10 (CAS: 13654-09-6)

Physical Form. Solids

Uses. Polybrominated biphenyls (PBBs) are compounds that were formerly used as flame retardants in electrical products and in business machines and motor housings. There are 209 possible bromobiphenyl congeners, although only a small number have been synthesized and used. All of the commercial products contained a mixture of several individual PBBs. Commercial production ceased in 1977.

Exposure. Inhalation; ingestion; skin absorption

Toxicology. PBBs are animal carcinogens, with the liver being the main organ affected.

The majority of the human toxicity data of PBBs stem from studies carried out after accidental addition of PBBs to farm feed in Michigan in 1973, resulting in exposure of large numbers of the rural population of Michigan by ingestion of PBB-contaminated food. Higher rates of dermatological, neurological, and musculoskeletal disorders were reported in a group of 933 Michigan farmers and residents than in 229 unexposed Wisconsin farmers considered as controls.[1] These included rashes, acne, darkening or thickening of the skin, erythema, and hair loss.

A high prevalence of abnormal liver functions tests (SGOT and SGPT) was observed among 614 Michigan adults compared with 141 Wisconsin adults considered as controls.[2]

A group of 55 workers who had been employed in the Michigan plant producing FireMaster BP-6 from 1970 to 1974 were examined, and all were found to have serum levels of PBBs greater than 1 mg/l.[3] An increased prevalence of respiratory symptoms and skin disorders was seen in this group compared with the available data on PBB-exposed farmers 1in Michigan.

Animal studies have shown that oral exposure to FireMaster PBB causes a wasting syndrome characterized by progressive decreased weight gain, with immediate moderate to severe body weight loss generally preceding death.[4]

The thyroid gland is a target organ in animals, although strong evidence for an effect in humans is lacking.[4] In rats exposed for acute and intermediate durations, effects have been decreases in serum levels of thyroxine and triiodothyronine along with histologic and ultrastructural changes in the thyroid. Hematologic changes indicative of anemia have also been reported as well as effects on the liver, skin, and stomach.

When administered by oral gavage for 6 months at 10 mg/kg, technical-grade hexabromobiphenyl (FireMaster FF-1) induced hepatocellular carcinomas in mice and rats of both sexes and cholangiocarcinomas and neoplastic nodules of the liver in rats of both sexes.[5]

In general, PBBs have been negative in genotoxic assays both *in vivo* and *in vitro*.[4]

The IARC considers that there is "sufficient evidence" that PBB is carcinogenic to experimental animals.[6]

Adverse effects on endocrine function and reproductive organs have been found in animal studies, including blockage of implantation when administered to rats on gestation days 0–14.[4] Follow-up of a cohort of daughters born to mothers enrolled in the Michigan PBB Exposure Registry found age at menarche was approximately 6 months earlier for girls who were in the upper decile of PBB exposure in utero and had been breast-fed compared with girls whose in utero exposure was less than or equal to 1 ppb.[7]

A threshold limit value-time-weighted average (TLV-TWA) for polybrominated biphenyls has not been assigned.

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POLYTETRAFLUOROETHYLENE DECOMPOSITION PRODUCTS

CAS: 9002-84-0

Perfluoroisobutylene

CAS: 382-21-8

Carbonyl fluoride

CAS: 353-50-4

$(CF_2CF_2)_{n=ca\ 1000}$

Synonyms: Teflon; Algoflon; Fluon; Tetran; PTFE

Physical Form. Grayish-white plastic

Uses. As a coating on cooking utensils, reaction vessels, and other industrial applications to prevent sticking

Exposure. Inhalation

Toxicology. Fumes of heated polytetrafluoroethylene (PTFE) cause polymer fume fever, an influenza-like syndrome.

When PTFE is heated to between 315°C and 375°C, the fumes cause influenza-like effects, including chills, fever, and tightness of the chest, that last 24–48 hours.[1,2] Symptoms suggestive of pulmonary edema, including shortness of breath and chest discomfort, have been observed in a few instances.[3] Although complete recovery usually occurs within 12–48 hours, a case of fatal acute pulmonary edema after exposure to the pyrolytic products of PTFE has also been reported.[4] Presenting symptoms were cough, dyspnea, abdominal fullness, and vomiting. A radiograph revealed diffuse bilateral pulmonary infiltrates. Despite incubation and mechanical ventilation, the patient developed severe hypoxemia and ventricular tachycardia and died 5 hours later.

Multiple episodes of PTFE-induced inhalation fever over an 18-month period were associated with marked progression of chronic obstructive pulmonary disease in a carding machine operator.[5] Permanent airway damage may occur in some individuals after repeated instances of polymer fume fever.

In rats, the LC_{50} dose for PTFE heated at 595°C was 45 mg/m^3 for a 30-minute exposure.[6] Conjunctival erythema and serous ocular and nasal discharge were observed immediately after exposure. Clinical signs included dyspnea, hunched posture, and lethargy. Pathologic findings included focal hemorrhages, edema, and fibrin deposition in the lungs. Disseminated intravascular coagulation developed in more than half the test animals, and its incidence and severity closely paralleled pulmonary damage.

The decomposition products, up to a temperature of 500°C, are principally the monomer, tetrafluoroethylene, but also include perfluoropropene, other perfluro compounds containing four or five carbon atoms, and an unidentified particulate waxy fume.[7] From 500°C to 800°C, the pyrolysis product is carbonyl fluoride, which can hydrolyze to form HF and CO_2.

Experiments with rodents have shown that the PTFE pyrolysis particles rather than toxic gases are the toxic agent causing pulmonary edema and hemorrhage.[8] Mortality of rats was prevented by removal of the submicron particles by filtration, even though the concentration of the measured toxic gases was not significantly decreased.

PTFE implanted subcutaneously in animals has induced local sarcomas, suggesting a foreign body reaction rather than chemical carcinogenesis; the IARC has determined that there is insufficient evidence to assess the carcinogenic risk, especially with regard to occupational exposure in humans.[9]

There is no assigned threshold limit value (TLV) for polytetrafluoroethylene, but air concentrations should be kept as low as possible.

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PORTLAND CEMENT

CAS: 65997-15-1

Portland cement refers to a class of hydraulic cements in which the two essential constituents are tricalcium silicate ($3CaO{\cdot}SiO_2$) and dicalcium silicate ($2CaO{\cdot}SiO_2$) with varying amounts of alumina, tricalcium aluminate, and iron oxide. It is insoluble in water. The quartz content of most finished cements is below 1%. Chromium may be present.

Physical Form. Solid

Use. Cement

Exposure. Inhalation

Toxicology. Portland cement is an irritant of the eyes and causes dermatitis.

Repeated and prolonged skin contact with cement can result in dermatitis of the hands, forearms, and feet; this is a primary irritant dermatitis and may be complicated in some instances by a secondary contact sensitivity to hexavalent chromium.[1] In a study of 95 cement workers, 15 had a mild dermatitis of the hands, which consisted of xerosis with erythema and mild scaling; of 20 workers who were patch tested with 0.25% potassium dichromate, one person had a mild reaction and the others were negative.

In a survey of 2278 cement workers, it was concluded that exposure to the dust of finished Portland cement caused no significant findings on chest roentgenograms, even after heavy and prolonged exposures.[2] However, in a follow-up study of 195 of these workers after further exposure of 17–20 years, 13 showed increases in lung markings on roentgenograms; an additional 6 workers who had been exposed largely to raw dusts that contained varying amounts of free silica had marked linear exaggeration with ill-defined micronodular shadows but no symptoms referable to the chest.[3]

In contrast, a study of 847 cement workers with at least 5 years of exposure to massive levels ranging up to 3020 mppcf in cement plants revealed that symptoms such as cough, expectoration, exertional dyspnea, wheezing, and chronic bronchitis syndromes were consistently more frequent than in a group of 460 control workers; a higher prevalence of these symptoms was also found in nonsmokers exposed to cement than in a control group of nonsmokers. It should be emphasized that these exposures were to cement dust not of Portland type.[3,4]

In a cross-sectional study of 2736 Portland cement workers and 755 controls, there were no significant differences in symptoms, except that 5.4% of the cement workers had dyspnea, compared with 2.7% of the controls.[5] The mean pulmonary function indices were similar for the two groups. The mean exposure concentrations were 0.57 mg/m^3 for respirable dust (ranging up to 46 mg/m^3) and 2.90 mg/m^3 for total dust (ranging up to 78.61 mg/m^3). The authors concluded that a close relation between exposure to cement plant dust at levels existing in the US and respiratory symptoms or ventilatory function is lacking.[5] Standard postero/anterior chest X rays obtained from these same workers and reported in a later study showed rounded and irregular opacities and pleural abnormality prevalence rates that were significantly elevated only among cement workers who currently smoked.[6]

The relation between exposure to Portland cement dust and cancer was examined in a population of 546 workers who had been exposed at some time before 1974 for 1 or more years. No increased risk of overall cancer, respiratory cancer, or stomach cancer was found among the cement workers compared with a referent population.[7]

Earlier studies have suggested increases in various types of cancer, including lung and stomach, with exposure to cement, but numerous limitations prevent any conclusions in this regard.[8–10]

A cohort study of nonsmoking Portland cement workers found a significant increase in sister chromatid exchange (SCE) incidences in peripheral blood lymphocytes.[11] The group mean SCE frequency in the cement workers and controls was 8.88% and 3.52%, respectively. When the SCE frequencies in the cement workers were stratified according to years of employment, they increased with increasing years of employment in the cement industry, from 6.98% for those employed for 1–5 years to 10.74% for those employed for 12–17 years. The authors concluded that Portland cement was clearly clastogenic, but because it is composed of a number of components including silicates, aluminates, and lime, it is difficult to identify which particular compound(s) is responsible for its clastogenicity.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for Portland cement is 10 mg/m^3 for total dust containing no asbestos and <1% crystalline silica.

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POTASSIUM HYDROXIDE
CAS: 1310-58-3

KOH

Synonyms: Caustic potash; KOH

Physical Form. White solid, usually as lumps, rods, or pellets

Uses. Strong alkali; manufacture of soft and liquid soaps; manufacture of potassium carbonate for use in manufacture of glass

Exposure. Inhalation

Toxicology. Potassium hydroxide is a severe irritant of the eyes, mucous membranes, and skin.

The effects of potassium hydroxide are similar to those of other strong alkalies such as sodium hydroxide. The greatest industrial hazard is rapid tissue destruction of eyes or skin on contact either with the solid or with concentrated solutions.[1] Contact with the eyes causes disintegration and sloughing of conjunctival and corneal epithelium, corneal opacification, marked edema, and ulceration.[2] After 7–13 days, either gradual recovery begins or there is progression of ulceration and corneal opacification, which may become permanent. If potassium hydroxide is not removed from the skin, severe burns with deep ulceration will occur.

In the rabbit eye, a 5% solution was corrosive and a 0.1% solution had no effect.[3] Applied to the skin of laboratory rodents, a 5% solution was highly corrosive.[3]

Although inhalation is usually of secondary importance, the effects from the dust or mist will vary from mild irritation to severe pneumonitis, depending on the severity of exposure.[1] Ingestion produces severe abdominal pain, corrosion of the lips, mouth, tongue, and pharynx, and the vomiting of large pieces of mucosa. In severe cases, circulatory failure, esophageal perforation, and peritonitis may occur.

The 2003 short-term excursion limit (STEL)/ceiling limit for potassium hydroxide is 2 mg/m^3.

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PROPANE
CAS: 74-98-6

C_3H_8

Synonyms: Dimethylmethane; propyl hydride

Physical Form. Colorless, odorless gas

Uses. Fuel gas; refrigerant; in organic synthesis

Exposure. Inhalation

Toxicology. Propane is a simple asphyxiant. The determining factor in exposure is available oxygen. Minimal oxygen content of air in the workplace should be 18% by volume under normal atmospheric pressure, equivalent to pO_2 of 135 mmHg.[1]

Concentrations of oxygen in the inspired air of 12–16% cause tachypnea, tachycardia, and slight incoordination.[2] Air containing 6–10% oxygen causes nausea, lethargic movements, and unconsciousness; breathing less than 6% oxygen produces convulsions, followed by apnea and cardiac arrest.[2]

Exposure to 100,000 ppm propane for a few minutes produced slight dizziness in volunteers but was not noticeably irritating to the eyes, nose, or respiratory tract.[3] No adverse effects were reported in humans exposed to

10,000 ppm for 10 minutes or after exposure to 1,000 ppm 8 hours/day for 9 days.

Intentional inhalation of 95% propane for approximately 1 minute produced feelings of euphoria, ataxia, and light-headedness; death, possibly due to hypoxemia secondary to propane inhalation, has been reported.[4,5] A recent study has also suggested that propane may have direct toxic effects (besides asphyxia from hypoxia) that may lead to death in some cases.[6] Specifically, when some oxygen continues to be available during prolonged exposure unconsciousness may be induced by direct central nervous system suppressive effects of propane.

Guinea pigs exposed at 47,000–55,000 ppm had tremors within 5 minutes and nausea, retching, and stupor after 30–120 minutes. No effects were observed in monkeys exposed to approximately 750 ppm for 90 days.[7]

Direct contact with the liquefied product causes burns and frostbite.[8]

Propane is odorless, and atmospheres deficient in oxygen do not provide adequate warning.[1]

The 2003 ACGIH threshold limit value-time weighted average (TLV-TWA) for propane is 2500 ppm (4508 mg/m^3)

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PROPANE SULTONE

CAS: 1120-71-4

$C_3H_6O_3S$

Synonyms: 1,3-Propane sultone; 3-hydroxy-1-propanesulfonic acid sultone; 1,2-oxathrolane 2,2-dioxide

Physical Form. White crystals or colorless liquid

Uses. Chemical intermediate to confer water solubility and anionic properties

Exposure. Inhalation

Toxicology. Propane sultone is a carcinogen in experimental animals and a suspected human carcinogen. No human data are available.[1]

It is a carcinogen in rats when given orally, intravenously, or by prenatal exposure and a local carcinogen in mice and rats when given subcutaneously.[1]

In rats, twice-weekly oral doses by gavage of 56 mg/kg for 32 weeks or 28 mg/kg for 60 weeks resulted in several malignant manifestations, including tumors of the brain, ear duct, and small intestine and leukemia.[2,3]

In mice, weekly subcutaneous injection of 0.3 mg caused tumors at the injection site in 21 of 30 mice, compared with no tumors in 30 controls.[4] Weekly subcutaneous injection of 15 and 30 mg/kg in rats resulted in death of 7 of 12 and 11 of 11 animals, respectively, with local sarcomas.[2,5] A single subcutaneous dose of 100 mg/kg produced local sarcomas in all of

18 treated rats. A single intravenous dose of 150 mg/kg in 32 rats caused the death of 1 rat with a brain tumor after 235 days and death of 9 others with malignant tumors of a variety of sites within 459 days. A single intravenous dose of 20 mg/kg given to pregnant rats on day 15 of gestation produced malignant neurogenic tumors in some of the offspring.

Propane sultone is genotoxic in a wide variety of *in vitro* assays; it also induces DNA strand breaks in vivo in rodents.[1]

The IARC has determined that there is sufficient evidence for carcinogenicity of propane sultone in experimental animals and that it is possibly carcinogenic to humans.[1]

A 2003 ACGIH threshold limit value (TLV) has not been established.

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PROPARGYL ALCOHOL

CAS: 107-19-7

C_3H_4O

Synonyms: Ethynol carbinol; acetylene carbinol; propiolic alcohol; 2-propyn-1-ol; 2-propynyl alcohol

Physical Form. Clear to slightly straw-colored liquid

Uses. To prevent the hydrogen embrittlement of steel; as a corrosion inhibitor, solvent stabilizer, soil fumigant, and chemical intermediate

Exposure. Inhalation; skin absorption

Toxicology. Propargyl alcohol is an irritant of the eyes and the skin; atmospheric concentrations of the chemical, readily attainable under room conditions, are dangerous to life even with exposures of short duration; it is highly toxic when ingested and is easily absorbed through the skin in toxic amounts.

No reports of adverse effects in humans are available.

Two of three rats died after a 6-minute exposure to an essentially saturated atmosphere, whereas a 12-minute exposure was fatal to all exposed animals.[1] A 2-hour LC_{50} of 850 ppm has been reported for both rats and mice.[2] Rats exposed to 80 ppm for 7 hours initially appeared to have eye irritation and to be lethargic.[1] Repeated exposures to this concentration for 5 days/week over a period of 3 months resulted in slight liver and kidney changes. Males had increased liver weights, and females had increases in both kidney and liver weights. Histopathologic examination showed degenerative changes in these organs, with females showing the most injury.

Oral LD_{50} values of 50 mg/kg for the mouse, 60 mg/kg for the guinea pig, and 70 mg/kg for the rat have been reported.[1] Hepatocytic megalocytosis and karyomegaly of the renal tubular epithelial cells was observed in rats dosed orally with 15 or 50 mg/kg for 13 weeks; some treatment-related mortality was also reported in the high-dose group.[3] Daily administration of 5 mg/kg for 13 weeks produced no apparent treatment-related effects.

Applied to the skin of rabbits, propargyl alcohol causes hyperemia, edema, and some superficial necrosis.[1] It is rapidly absorbed through a skin of rabbits in lethal amounts, with a LD_{50} of approximately 16 mg/kg. A 10% solution is slightly irritating and may

be lethal if exposure is extensive or prolonged. A 1% solution appears to be without adverse effects. Repeated dermal exposures of 10 mg/kg/day for 2 months or 20 mg/kg/day for 1 month caused no systemic effects, as evidenced by weight gain, hematology, and histopathologic examination of the tissues.

Instilled in the eyes of rabbits, the undiluted material causes marked pain, irritation, and corneal injury; a 10% solution is slightly irritating, and a 1% solution has no effect.[1]

Propargyl alcohol induced chromosomal aberrations in Chinese hamster ovary (CHO) cells *in vitro* with and without metabolic activation; it was negative in the mouse bone marrow micronucleus test and in the *Salmonella*/mammalian microsome assay.[4]

Propargyl alcohol is reported to have a geranium-like odor that is not adequate to provide warning of overexposure.

The 2003 ACGIH threshold limit value-time-weighted aerage (TLV-TWA) for propargyl alcohol is 1 ppm (2.3 mg/m^3) with a notation for skin absorption.

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PROPENE
CAS: 115-07-1

C_3H_6

Synonyms: Propylene; methylethene; methylethylene

Physical Form. Colorless gas

Uses. In the production of polypropylene, acrylonitrile, isopropyl alcohol, and propene oxide, as well as gasoline and synthetic rubber; as an aerosol propellant or component

Exposure. Inhalation

Toxicology. Propene is of low toxicity. It is a simple asphyxiant and mild anesthetic, with a physiological effect only at extremely high concentrations.

Concentrations of approximately 50% propene induced anesthesia in volunteers in 2 minutes, followed by complete recovery without adverse side effects.[1,2] In another report, exposure to 40%, 50%, and 75% for a few minutes caused reddening of the eyelids, flushing of the face, lacrimation, coughing, and sometimes flexing of the legs, without variation in respiratory or pulse rates or electrocardiograms. At 35–40%, two subjects vomited, and one complained of severe vertigo. Exposure to 13% for 1 minute or 6% for 2 minutes produced mild intoxication, paresthesias, and inability to concentrate. Propene also is considered to be a weak heart sensitization agent in humans.[3]

In rats, 40% propene caused light anesthesia with no other toxic symptoms within 6 hours; 55% propene for 3–6 minutes or 70% propene for 1–3 minutes produced deep anesthesia with no additional central nervous system disturbances.[1,2] Animal experiments with cats have shown no toxic signs when anesthesia was induced at concentrations of 20–31%; however, 70% propene resulted in a drop in blood pressure and an increased pulse rate, and an unusual ventricular ectopic beat occurred at concentrations ranging from 50% to 80%.

Limited information is available on the effects of chronic propene exposure. In mice, chronic exposure to minimal narcotic concentrations caused moderate to very slight fatty degeneration of the liver.[1,2]

No significant evidence for propene carcinogenicity was found in rats or mice exposed by inhalation to 5000–10,000 ppm 6 hours/day for 103 weeks.[4] However, signs of nasal cavity pathology were observed in rats, including an increased incidence of nonneoplastic lesions consisting of epithelial hyperplasia and squamous metaplasia. In addition, inflammatory changes were noted, characterized by an influx of lymphocytes, macrophages, and granulocytes into the submucosa. A slight increase in the incidence of vascular tumors was observed in female mice. Other more limited animal studies also have failed to find a carcinogenic response to propene.[5]

The IARC has determined that there is inadequate evidence in humans and in experimental animals for the carcinogenicity of propene.[6] Overall, propene is not classifiable as to its carcinogenicity to humans.[6]

Propene has been reported to be nonmutagenic to both *Escherichia coli* and *Salmonella typhimurium*, either with or without metabolic activation; interestingly, the purported reactive metabolite of propene, propene oxide, is widely accepted as a mutagen.[2,6] Furthermore, propene oxide forms hemoglobin adducts in exposed animals.[6]

Propene gas is not an irritant to the skin or eyes, but direct contact with the liquid may cause frostbite.[7]

An important factor in the use of propene is the fact that explosive concentrations of the gas are reached well before any physiological changes occur, and the gas or compressed liquid should be handled according to strict safety precautions.

According to the ACGIH propene is classified as a simple asphyxiant.

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β-PROPIOLACTONE

CAS: 57-57-8

$C_3H_4O_2$

Synonyms: BPL; 2-oxetanone; hydracrylic acid; β-lactone

Physical Form. Colorless liquid

Uses. Vapor sterilant and disinfectant; intermediate in the production of acrylic acid and esters

Exposure. Inhalation; skin absorption

Toxicology. β-Propiolactone (BPL) is an irritant, and in animals it is carcinogenic.

Acute exposure to the liquid or vapor can cause irritation and blistering of the skin, hair loss, and scarring.[1] Eye contact with liquid can

cause permanent corneal opacification. In rats, the 30-minute LC_{50} was 250 ppm whereas for 6 hours the LC_{50} was 25 ppm.[2] Oral or intraperitoneal administration caused muscular spasms, respiratory difficulty, convulsions, and death in rodents.[1] Intravenous injection caused kidney tubule and liver damage.[1]

BPL applied to mouse skin one to seven times (over a period of 2 weeks) as undiluted BPL or in solutions of corn oil or acetone at doses of 0.8–100 mg caused skin irritation; the effects ranged from erythema to hair loss and scarring.[3] Lifetime painting (3 times/week) with acetone and corn oil solutions showed that BPL produced both papillomas and cancer of the mouse skin; 0.25 mg in acetone caused papillomas in 12 of 30 animals and cancers in 3, whereas 5 mg produced tumors in 21 of 30 animals and cancers in 11. In corn oil, 0.8 mg caused tumors in 27 of 30 mice; 12 of the tumors were malignant.[3] Papillomas developed in 11 of 90 and 14 of 80 of the acetone and corn oil control groups, respectively.[3]

After weekly subcutaneous injection of 0.73 mg BPL in tricaprylin for 503 days, 89 mice developed fibrosarcomas, 3 adenocarcinomas, 7 squamous cell carcinomas, and 3 squamous papillomas, all at the injection site. The number of months to the first tumor was 7, and no local tumors developed in 110 controls treated with tricaprylin alone for up to 581 days.[4]

All of 10 rats injected biweekly for 44 weeks with 1 mg of BPL in arachis oil developed injection-site sarcomas; no local sarcomas were observed in 7 controls given repeated injections of 0.5 mg of arachis oil for 54 weeks.[5]

Repeated gastric administration of 10 mg BPL/0.5 ml tricaprylin/week for 70 weeks caused squamous cell carcinomas of the forestomach in three of five rats; there were no tumors in controls treated with tricaprylin alone.[4]

BPL is a direct-acting alkylating agent and forms DNA adducts. It is mutagenic in a wide variety of in vitro and in vivo systems, both in somatic and germ cells.[6] The IARC has determined that BPL is carcinogenic in experimental animals and that it is possibly carcinogenic to humans.[6]

Because of high acute toxicity and demonstrated skin tumor production in animals, human contact by all routes should be avoided.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for β-propiolactone is 0.5 ppm (1.5 mg/m^3) with an A2-suspected human carcinogen designation.

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PROPIONIC ACID
CAS: 79-09-4

CH_3CH_2COOH

Synonyms: Methylacetic acid; ethylformic acid; ethanecarboxylic acid; propanoic acid

Physical Form. Colorless oily liquid with pungent odor

Uses/Sources. Synthesis of fungicides, herbicides, pharmaceuticals, flavorings, and perfumes; production of propionates and cellulose propionate plastics; present naturally in dairy products

Exposure. Inhalation, ingestion, skin absorption

Toxicology. Propionic acid is an irritant to skin, eyes, and mucous membranes. Propionic acid is a normal intermediary metabolite during the oxidation of fatty acids. It occurs ubiquitously in the gastrointestinal tract as an end product of microbial digestion of carbohydrates. It represents up to 4% of the normal total plasma fatty acids.[1]

Local damage may occur to skin, eye, or mucosal surfaces on contact with concentrated solutions.[1] Dermal applications of 0.5 ml to rabbits for 24 hours resulted in maximal scores for erythema and edema, with chemical burns within 1 hour after treatment.[2]

In rats, the oral LD_{50} was 4.3 g/kg; the dermal LD_{50} in rabbits was 500 mg/kg.[1] Rats, mice, and hamsters fed diets containing 4% propionic acid for 7 days showed evidence of damage and cellular proliferation in the epithelium of the stomach.[3] Treatment-related histologic changes in the epithelium of the forestomach including acanthosis, hyperkeratosis, basal cell hyperplasia, and intracellular vacuolation were found in rats 14 days after treatment.[4] Persistent damage to cells of the forestomach and associated proliferative responses have been common factors in rodent forestomach tumorigenesis.[4] The relevance to humans, however, has not been determined.

Propionic acid does not appear to be genotoxic. In vitro mutagenicity assays with propionic acid, using *Salmonella typhimurium* or *Saccharomyces cerevisiae*, were negative with or without metabolic activation.[1]

No effect on maternal or fetal survival and no increase in the number of fetal abnormalities were seen after administration in the diet of pregnant mice and rats (up to 300 mg/kg/day for 10 days), hamsters (up to 400 mg/kg/day for 5 days), or rabbits (up to 400 mg/kg/day for 13 days).[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for propionic acid is 10 ppm (30 mg/m^3).

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n-PROPYL ACETATE

CAS: 109-60-4

$C_3H_7COOCH_3$

Synonyms: Acetic acid *n*-propyl ester

Physical Form. Colorless liquid

Uses. Solvent; in flavoring agents and perfumes

Exposure. Inhalation

Toxicology. In animals, *n*-propyl acetate is an irritant of the skin, eyes, and mucous membranes. At high concentrations it causes narcosis, and it is expected that severe exposure will produce the same effect in humans.

No chronic or systemic effects have been reported in humans.

In cats, 24,000 ppm caused narcosis in 13–18 minutes; 30-minute exposures were lethal to

some animals within 4 days after exposure.[1] Exposure for 5 hours caused narcosis and some deaths in cats at 7400 ppm. Moderate irritation and salivation were observed at 5300 ppm for 6 hours/day.

n-Propyl acetate has a pearlike odor, but the odor threshold has not been determined.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for *n*-propyl acetate is 200 ppm (835 mg/m^3) with a short-term excursion limit (STEL)/ceiling of 250 ppm (1040 mg/m^3).

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n-PROPYL ALCOHOL

CAS: 71-23-8

$CH_3CH_2CH_2OH$

Synonyms: 1-Propanol; *n*-propanol; propyl alcohol; ethyl carbinol

Physical Form. Clear liquid

Uses. Solvent; organic syntheses

Exposure. Inhalation; minor skin absorption

Toxicology. *n*-Propyl alcohol is an irritant of the eyes and mucous membranes. At high concentrations it causes narcosis in animals, and it is expected that severe exposure in humans will produce the same effect.

On the basis of acute animal studies, *n*-propyl alcohol appears to be slightly more toxic than isopropyl alcohol. No chronic effects have been reported in humans, although a human fatality has been ascribed to ingestion.[1] Exposure to 400 ppm for 3–5 minutes will reportedly produce mild irritation of the eyes, nose, and throat.[2]

Mice exposed to 3250 ppm developed ataxia in 90–120 minutes, and prostration was evident in 165–180 minutes; deep narcosis was manifest in 240 minutes at 4100 ppm.[2] Exposure to 13,120 ppm for 160 minutes or 19,680 ppm for 120 minutes was lethal to mice.[2] Exposure of rats to 20,000 ppm for 1 hour resulted in no mortalities during a 14-day postexposure observation period.[2] *n*-Propyl alcohol is not appreciably irritating to the skin of rabbits even after prolonged contact, but it can be absorbed in significant amounts if confined to the skin. Application of 38 ml/kg/day for 30 days resulted in death of one-third of the rabbits.[2]

Instilled in rabbit eyes, 0.1 ml produced marked conjunctivitis, corneal opacities, and ulcerations.[2]

In a limited study, lifetime administration of *n*-propyl alcohol by intubation or subcutaneous injection caused severe liver injury, hematopoietic effects, and a number of malignant tumors not found in controls.[1] It was not carcinogenic to mice in a skin painting assay.[3]

n-Propyl alcohol was not mutagenic in bacterial assays, nor did it induce micronuclei or sister chromatid exchanges in cultured cells.[3]

Administered to pregnant rats on days 1–19 of gestation for 7 hours/day concentrations in excess of 5000 ppm produced congenital malformations in offspring and maternal toxicity in dams.[4]

The odor threshold (40 ppm) and irritant properties of *n*-propyl alcohol are expected to prevent inadvertent exposure to hazardous concentrations.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for *n*-propyl alcohol is 200 ppm (492 mg/m^3) with a short-term excursion limit (STEL)/ceiling of 250 ppm (614 mg/m^3) and a notation for skin absorption.

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PROPYLENE DICHLORIDE

CAS: 78-87-5

$C_3H_6Cl_2$

Synonyms: 1,2-Dichloropropane; propylene chloride

Physical Form. Colorless liquid

Uses. Solvent; stain remover; chemical intermediate; fumigant

Exposure. Inhalation

Toxicology. Propylene dichloride is an eye and respiratory irritant; at very high concentrations it is a central nervous system depressant and may cause liver injury.

Ingestion or inhalation of high levels caused severe liver damage, acute renal failure, hemolytic anemia, and disseminated intravascular coagulation in three reported cases.[1] Symptoms from inhalation included anorexia, abdominal pain, vomiting, ecchymoses, and hematuria. In all cases, more than 24 hours elapsed between exposure and onset of symptoms. Because 80–90% of propylene dichloride and its metabolites are eliminated within 24 hours, analysis of blood, urine, and feces for solvent is useless once symptoms appear.[1]

Workers tolerated short-term exposures to 400–500 ppm without apparent adverse effects. Inhalation of a 98% solution over the course of an evening resulted in acute liver damage, as determined by laboratory tests (AST, ALT, total bilirubin, prothrombin); the patient recovered after 3 weeks of hospitalization.[1]

Guinea pigs repeatedly exposed to 2200 ppm for 7 hours developed severe conjunctival swelling, as well as signs of respiratory irritation and incoordination; 11 of 16 animals died after daily exposure and had severe liver injury and some kidney injury.[2] Rats dying from repeated inhalation of 1000 ppm showed weakness, general debility, and signs of respiratory irritation a few days before death; mice died after a few hours of exposure to 1000 ppm. In general, animals that survived 35 or more 7-hour exposures to 1000–2200 ppm showed no significant lesions at autopsy.

At 400 ppm, rats, guinea pigs and dogs exposed for up to 140 daily 7-hour exposures showed no adverse effects.[3] There was a high percentage of mortality among mice repeatedly exposed to 400 ppm. In mice of a susceptible strain, hepatomas were found that were similar histologically to those induced by carbon tetrachloride. Oral administration of 100, 250, 500, or 1000 mg/kg to rats for up to 10 days caused body weight loss and central nervous system depression.[4] Morphologic changes in the liver were apparent in the two highest-dosed groups. Resistance to propylene dichloride hepatotoxicity over the 10 days of exposure was reflected by progressively lower serum enzyme levels and by decreases in the severity and incidence of toxic hepatitis and periportal vacuolization.

Female rats given 250 mg/kg/day by gavage for 103 weeks had a marginal, but statistically significant, increased incidence of adenomas of the mammary gland.[5] A dose-related increase in liver adenomas for both male and female mice was observed with treatment with 125 or 250 mg/kg/day for 103 weeks. The NTP concluded that there was equivocal evidence of carcinogenicity in female rats and some evidence of carcinogenicity in male and female mice.[5]

Propylene dichloride was mutagenic in various strains of *Salmonella* and in mouse lymphoma cells, and it induced chromosomal aberrations in Chinese hamster cells.[6]

No indication of teratogenic effects was observed in rats or rabbits administered propy-

lene dichloride by gavage during periods of major organogenesis.[7] Developmental effects (delayed ossification of skull bones) were considered to be secondary to maternal toxicity. Administered in drinking water of rats for two generations, propylene dichloride did not effect fertility.[8] It was not mutagenic in the dominant lethal assay.

Some skin absorption may occur; the dermal LD_{50} for rabbits was 8.75 ml/kg.[1] The liquid is moderately irritating to the eye but does not cause serious or permanent injury.[9] Repeated or prolonged skin contact with propylene dichloride may result in skin irritation due to defatting.[9]

The liquid has a characteristic unpleasant, chloroform-like odor; human subjects described the odor as "strong" at 130–190 ppm and "not noticeable" at 15–23 ppm.[9]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for propylene dichloride is 75 ppm (347 mg/m^3) with a short-term excursion limit (STEL) of 110 ppm (508 mg/m^3).

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PROPYLENE GLYCOL DINITRATE
CAS: 6423-43-4

$C_3H_6N_2O_6$

Synonyms: Methylnitroglycol; propanediol dinitrate; dinitrate dipropylene glycol; PGDN

Physical Form. Red-orange or colorless liquid with a disagreeable odor

Uses. In the torpedo propellant Otto fuel II

Exposure. Inhalation; skin absorption

Toxicology. Propylene glycol dinitrate (PGDN) is a vasodilator, and at extremely high concentrations it causes methemoglobin formation.

An early consequence of overexposure to PGDN is vasodilation of the cerebral vessels, which is the major factor in the development of headache.[1] With more severe exposure, relaxation of the vascular smooth muscle can result in a fall in blood pressure followed by a compensatory vasoconstriction.

Male volunteers 22–25 years of age were exposed to PGDN at 0.03, 0.1, 0.2, 0.35, 0.5, and 1.5 ppm for single or daily exposures of various time periods.[2] At the 0.1 ppm exposure

level two of nine subjects reported mild headaches; seven of nine had headaches at 0.2 ppm that decreased dramatically with repeat exposures. At this level most subjects could detect the odor for just 5 minutes. Progressive throbbing headaches were noted in seven of nine volunteers exposed at 0.5 ppm, and after 6 hours one subject was dizzy and nauseous. By 8 hours, three subjects had abnormal Romberg and heel-to-toe neurological tests and narrowed pulse pressures with an increase in diastolic pressure. Alteration in visual evoked response was the only other effect noted. At 1.5 ppm all eight subjects could detect odor, had eye irritations within 40 minutes of exposure, and developed headaches. The headaches were so severe that exposure was stopped at 3 hours. All symptoms resolved within the subsequent 8 hours. There was no biochemical or hematologic evidence of organ damage in the studied exposure range.

A study of 87 naval employees chronically exposed to PGDN noted acute headaches and nasal congestion of presumed vascular origin but no chronic cardiovascular or neurotoxic disorders.[3] Twenty-nine subjects from this study group were tested before and immediately after PGDN exposure during torpedo maintenance procedure or turnaround. Significant changes in oculomotor function tests were observed although peak airborne concentrations were below 0.2 ppm. Although changes in these test scores were noted, there was no correlation between exposure levels and biological effects. The authors concluded that PGDN could exert acute neurophysiological effects, but at this exposure level they were not functionally significant.

A cohort of 1352 male Navy torpedo munition workers exposed to PGDN between 1970 and 1979 had elevated rates and significantly elevated risks of angina pectoris and myocardial infarction.[4] The age-adjusted incidence rate for myocardial infarction was 18/10,000 in PGDN-exposed workers vs. 8/10,000 for a group of nonexposed torpedomen; for angina pectoris incidence rates were 9.8/10,000 in exposed workers vs. 2.6/10,000 in nonexposed munitions workers. It was noted that two of the angina cases had no coronary atheromatous disease on angiography, a finding suggestive of vasoplastic etiology associated with PGDN exposure in these cases.

Pregnancy outcomes in women munitions workers were investigated between 1980 and 1983.[5] Spontaneous abortions among all female torpedo munitions workers were the same or lower compared with hospital employees (enlisted female health care workers) or all other Navy women. There were no spontaneous abortions among the few PGDN-exposed pregnant women.

Acute LD_{50} values have been reported in various animal species.[6] The oral LD_{50} in female rats was 1190 mg/kg; subcutaneous LD_{50} values in milligrams per kilogram were 463 for female rats, 524 for male rats, 1208, for female mice, and 200–300 for female cats. The LD_{50} in rats resulted in almost complete conversion of hemoglobin to methemoglobin, with lower conversion rates at lower doses. Death was due to anoxia. Methemoglobin levels were not measured in the mice or cats, but premorbid signs were consistent with methemoglobinemia in these species as well.

Blood pressure effects were recorded from cannulized femoral arteries in anesthetized rats after subcutaneous injection.[6] Maximal falls in blood pressure occurred within 30 minutes of injection. Small responses were seen at the 5 mg/kg level, but as the dose was increased marked hypotension occurred.

Continuous 90-day exposure studies were conducted in rats, guinea pigs, dogs, and monkeys.[7] At 10 ppm, dogs had hemosiderin deposits in the liver and similar pigment was found in the proximal convoluted tubules of the kidney. Guinea pigs showed foci of pulmonary hemorrhage at 15 ppm, whereas monkeys had increased serum urea nitrogen and decreased alkaline phosphatase, suggesting the possibility of renal damage at this level. At 35 ppm hemosiderin deposits were found in the liver, spleen, and kidneys of dogs, female rats and four of nine monkeys. Methemoglobin values peaked at week 2 with values of 20% in dogs and monkeys. No changes in behavior patterns were observed in monkeys trained to perform a visual discrimination test and exposed continuously to 35 ppm for 90 days.

Rabbit skin applications were made daily for a 20-day subacute study.[7] At 1 g/kg there was reversible erythema and no signs of systemic effect. At 2 g/kg the rabbits appeared weak and slightly cyanotic and had rapid, shallow breathing. At 4 g/kg, 13 of 14 animals were dead by the fifth application. Methemoglobin was measured at 35% at death. Autopsies showed overall weight loss and dark, blue-gray internal organs, and the urinary bladder was markedly distended. The hemoglobin and hematocrit values were depressed, and urinary nitrates accounted for approximately 7% of the PGDN given at the 4 g/kg level.

Applied to rabbit eyes, 0.1 ml was only slightly irritating and the irritation disappeared within 24 hours.[7]

Negative results were reported in various mutagenic assays including the Ames *Salmonella* assay (with or without microsomal activation), sister chromatid exchange assay in mouse lymphoma cells, mouse bone marrow cytogenic analysis, and mouse dominant lethal assay.[5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for propylene glycol dinitrate is 0.05 ppm (0.34 mg/m^3) with a notation for skin absorption.

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PROPYLENE GLYCOL MONOMETHYL ETHER

CAS: 107-98-2

$C_4H_{10}O_2$

Synonyms: Propylene glycol methyl ether; PGME; 1-methoxy-2-propanol; Dowanol PM Glycol Ether; Propasol Solvent M; Poly-solv MPM Solvent

Physical Form. Colorless liquid

Uses. Solvent

Exposure. Inhalation

Toxicology. Propylene glycol monomethyl ether (PGME) is low in systemic toxicity but causes irritation of the eyes, nose, and throat, with discomfort from the objectionable odor.

In human studies, 100 ppm was reported as having a transient objectionable odor. At 1000 ppm, there was irritation of the eyes, nose, and throat and signs of central nervous system impairment.[1]

The LC_{50} in rats was 10,000 ppm for 5–6 hours, with death caused by central nervous system depression.[2] Rats and monkeys exposed for 132 daily exposures to 800 ppm over a period of 186 days showed no evidence of adverse effects.

Exposure of rats to 3000 ppm 6 hours/day for a total of 9 days over an 11-day interval caused central nervous system depression that

was reversible.[3] An adaptive response to PGME was observed in rats and mice chronically exposed at the 3000 ppm level for up to 2 years; the pronounced sedation of animals resolved by the second week of exposure.[4] An increase in liver weights was also observed during this time. It has been suggested that high concentrations of PGME cause an adaptive hepatic response whereby an increase in hepatocytes results in increased metabolism of PGME.

Exposure of pregnant rats and rabbits by inhalation to 500, 1500, or 3000 ppm for 6 hours/day on days 6–15 (rats) or 6–18 (rabbits) of gestation did not cause teratogenic or embryotoxic effects. Slight fetotoxicity in the form of delayed sternebral ossification was observed in the offspring of rats exposed at 3000 ppm—a dose that was also maternally toxic.[5] In a two-generation reproduction study, the F_1 and F_2 offspring of rats exposed to concentrations up to 3000 ppm (during mating and gestation) had decreased body weights, reduced survival and litter size, and histologic changes in the liver and thymus that appeared to be secondary to maternal toxicity.[6] In a continuous breeding study no change in reproductive parameters was observed in mice repeatedly administered 3333 mg/kg orally.[7]

The oral LD_{50} was 6.6 g/kg for rats and was on the order of 9.2 g/kg for dogs.[8,9] The dermal LD_{50} was in the range of 13–14 g/kg in rabbits, indicating minimal skin absorption.[2]

The liquid on the skin of rabbits caused only a very mild, transient irritation after several weeks of constant application. In the rabbit eye, there was mild, reversible irritation.

PGME was not genotoxic in a variety of assays.[10]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for propylene glycol monomethyl ether is 100 ppm (369 mg/m^3) with a short-term excursion limit (STEL) of 150 ppm (553 mg/m^3).

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PROPYLENEIMINE
CAS: 75-55-8

C_3H_7N

Synonyms: 2-Methylaziridine; 1,2-propyleneimine; 2-methylethylenimine

Physical Form. Flammable liquid

Uses. Intermediate in production of polymers, coatings, adhesives, textiles, and paper finishes

Exposure. Inhalation; skin absorption

Toxicology. Propyleneimine vapor is an eye and respiratory tract irritant. It was carcinogenic to rats, the only species tested.

Inhalation may cause vomiting, breathing difficulty, and irritation of eyes, nose, and throat; on prolonged exposure, vapors tend to redden the whites of the eyes.[1]

Exposure of rats at 500 ppm for 4 hours was fatal, but inhalation for 2 hours resulted in no deaths.[2] Rats given 20 mg/kg by gavage twice weekly suffered from advanced flaccid paralysis after 18 weeks, and the mortality rate was high.[3] At 10 mg/kg, paralysis occurred to a lesser extent after 30 weeks. Granulocytic leukemia, squamous cell carcinoma of the ear duct, and brain tumors (glioma) were observed in the rats after 60 weeks at the 10 mg/kg dose; females showed mammary adenocarcinomas, a number of which metastasized to the lung.[3] Propyleneimine is DNA damaging and mutagenic to bacteria. In cultured mammalian cells it induces cell transformations.[4]

No information is available to assess the carcinogenic risk to humans.[5] The IARC has determined that there is sufficient evidence of carcinogenicity in animals and that propyleneimine is possibly carcinogenic to humans.

Instilled in the eye of a rabbit, a 5% aqueous solution produced corneal damage.[2] Contact with the liquid on the skin causes burns, and burns of the mouth and stomach would be expected with ingestion.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for propyleneimine is 2 ppm (4.7 mg/m^3) with an A2-suspected human carcinogen classification.

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PROPYLENE OXIDE
CAS: 75-56-9

CH_3CHOCH_2

Synonyms: 1,2-Epoxypropane; propene oxide; methyloxirane; propylene epoxide

Physical Form. Colorless liquid

Uses. Primarily as a chemical intermediate to produce polyether polyols, propylene glycols and propylene glycol ethers; fumigant; preservative

Exposure. Inhalation

Toxicology. Propylene oxide is an irritant of the eyes, mucous membranes, and skin. At high concentrations it causes narcosis in animals, and it is expected that severe exposure will produce the same effect in humans. It is carcinogenic in experimental animals.

In direct contact with the skin or mucous membranes propylene oxide has an irritant or corrosive effect, depending on the concentration; allergic contact dermatitis has been reported, and corneal burns from the vapor have also been described.[1]

The LC_{50} for rats exposed for 4 hours was 4000 ppm; for mice, it was 1740 ppm.[2] Rats and guinea pigs exhibited irritation, dyspnea,

drowsiness, weakness, and some incoordination at concentrations of 2000 ppm or more.[3] Dogs exposed to 2030 ppm for 4 hours showed lacrimation, salivation, nasal discharge, and vomiting, and there were some deaths.[2]

Rats, guinea pigs, rabbits, and a monkey were given repeated (79 or more) 7-hour exposures to 457 ppm. Irritation of the eyes and respiratory passages was noted in the rats and guinea pigs; rats had increased mortality due to pneumonia.[3] There were no adverse effects on the monkey or the rabbits.[3] Rats exposed at 1500 ppm 6 hours/day, 5 days/week for 7 weeks developed ataxia in the hind legs. The main pathologic change was axonal degeneration of the myelinated fibers in both the hind leg nerve and the fasciculus gracilis.[4]

No significant neurophysiological effects (as determined by nerve conduction velocity and neuropathology) were found in monkeys exposed at 100 or 300 ppm 7 hours/day, 5 days/week for 24 months.[5]

Rats exposed to 500 ppm 7 hours/day for 15 days 3 weeks before breeding and during gestation had a significant reduction in the numbers of corpora lutea, implants, and live fetuses.[6] For pregnant rats exposed on gestation days 6–15, there were no exposure-related effects, except for an increased frequency of seventh cervical ribs in fetuses at the maternally toxic exposure level of 500 ppm.[7] In another report, inhalation exposure at levels up to 300 ppm over two generations did not produce any adverse effects on reproductive function.[8] Fetotoxicity was limited to minor skeletal abnormalities for exposed litters. Propylene oxide did not cause sperm abnormalities in mice treated 7 hours/day for 5 days by inhalation.[9]

Repeated subcutaneous administration of up to 2.5 mg/week for 95 weeks caused local sarcomas in mice.[10] Administered by oral gavage to rats twice a week for 2 years, propylene oxide caused a dose-dependent increase in forestomach tumors, which were mainly squamous cell carcinomas.[11]

In inhalation studies, there was some evidence of carcinogenicity in rats exposed at 400 ppm, as indicated by an increased incidence of papillary adenomas of the nasal turbinates.[12] In mice, there was clear evidence of carcinogenicity at this dose, as indicated by increased incidence of hemangiomas and hemangiosarcomas of the nasal turbinates. In the respiratory epithelium of the nasal turbinates, propylene oxide also caused suppurative inflammation, hyperplasia, and squamous metaplasia in rats and inflammation in mice. The IARC has determined that there is sufficient evidence for carcinogenicity to animals.[9]

One case-control study in humans found no significant associations between exposure and various cancers; no information was given on exposure levels or possible confounding effects of other exposures.[9] The IARC has determined that there is inadequate evidence in humans for the carcinogenicity of propylene oxide but that it is possibly carcinogenic to humans.[9]

Propylene oxide was mutagenic to yeast, fungi, and bacteria. In mammalian cells *in vitro* it also induced DNA damage and gene mutation as well as sister chromatid exchange and chromosomal aberrations.[9] Propylene oxide forms adducts with proteins such as hemoglobin in a variety of species including humans. In mice the concentration of the N-terminal valine adduct of propylene oxide in hemoglobin is linearly related to administered dose.

Aqueous solutions of 10% and 20% propylene oxide applied to the skin of rabbits caused hyperemia and edema when the duration of skin contact was 6 minutes or longer; severe exposures resulted in scar formation.[3]

The odor has been described as sweet, alcoholic, and similar to natural gas, ether, or benzene. The median detectable concentration is 200 ppm, which does not provide sufficient warning for prolonged or repeated exposures.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for propylene oxide is 20 ppm (48 mg/m^3).

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n-PROPYL NITRATE

CAS: 627-13-4

$C_3H_7NO_3$

Synonyms: Nitric acid *n*-propyl ester

Physical Form. Clear to yellow liquid

Uses. Fuel ignition promoter; rocket propellants; organic intermediate

Exposure. Inhalation

Toxicology. *n*-Propyl nitrate in animals causes anoxia owing to the formation of methemoglobin, as well as anemia and hypotension.

There have been no reports of human intoxication. It is speculated that, in humans, exposure severe enough to cause methemoglobin formation is unlikely because lower concentrations produce sufficient warning in the form of irritation, headache, and nausea.[1]

Exposure of rats to 10,000 ppm for 4 hours caused nasal irritation, dyspnea, methemoglobinemia, weakness, cyanosis, and death; dogs appeared to be more susceptible to *n*-propyl nitrate with a 4-hour LC_{50} of 2500 ppm.[1] In dogs repeatedly exposed to 260 ppm for 26 weeks, hemoglobinuria and mild anemia appeared during the first 2 weeks of exposure but then subsided; at 900 ppm for 6 days, effects were cyanosis, methemoglobinemia, hemolytic anemia, hemoglobinuria, collapse, and death.[1]

Anesthetized dogs given 50–250 mg/kg intravenously immediately showed hypotension, arrest of gut activity, respiratory paralysis, hyperpnea, and moderate methemoglobinemia. Because death was produced with methemoglobin levels of only 4%, *n*-propyl nitrate intoxication may be caused in part by a direct action on vascular smooth muscle.[2] (It has been noted that the oral toxicity of *n*-propyl nitrate is very low compared with intravenously administered doses, in which mg/kg doses were lethal versus g/kg orally.[3])

The liquid instilled into the eyes of rabbits

caused mild, transient inflammation with no evidence of corneal damage.[3] The liquid applied to the skin of rabbits daily for 10 days caused staining, inflammation, and thickening of the skin but no evidence of systemic toxicity.[4]

The odor of *n*-propyl nitrate is detectable at 50 ppm and above.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for *n*-propyl nitrate is 25 ppm (107 mg/m^3) with a short-term excursion limit (STEL)/ceiling of 40 ppm (172 mg/m^3).

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PYRETHRUM
CAS: 8003-34-7

$C_{21}H_{28}O_3$
Pyrethrum I: $C_{22}H_{28}O_5$
Pyrethrum II: $C_{20}H_{28}O_3$

Synonyms: Pyrethrin I or II; Cinerin I or II; Jasmolin I or II. *Note*: Pyrethrum flowers yield "pyrethrum extract," of which the insecticidal constituents are collectively the "pyrethrins" or the "natural pyrethrins"

Physical Form. Dust

Use. Insecticide

Exposure. Inhalation

Toxicology. Pyrethrum dust causes dermatitis and occasionally sensitization.

Under practical conditions, pyrethrum and its derivatives are probably some of the least toxic to mammals of all insecticides currently in use.[1] It was used for many years as an anthelmintic agent at a suggested oral dose of 20 mg/day for 3 days with no apparent ill effects. However, ingestion of 14 mg was lethal to a 2-year-old. Symptoms in an 11-month-old infant who ingested the powder included pallor, intermittent convulsions, vomiting, and bradycardia; there was extreme reddening of the lips and tongue and slight inflammation of the conjunctivae.[1]

Very young children are perhaps more susceptible to poisoning because they may not hydrolyze the pyrethrum esters efficiently.[1] Animal studies indicate that pyrethrum may undergo efficient destruction in the liver and/or be slowly absorbed from the gastrointestinal tract, because oral LD_{50} values are several magnitudes of order higher than intravenous values.[1]

The primary effect in humans from exposure to pyrethrum is dermatitis.[2] The usual lesion is a mild erythematous dermatitis with vesicles, papules in moist areas, and intense pruritis; a bullous dermatitis may develop.[2]

In a study of workers engaged in processing pyrethrum powder, 30% had erythema, skin roughening, and pruritis, which subsided on cessation of exposure.[3] One of these workers had an anaphylactic-type reaction. Shortly after the worker entered a dust-filled room, the facial skin turned red and the worker felt a sensation of burning and itching. The cheeks and eyes rapidly became swollen, and pruritis became severe; the entire condition disappeared within 2 days after removal from exposure.[3]

Some persons exhibit sensitivity similar to pollinosis, with sneezing, nasal discharge, and nasal stuffiness.[2] A few cases of asthma due to pyrethrum mixtures have been reported; some of the people involved had a previous history of asthma with allergy to a wide spectrum of substances.[2]

In one anecdotal case a fatality was associated with pyrethrin inhalation.[4] Death was attributed to sudden irreversible bronchospasm.

Dogs fed pyrethrins at a dietary level of 5000 ppm for 90 days showed tremor, ataxia, labored respiration, and salivation during the first month of exposure.[1] Rats given up to 5000 ppm in their diets for 2 years suffered no significant effects on growth or survival but had slight liver damage.[1] A daily gavage dose of 50, 100, or 150 mg/kg on days 6–15 of pregnancy caused an increased incidence of resorptions in rats compared with controls.[4]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for pyrethrum is 5 mg/m^3.

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PYRIDINE

CAS: 110-86-1

NC_5H_5

Synonyms: Azabenzene; azine

Physical Form. Colorless liquid

Uses. Solvent; organic syntheses, especially agricultural chemicals

Exposure. Inhalation; skin absorption

Toxicology. Pyridine is an irritant and a central nervous system depressant; ingestion may cause liver and kidney damage.

Chemical plant workers chronically exposed to 6–12 ppm developed headache, vertigo, nervousness, sleeplessness, nausea, and vomiting.[1] Similar symptoms have occurred in workers repeatedly exposed to 125 ppm; in some cases, lower abdominal or back discomfort with urinary frequency was observed without associated evidence of liver or kidney damage.[2] Serious liver and kidney injury has been reported after oral administration of 1.8–2.5 ml of pyridine daily for 2 months in the treatment of epilepsy.[3] Skin irritation may result from prolonged or repeated contact with the chemical.

Exposure of rats to 23,000 ppm was lethal in 1.5 hours, and exposure to 3600 ppm for 6 hours was fatal to two of three rats tested.[2] The oral LD_{50} for rats was 1.58 g/kg; the dermal LD_{50} was 1–2 ml/kg in guinea pigs.[2] In the eye of a rabbit, a 40% solution caused corneal necrosis. In animals, inhalation of pyridine can cause necrotic damage of the nasal epithelium and repeated feeding results in kidney and liver injury.[2]

In 2-year drinking water studies mice showed increased incidences of hepatocellular carcinomas and hepatoblastomas; male Fischer 344 rats had increased incidences of renal tubule adenomas, and male Wistar rats showed evidence of interstitial cell adenoma of the testis.[5] No increase in tumor incidence at any site was observed in rats after chronic subcutaneous injection.[6] The IARC has determined that there is limited evidence in experimental animals for the carcinogenicity of pyridine and that it is not classifiable as to its carcinogenicity to humans.[6] Pyridine was not genotoxic in a variety of assays.[6]

Pyridine has an unpleasant odor detectable at 1 ppm; the odor is objectionable to unacclimatized individuals at 10 ppm but does not provide sufficient warning of hazardous concentrations because olfactory fatigue occurs quickly.[4]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for pyridine is 5 ppm (16 mg/m^3).

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QUINONE
CAS: 106-51-4

$C_6H_4O_2$

Synonyms: *p*-Benzoquinone; 1,4-cyclohexadiendione; *p*-quinone

Physical Form. Yellow crystalline solid

Uses. As an oxidizing agent; in photography; tanning hides; intermediate in the manufacturing of dyes, fungicides, and hydroquinone

Exposure. Inhalation

Toxicology. Quinone affects the eyes.

Acute exposure causes conjunctival irritation and, in some cases, corneal edema, ulceration, and scarring; transient eye irritation may be noted above 0.1 ppm and becomes marked at 1–2 ppm.[1] Chronic exposure causes the gradual development of changes characterized as 1) brownish discoloration of the conjunctiva and cornea confined to the intrapalpebral fissure, 2) small opacities of the cornea, and 3) structural corneal changes that result in loss of visual acuity.[2,3] The pigmentary changes are reversible, but the more slowly developing structural changes in the cornea may progress. Although pigmentation may occur with less than 5 years of exposure, this is uncommon and usually is not associated with serious injury. Skin contact may cause discoloration, erythema, swelling, and the formation of papules and vesicles; prolonged contact may lead to necrosis. Systemic effects from industrial exposure have not been reported.

Administration of large doses of quinone to experimental animals caused local irritation, clonic convulsions, respiratory difficulties, drop in blood pressure, and death due to paralysis of the medullary centers. In chronic studies, quinone has been tested in mice by skin application and inhalation and in rats by subcutaneous injection.[4] The IARC has determined that there is inadequate evidence in experimental animals for carcinogenicity of quinone and that it is not classifiable as to its carcinogenicity to humans.[5]

The odor and irritant properties do not provide adequate protection from levels capable of producing chronic eye injury.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for quinone is 0.1 ppm (0.44 mg/m^3).

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RADON

CAS: 10043-92-2

Radon-222: CAS: 14859-67-7

Synonyms: None

Physical Form. Radon is a chemically inert, colorless, odorless, tasteless radioactive gas that is formed from the normal radioactive decay of uranium-238.

Source. Uranium-238 is present in small amounts in most rocks and soil. Uranium has a half-life of 4.5 billion years.[1] It decays to other elements such as radium, which breaks down to radon. Some of the radon moves to the soil surface and enters the air, whereas some remains below the soil surface and enters the groundwater.

Radon-222 also undergoes radioactive decay and has a radioactive half-life of 3.8 days. Radon-220 and -219 have half-lives measured in seconds and are not nearly as abundant as Radon-222. Thus the discussion of radon health effects here centers on Radon-222. Radon-222 decays into radon daughters or progeny, which are radioactive elements. Two of these (polonium-218 and polonium-214) emit alpha particles (high-energy, high-mass particles, each consisting of two protons and two neutrons), which are highly effective in damaging lung tissues. The decay rate of radioactive elements has traditionally been specified in curies (Ci). The curie is approximately 37 billion disintegrations (37×10^9 disintegrations) per second. In discussing radon, the picocurie (pCi) is used, where 1 pCi is equal to 1×10^{-12} Ci.

Exposure. Inhalation (radon daughters attach to lung tissue and decay, resulting in the deposition of radiation, in the form of alpha particles, in the lung tissue); ingestion of radon-containing groundwater.

Toxicology. Radon is a known human lung carcinogen.

When inhaled, radon decay products (polonium-218 and polonium-214, solid form), alone or attached to the surface of aerosols, dusts, and smoke particles, deposit in the lungs.[2] Here, they radiate alpha particles and penetrate the cells of mucous membranes, bronchi, and other pulmonary tissues. The ionizing radiation energy occurs in those areas where mucociliary action is either absent or ineffective in removing the particles. Particles moving with the mucous flow cause essentially no radiation dose to tissue because of the short range of travel of alpha particles in liquids. The radiation initiates the process of carcinogenesis in the bronchial epithelial cells. Although radon-related lung cancers are mainly seen in the upper airways, radon increases the incidence of all histologic types of lung cancer, including small cell carcinoma, adenocarcinoma, and squamous cell carcinoma. Alpha radiations travel only extremely short distances in the body. Thus alpha radiations from decay of radon progeny in the lungs cannot reach cells in any other organs, so it is likely that lung cancer is the only potentially important cancer hazard posed by radon. In studies done on miners, variables such as age, duration of exposure, time since initiation of exposure, and especially the use of tobacco have been found to influence individual risk. Tobacco use multiplies the risk of radon-induced lung cancer significantly. No deaths in humans have been reported from acute radon exposure.[1] Several

epidemiological studies of workers exposed over long periods have reported significant increases in early mortality owing to cancer and nonneoplastic diseases.[2] Increased mortality as a result of emphysema and pulmonary fibrosis has been reported in uranium miners exposed to radon and daughters at levels in the range of 100–10,000 pCi radon-222/l air.[3] In a more recent study, there was a 12.7-fold mortality risk for lung cancer for nonsmoking uranium miners, compared with nonsmoking US veterans.[4] Mortality from nonmalignant respiratory disease (NMRD) among the nonsmoking uranium miners was 11.7 times higher than expected, based on 8 observed and 0.682 expected deaths. NMRD causes of death in the cohort included silicosis (3), chronic obstructive pulmonary disease (3), fibrosis (1), and emphysema (1). These results indicated that exposure to radon daughters in the absence of cigarette smoking is a potent carcinogen.[5] The US Surgeon General has stated that indoor radon from soil is the second leading cause of lung cancer.[6] The National Academy of Sciences has estimated that radon from soil causes about 15,000–22,000 lung cancer deaths each year in the US.[7] The risk of developing lung cancer is directly proportional to the levels and duration of exposure to radon: the higher the radon concentration, the higher the lung cancer risk. The EPA has set a guideline for radon in air inside homes of 4 pCi/l of air. This remediation "Action Level" is based on current mitigation technology.[8,9] Mitigation technology can usually reduce high radon concentration levels to below 4 pCi/l and to 2 pCi/l or less 70–80% of the time. The average radon level in homes is about 1.25 pCi/l. Although The US Congress passed legislation in 1988 establishing a national goal that indoor radon levels not exceed ambient outdoor radon levels (0.2–0.7 pCi/l), this goal is not yet technologically achievable.

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RDX
CAS: 121-82-4

$C_3H_6N_6O_6$

Synonyms: Cyclonite; hexahydro-1,3,5-trinitro-1,3,5-triazine; hexogen

Physical Form. Colorless crystals

Uses. High explosive; rodenticide

Exposure. Inhalation

Toxicology. RDX is a convulsant.

Workers exposed to RDX in an explosives plant complained of nausea and exhibited vomiting, epileptiform seizures, and unconsciousness, which lasted a few minutes to 24 hours with periods of stupor, nausea, vomiting, and weakness.[1] Recovery was complete with no sequelae. In a more recent case, a worker, handling cyclonite without adequate protection, experienced malaise with dizziness, headache, and nausea that progressed to unconsciousness and generalized seizures.[2] The role of dermal absorption was unclear because of concomitant exposure to the dust.

In an epidemiological study at a munitions plant where workers were exposed to 0.28 mg/m^3 time-weighted average (TWA), there were no abnormalities of the hematologic, hepatic, or renal systems.[3]

In male rats dosed by gavage at doses up to 60 mg/kg, spontaneous seizures occurred at 12.5 mg/kg, the lowest dose used.[4] Chronic oral studies in rats revealed no evidence of neoplasms, whereas one study in mice found an increased incidence of combined hepatocellular adenomas and carcinomas in females.[5] It has been noted that these tumors in mice are poor predictors for malignancy in other species. A number of studies suggest that RDX is not mutagenic.[5]

The 2003 time-weighted average-threshold limit value (TWA-TLV) for RDX is 0.5 mg/m^3.

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RESORCINOL
CAS: 108-46-3

$C_6H_4(OH)_2$

Synonyms: *m*-Dihydroxybenzene; resorcin; 1,3-benzenediol; 1,3-dihydroxybenzene

Physical Form. White crystals that turn pink on exposure to air

Uses. Manufacture of rubber products, wood adhesives, dyes, explosives, and cosmetics; in photography

Exposure. Inhalation; skin absorption

Toxicology. Resorcinol is an irritant of the eyes and the skin; in animals exposed at high concentrations it affects the central nervous system.

Workers exposed to airborne levels of 10 ppm (45 mg/m^3) for periods of 30 minutes or more reported no irritation or discomfort.[1] Application to the skin of solutions or ointments containing from 3% to 25% resulted in hyperemia, itching, dermatitis, edema, and corrosion.[2] Systemic effects from skin absorption have been restlessness, methemoglobinemia, convulsions, tachycardia, dyspnea, and death.[3] Ingestion of resorcinol induces similar signs and symptoms. Resorcinol also has been reported to cause sensitization and goiter.[3]

No toxic signs were observed in rats exposed by inhalation to 7800 mg/m^3 (1733 ppm) for 1 hour or 2800 mg/m^3 (625 ppm) for 8 hours.[1] When rats, rabbits, and guinea pigs

were exposed to 34 mg/m^3 6 hours/day for 2 weeks, no toxic effects were observed.[1]

Repeated gavage doses ranging from 55 mg/kg/day to 450 mg/kg/day, 5 days/week, for 2 weeks caused tachypnea and hyperexcitability within 30 minutes of dosing to F344/N rats.[4] In 13-week studies rats given 65 mg/kg/day or more had increased liver weights, whereas mice had significantly reduced adrenal weights when administered 28 mg/kg/day or more for the same period.[4] There was no evidence of carcinogenicity in rats or mice receiving up to 225 mg/kg/day, 5 days/week, for 2 years.[4] In a dermal oncogenicity study, three groups of female Swiss mice were treated with 0.02 ml of 5%, 25%, and 50% solutions of resorcinol in acetone twice weekly for 100 weeks.[5] The percentage of tumor-bearing animals was similar in the resorcinol-treated, untreated, and acetone-treated groups. Under the conditions of the test, resorcinol was considered noncarcinogenic.

The IARC has determined that there is inadequate evidence for the carcinogenicity of resorcinol in animals and that it is not classifiable as to its carcinogenicity in humans.[6]

Resorcinol was not genotoxic in bacterial assays or in *in vivo* mammalian assays; it did cause chromosomal aberrations in human lymphocytes *in vitro* but not in cultured human fibroblasts.[6]

A 10% solution in rabbit eyes has caused pain, conjunctivitis, and corneal vascularization.[7] Dry, powdered resorcinol applied to rabbit eyes has caused necrosis and corneal perforation.

No evidence of teratogenicity was found in rats receiving up to 250 mg/kg/day on days 6–15 of gestation.[8] This dose was maternally toxic, causing reduced body weight.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for resorcinol is 10 ppm (45 mg/m^3) with a short-term excursion limit (STEL) of 20 ppm (90 mg/m^3).

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RHODIUM (and Compounds)
CAS: 7440-16-6

Rh

Principal Compounds: Rhodium trichloride; rhodium trioxide; rhodium (II) acetate; rhodium nitrate; rhodium potassium sulfate; rhodium sulfate; rhodium sulfite

Physical Form. Silver-white metal

Uses. Electroplating; manufacture of rhodium-platinum alloys; manufacture of high-reflectivity mirrors

Exposure. Inhalation

Toxicology. There are no data demonstrating acute or chronic rhodium-related diseases; irritation and sensitization have occasionally been reported in humans from exposure to the salts of rhodium. Solutions of insoluble salts splashed in the eye may cause mild irritation.

There are few reports of contact dermatitis from rhodium.[1–3] Of 12 workers in a precious metal factory suffering from contact dermatitis 7 were sensitized to rhodium according to scratch-patch tests.[2] In one report, a woman working in a goldsmith's shop suffered occupational contact dermatitis from rhodium sulfate.[1] The investigators concluded that rhodium may be a potential sensitizer as a salt but not as a metal. Although metallic rhodium appears to have no sensitizing potential, when used as a coating for objects made of other metals, it may not prevent the sensitizing capacity of the underlying material (e.g., nickel).[1]

The LD_{50} for rhodium trichloride in rabbits by intravenous injection was 215 mg/kg; the clinical signs presented shortly after injection were increasing lethargy and waning respiration.[4] There were no abnormal findings at autopsy, but the rapid onset of death suggested central nervous system effects.

A solution of rhodium trichloride in the eye of a rabbit gave a delayed injurious reaction; 0.1 mg of solution adjusted to pH 7.2 with ammonium hydroxide was placed for 10 minutes in a rabbit eye after the corneal epithelium had been removed; an orange coloration of the cornea occurred that faded to faint yellow within 8 weeks.[5] During the first 2–3 weeks, the cornea was slightly hazy; in the third week, white opacities gradually developed; and, finally, there was extensive opacification and vascularization.

Lifetime exposure to 5 ppm rhodium trichloride in the drinking water caused a minimally significant increase in malignant tumors in mice; lymphomas, leukemias, and adenocarcinomas were most prevalent.[6]

Chick embryos exposed to rhodium on the eighth day of incubation were stunted; mild reduction of limb size and feather growth inhibition were also observed.[7] A number of rhodium compounds have tested positive in bacterial assays for genetic altering capability.[8]

The 2003 ACGIH threshold limit value-time-weighted averages (TLV-TWAs) are 1.0 mg/m^3 for the metal, 1.0 mg/m^3 as Rh, insoluble compounds, and 0.01 mg/m^3 as Rh, soluble compounds.

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RONNEL
CAS: 299-84-3

$(CH_3O)_2P(S)OC_6H_2Cl_3$

Synonym: *O*, *O*-Dimethyl-*O*-(2,4,5-trichlorophenyl) phosphorothioate; Fenchlorfos

Physical Form. White, crystalline powder

Uses. Systemic insecticide in livestock

Exposure. Inhalation; ingestion

Toxicology. Ronnel is a weak cholinesterase inhibitor and has low toxicity.

On both single and repeated doses, ronnel affects the pseudoesterase of the plasma rather than the true acetylcholinesterase of the red blood cells.[1]

In an experiment on humans to evaluate the primary skin irritating and skin sensitizing potential of ronnel, 50 subjects received three applications/week for 3 weeks of gauze saturated with a 10% suspension of ronnel in sesame oil; there were no significant effects on the skin.[1]

In male rats, the oral LD_{50} was 1.7 g/kg; effects were salivation, tremor, diarrhea, miosis, and respiratory distress—all attributed to the anticholinesterase effect of ronnel.[1] Rats fed 50 mg/kg body weight in the diet for 105 days developed slight liver and kidney damage.

Dogs fed 10 mg/kg/day for 2 years showed no overt clinical signs or evidence of any effect on urinalysis, hematologic analysis, organ weight measurement, or histologic evaluation of the tissues; depression of plasma cholinesterase was the only significant finding.[2]

When a small amount of ronnel powder was placed in the eye of a rabbit, effects were slight discomfort and transient conjunctival irritation, which subsided within 48 hours.[1]

Daily oral administration of 600 or 800 mg/kg ronnel to dams on days 6 through 15 of gestation caused a significant dose-related increase in fetuses with an extra rib.[3]

Ronnel has not been shown to potentiate the effect of other commonly used organophosphorus insecticides.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for ronnel is 10 mg/m^3.

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ROTENONE
CAS: 83-79-4

$C_{23}H_{22}O_6$

Synonyms: Derrin; nicouline, tubatoxin

Physical Form. Colorless crystals

Uses. Insecticide; lotion for chiggers; emulsion for scabies

Exposure. Inhalation; ingestion

Toxicology. Rotenone is an irritant and affects the nervous system, causing convulsions.

The lethal oral dose in humans is estimated to be 0.3–0.5 g/kg.[1] Symptoms of inhalation, absorption, or ingestion in humans (inferred mostly from animal studies) may include numbness of oral mucous membranes, nausea, vomiting, abdominal pain, muscle tremor, incoordination, clonic convulsions, and stupor.[1] Local effects from the dust include

conjunctivitis, dermatitis, pharyngitis, and rhinitis.[2]

Animals repeatedly fed derris power (a botanical source containing 9.6% rotenone) at levels from 312 to 5000 ppm developed focal liver necrosis and mild kidney damage.[2] The oral LD_{50} values vary greatly depending on particle size, manner of dispersion, activity of sample, and species tested. Values ranging from 25 mg/kg in rats to more than 3000 mg/kg in rabbits have been reported.[3]

At the cellular level, rotenone inhibits cellular respiration by blocking electron transport between flavoprotein and ubiquinone. It also inhibits spindle microtubule assembly.[3]

Rotenone has been reported to induce tumors in female Wistar rats. Of 40 female rats given daily intraperitoneal injections of 1.7 mg/kg body weight rotenone in sunflower oil for 42 days, over 60% developed mammary tumors 6–11 months after the end of treatment. Most of the tumors were mammary adenomas, and one was a differentiated adenocarcinoma. None of the control animals had tumors when examined 19 months after treatment.[4]

Recent attempts to replicate these results have not been successful. Specifically, rotenone was not carcinogenic for the mammary gland in female Wistar rats when injected ip 5 days/week for 8 weeks, at 1.0 or 2.0 mg/kg body weight in vehicles of sunflower oil or sunflower oil: chloroform.[5] Furthermore, tumors at other sites were not significantly different from those observed in control animals. Additional studies, including a 14-month oral gavage bioassay in Wistar rats, an 18-month ip injection bioassay in Sprague-Dawley rats, an 18-month feeding study in Syrian golden hamsters, and a 2-year feeding study in Fischer 344 rats and B6C3F1 mice, have also shown no evidence of carcinogenicity for rotenone.[6,7]

Administered orally to rats on days 6–15 of pregnancy, 10 mg/kg was highly toxic to dams, killing 12 of 20; there was a significant decrease in the number of live fetuses per surviving dam and an increase in the proportion of resorptions.[8] In the 5 mg/kg group, there was an increased frequency of skeletal aberrations such as extra rib, delayed ossification of sternebra, and missing sternebrae.[8]

In human lymphocyte culture assays rotenone did not increase the frequency of chromosomal aberrations or sister chromatid exchanges but did cause an increase in the frequency of binucleated micronuclei and a delay in cell cycle.[9]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for rotenone is 5 mg/m^3.

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RUBBER, NATURAL LATEX
CAS: 9006-04-6

Synonyms: Natural latex—milky fluid that consists of extremely small particles of rubber obtained from plants, principally from the Hevea brasiliensis (rubber) tree, dispersed in an aqueous medium.[1] It contains a variety of naturally occurring substances in a colloidal suspension, including about 1% proteins (e.g., α-globulins, hevein), which are the allergenic fraction.[2]

Natural rubber—name for all materials made from or containing natural latex.[1] Products that contain natural rubber are made using two commonly employed manufacturing processes, the natural rubber latex (NRL) process and the dry natural rubber (DNR) process. The NRL manufacturing process involves the use of natural latex in a concentrated colloidal suspension. Products are formed from natural rubber latex by dipping, extruding, or coating and are typically referred to as containing or being made of "natural rubber latex." Examples of products that may contain natural rubber latex include medical gloves, catheters, tracheostomy tubes, and condoms.

The DNR manufacturing process involves the use of coagulated natural latex in the form of dried or milled sheets. Products are formed from dry natural rubber by compression molding or extrusion or by converting the sheets into a solution for dipping. These products are typically referred to as containing or being made of dry natural rubber or "crepe" rubber. Examples of products that may contain dry natural rubber include syringe plungers, vial stoppers, and injection ports on intravascular tubing.

"Synthetic latex" or "synthetic rubber" can contain natural rubber in their formulations, but synthetic latex and synthetic rubber can also be manufactured without natural rubber.

Physical Form. milky fluid; solid

Uses. Natural rubber latex is a starting material for the rubber industry (see *Synonyms*).

Exposure. Inhalation (dust); skin contact

Toxicology. NRL causes allergic skin reactions of type I (immediate-type) and type IV [delayed-type hypersensitivity (DTH)].

The immediate, type I reaction is IgE mediated and is a reaction to small proteins found in the latex.[3,4] Severe systemic allergic reactions have been life-threatening. Fifteen deaths from anaphylactic shock were caused in the early 1990s by barium enema catheter tips, which prompted the FDA to recall a particular brand of barium enema catheter tips.[5,6] Many of the type I reactions have resulted from contact with NRL gloves. First exposure to NRL may induce sensitization by inducing plasma cells to produce NRL-specific IgE or IgG4 antibodies that bind to high-affinity receptors on mast cells. Subsequent exposure to NRL triggers the immediate allergy, which is a typical example of contact urticaria syndrome.[7] This consists of localized urticaria (stage 1), angioedema (stage 2), asthma (stage 3), and anaphylaxis (stage 4). Typical reactions occur within an hour of exposure. Clinical manifestations depend on exposure route. Immediate itching and urticarial wheals are the most common manifestations of allergy to NRL gloves.[3] Glove-induced asthma is caused by the NRL proteins binding to cornstarch glove powder and becoming airborne.[8]

Type IV reactions are due to chemicals added during manufacture of NRL, which include accelerators, antioxidants, antiozonants, emulsifiers, stabilizers, extenders, colorants, retarders, stiffeners, and biocides. Accelerators primarily control the rate, uniformity, and completeness of vulcanization. The most common accelerators include thiurams, carbamates, and mercaptobenzothiazoles.[9] These chemicals are covered in detail in their specific monographs in this volume.

The upsurge of latex allergy is traced back to a CDC report published on August 21, 1987 that came to be known as "universal precautions." It emphasized the need for all health care workers to routinely use appropriate barrier precautions, such as gloves, when contacting body fluids.[3] New and inexperienced glove manufacturers entered the glove market and produced poorly compounded,

inadequately leached products. These gloves contained unprecedented concentrations of protein allergens, which sensitized thousands. During the late 1980s, an oversupply of gloves occurred, prices plummeted, and many new manufacturers went out of business. However, a newly sensitized population continues to have problems even with high-quality products.

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SELENIUM (and Compounds)
CAS: 7782-49-2

Se

Compounds: Selenium dioxide; selenium trioxide; selenium oxychloride; sodium selenite; sodium selenate; hydrogen selenide; selenic acid; selenium sulfide; selenium disulfide

Physical Form. Elemental selenium occurs as gray to black crystals; many compounds are solids, although hydrogen selenide is a colorless gas.

Uses. In electronics; selenium rectifiers and photocells; used to coat the metal cylinders from which a photographic image is transferred in xerography; glass and ceramics manufacture (exposure also may occur during smelting and refining of ores containing selenium)

Exposure. Inhalation

Toxicology. Selenium is an essential trace element that can be toxic in excessive amounts. Elemental selenium and selenium compounds as dusts, vapors, and fumes are irritants of the eyes, mucous membranes, and skin. Chronic exposure may cause central nervous system effects, gastrointestinal disturbances, and loss of hair and fingernails.

Selenium dusts produce respiratory tract irritation manifested by nasal discharge, loss of smell, epistaxis, and cough.[1] A group of workers briefly exposed to unmeasured but high concentrations of selenium fume developed severe irritation of the eyes, nose, and throat, followed by headaches. Transient dyspnea occurred in one case.[2] Workers exposed to an undetermined concentration of selenium oxide developed bronchospasm and dyspnea followed within 12 hours by metal fume fever (chills, fever, headache) and bronchitis, leading to pneumonitis in a few cases; all were asymptomatic within a week.[3]

In a study of workers in a selenium plant, workroom air levels ranged from 0.2 to 3.6 mg/m^3 and urinary levels ranged from below 0.10 mg/l to 0.43 mg/l of urine. The chief complaints were garlic odor of the breath, metallic taste, gastrointestinal disturbances, and skin eruptions.[4]

An endemic disease in China, characterized by loss of hair and nails, skin lesions, and abnormalities of the nervous system, including some paralysis and hemiplegia, was attributed to chronic selenium poisoning.[5] The daily intake for six affected individuals averaged 5.0 mg versus 0.1 mg for people from an unaffected area. Changing the diet led to

recoveries. There have been no reports of disabling chronic disease or death from industrial exposure.

An accidental spray of selenium dioxide into the eyes of a chemist caused superficial burns of the skin and immediate irritation of the eyes. Within 16 hours, the subject's vision was blurred and the lower portions of both corneas appeared dulled. Sixteen days after the accident, the corneas were normal.[6]

Elemental selenium is not particularly irritating, but various compounds such as selenium oxychloride and selenium dioxide are strong vesicants.[7] Skin contact with the fume of heated selenium dioxide caused an acute, weeping dermatitis, with the development of hypersensitivity in some cases.[8] Selenium dioxide forms selenious acid when in contact with water; if allowed to penetrate beneath the fingernails, it causes an especially painful inflammatory reaction.[8]

In livestock, selenium has been found to be the cause of "blind staggers" and alkali disease. Blind staggers occurs as a result of acute ingestion of seleniferous plants and is characterized by impaired vision, depressed appetite, a tendency to wander in circles, paralysis, and death from respiratory failure.[9] A more chronic syndrome described in horses and livestock is alkali disease, which also is associated with consumption of grains or plants containing selenium. The disease is characterized by lack of vitality, loss of appetite, emaciation, deformed hoofs, loss of hair, erosion of the joints of long bones, anemia, cirrhosis, and cardiac atrophy.[9]

In a number of reproductive studies in mammals, using a variety of selenium compounds, adverse effects have only been seen at doses that are associated with maternal toxicity[10,11]

Epidemiological studies in humans do not suggest an association between excess exposure to selenium and cancer.[11] Low levels of intake, however, have been associated with an increased risk of developing many kinds of cancers. With the exception of selenium sulfide, most animal studies have shown that selenium compounds inhibit tumorigenesis.[11] High doses of selenium sulfide administered by gavage caused liver tumors in rats and lung and liver tumors in female mice.[12] Mutagenic and antimutagenic effects of selenium also have been reported.[11,13]

(See separate entries on selenium hexafluoride and hydrogen selenide.)

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for selenium and compounds is 0.2 mg/m^3, as Se.

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SELENIUM HEXAFLUORIDE
CAS: 7783-79-1

SeF_6

Synonym: Selenium fluoride

Physical Form. Colorless gas

Uses. Gaseous electric insulator

Exposure. Inhalation

Toxicology. Selenium hexafluoride is a severe pulmonary irritant in animals; heavy exposure is expected to cause the same effect in humans.

There are no reports of human exposure to selenium hexafluoride.

Exposure of four animal species to 10 ppm for 4 hours was fatal; 5 ppm for 5 hours was not fatal but caused pulmonary edema, whereas 1 ppm produced no effects.[1] Animals exposed to 5 ppm 1 hour daily for 5 days developed signs of pulmonary injury; 1 ppm for the same time period caused no effects.

The 2003 ACGIH time-weighted average-threshold limit value (TWA-TLV) for selenium hexafluoride is 0.05 ppm (0.16 mg/m^3).

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SILICA, AMORPHOUS—DIATOMACEOUS EARTH
CAS: 68855-54-9

SiO_2

Synonyms: Diatomite; diatomaceous silica; infusorial earth

Physical Form. Solid; soft, chalky powder

Uses. Production of filters, polishes, absorbents, insulators

Exposure. Inhalation

Toxicology. Amorphous silica, natural diatomaceous earth, is usually considered to be of low toxicity; however, pure amorphous silica is rarely found. Processing of amorphous silica by high-temperature calcining alters the silica from the benign amorphous to the pathogenic crystalline form (cristobalite), which causes fibrosis. Characteristically, natural diatomite contains no measurable cristobalite. Depending upon the source, it may contain a low percentage of contaminating quartz, rarely over 2%. Non-flux-calcined diatomite may contain from 20% to 30% cristobalite, whereas flux-calcined diatomite may contain as much as 60% cristobalite.[1–3] Non-flux-calcined and flux-calcined diatomite can produce severe and disabling pneumoconiosis, which is attributed to their cristobalite content. Although a form of silicosis, it characteristically produces pathologic and radiographic changes, which are different from classic quartz silicosis. Diffuse, rather than modular, changes are more common.[2]

In a study of diatomaceous earth workers, those employed in the quarry for more than 5 years and exposed only to natural diatomaceous earth had no significant roentgenologic changes. Of others employed for more than 5 years in the milling process and exposed to calcined material, 17% had simple pneumoconiosis and 23% had the confluent form, probably the result of fibrogenic action of the crystalline silica formed by calcination of the naturally occurring mineral.[3,4]

In humans, calcined diatomaceous earth pneumoconiosis is characterized roentgenographically by fine linear and/or minute nodular shadows, either or both of which may be accompanied by conglomerate fibrosis. In the simple phase of the disease the upper lobes are affected more than the lower lobes, and the condition progresses by an increase in the apparent number of the nodules, which rarely

attain the density or size of nodules often seen in quartz silicosis.[4] In the early confluent stage of the disease, the linear and nodular changes in the upper lung fields become more circumscribed and homogeneous. Histologically, there is an absence of the focal, discrete, hyalin nodules or the whorled pattern of collagenous fibers of typical silicosis.[4,5]

Chest radiography of 492 diatomaceous earth workers employed in a mine-processing facility in California revealed profusion abnormalities in 5%; the prevalence of profusion abnormalities was significantly higher in workers with more than 12.5 years of employment.[6]

A cohort study of diatomite facility workers in Iceland exposed for at least 5 years to diatomaceous earth and cristobalite found increased incidences of lung, skin, and brain cancer.[7]

Amorphous silica has been tested for carcinogenicity in a variety of animal studies by a number of routes.[8] Most of the tests were negative or were inadequate primarily because of poorly defined physiochemical characteristics of the silica. The IARC concluded that evidence is inadequate to describe amorphous silica as carcinogenic in either experimental animals or humans. Crystalline silica, however, has been designated by IARC as a probable human carcinogen (category 2A), based on "sufficient evidence" in experimental animals and "limited evidence" in humans.[2,8,9] Therefore, although evidence for the carcinogenicity of crystalline silica in humans is unconvincing, certainly from exposures insufficient to cause silicosis, appropriate hazard warnings are obligatory in the United States. These apply to all materials containing 0.1% or more of crystalline silica (quartz, cristobalite, and/or tridymite).[2]

The 2003 ACGIH proposed threshold limit value-time-weighted average (TLV-TWA) for amorphous silica, natural diatomaceous earth, is 10 mg/m^3 for the inhalable particulate and 3 mg/m^3 for respirable dust containing no asbestos and <1% quartz.

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SILICA, AMORPHOUS—FUME
CAS: 69012-64-2

SiO_2

Physical Form. Fine white powder with particle sizes generally below 1 μm. This is not the same as the commercial products "fumes silica," "silica gel," "precipitated silica," or "fused silica." It is formed during the electric arc production of elemental silicon from

quartz, which is reduced to silicon monoxide, escaping from the furnace and oxidized by air to silicon dioxide. This condenses to form spherical particles. For the production of ferrosilicon, iron metal is added to the charge; during charging there is also exposure to crystalline silica.[1]

Uses. None; produced only as a by-product.

Exposure. Inhalation

Toxicology. Amorphous silica fume exposure is associated with recurrent fever, similar to metal fume fever, and nonprogressive pulmonary changes.

Adverse effects on the lungs of workers exposed to the fumes of ferrosilicon furnaces have been recognized since 1937. Subsequent clinical studies of workers exposed to amorphous silica fume in silicon and ferrosilicon plants reported pulmonary symptoms and X-ray findings difficult to differentiate from classic silicosis due to crystalline silica, especially because there is often concurrent exposure to quartz dust during furnace operations.[1–4]

The disease process in workers exposed to silica fume was originally described as silicosis or acute silicosis, but it is now recognized that the X-ray pattern and symptom complex are different from both, the severity of the symptoms is less, and there is apparently no progression. It has been postulated that heavy exposure to freshly formed silica fume causes an acute reaction similar to metal fume fever. Continued or repeated exposure causes the "ferroalloy disease," which has been described.[1,2,5] This is characterized by recurrent fever over a period of 3–12 weeks, with the appearance of X-ray markings similar to silicosis. The development of classic silicosis may be the result of long, continued exposure to amorphous silica fume, or possibly concurrent exposure to crystalline silica.[1,5]

Of 900 African production workers in a ferroalloy plant, 35 cases of "ferroalloy worker disease" were identified over a 10-year period. These were either acute episodes of metal fume fever or pulmonary fibrosis recognized by X ray. Over a period of 2–6 years after first diagnosis, 22 cases remained static, regressed, or returned to normal; 8 cases progressed with increased fibrosis and nodulation by X ray.[4–6]

Autopsy of cases of alleged silicosis in Swedish ferrosilicon workers revealed no silicosis, and it was postulated that pulmonary conditions that had been recognized by X ray may have been due to unspecified infectious changes.[7] This study also concluded that "exposure to fumes and dust particles, for the most part amorphous SiO_2, in ferrosilicon alloy melting works, does not seem to give rise to a serious risk of silicosis although the additional handling of quartz in this industry certainly constitutes a grave risk of silicosis."

More recently, the importance of silica fume particle size on toxicity has been noted.[8] Specifically, particles of the ultrafine size range may be expected to have higher toxicity compared with particles of larger size.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for amorphous silica fume is 2 mg/m^3 for the respirable fraction of dust.

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SILICA, CRYSTALLINE—QUARTZ

CAS: 14808-60-7

SiO_2

Synonyms: Silicon dioxide; silicic anhydride

Physical Form. Colorless crystals

Uses. Manufacture of glass, porcelain, and pottery; metal casting; sandblasting; granite cutting; manufacture of refractory, grinding, and scouring compounds

Exposure. Inhalation

Toxicology. Crystalline silica causes silicosis and is associated with an increased risk of lung cancer.

Silicosis is a form of disabling, progressive, and sometimes fatal pulmonary fibrosis characterized by the presence of typical nodulation in the lungs.[1] The earliest lesions are seen in the region of the respiratory bronchioles. Lymphatics become obliterated by infiltration with dust-laden macrophages and granulation tissue. Morphologically, the typical lesion of silicosis is a firm nodule composed of concentrically arranged bundles of collagen; these nodules usually measure between 1 and 10 mm in diameter and appear around blood vessels and beneath the pleura, as well as in mediastinal lymph nodes. There may be conglomeration of nodules as the disease progresses, leading to massive fibrosis.[1] The pulmonary pleura is usually thickened due to fibrosis and is often adherent to the parietal pleura, especially over the upper lobes and in the vicinity of underlying conglomerate lesions.[2]

Histologically, the silicotic nodule consists of a relatively acellular, avascular core of hyalinized reticulin fibers arranged concentrically and blending with collagen fibers toward the periphery, which has well-defined borders.[3]

The clinical signs and symptoms of silicosis tend to be progressive with continued exposure to quantities of dust containing free silica, with advancing age, and with continued smoking habits.[1] Symptoms may also be exacerbated by pulmonary infections and cardiac decompensation. Symptoms include cough, dyspnea, wheezing, and repeated nonspecific chest illnesses. Impairment of pulmonary function may also be progressive. In individual cases, there may be little or no decrement when simple discrete nodular silicosis is present, but when nodulations become larger or when conglomeration occurs, recognizable cardiopulmonary impairment tends to occur.

The progression of symptoms may continue after dust exposure ceases. Although there may be a factor of individual susceptibility to a given exposure to silica dust, the risk of onset and the rate of progression of the pulmonary lesion are clearly related to the character of the exposure (dust concentration and duration).[1] The disease tends to occur after an exposure measured in years rather than in months. It is generally accepted that silicosis predisposes to active tuberculosis and that the combined disease tends to be more rapidly progressive than uncomplicated silicosis.

The earliest radiographic evidence of nodular silicosis consists of small, discrete opacities of 1- to 3-mm diameter appearing in the upper lung fields. As the disease advances, discrete opacities increase in number and size and are seen in the lower as well as the other zones of the lung fields. Small conglomerations may then appear, subsequently developing into large, irregular, and sometimes massive opacities occupying the greater part of both lung fields. Bullae may be seen in the vicinity of conglomerations.[2]

A group of 972 granite shed workers were studied to relate exposure levels to incidence of silicosis.[4] The workers were grouped according to four average exposure levels: 1) 37–60, 2)

27–44, 3) 20, and 4) 3–9 mppcf. Those with the highest dust exposure showed development of early silicosis in 40% of the workers after 2 years and 100% after 4 years of exposure. The development of silicosis in the remaining workers appeared to be proportional to the dust exposure. At the second-highest exposure level (27–44 mppcf), early stages of silicosis appeared after 4 years of exposure and more advanced stages developed by the seventh year. In the group exposed at an average of 20 mm, there was little indication of severe effects on the health of the workers. In the lowest-exposure group, where the average dust concentration was 6 mm (range 3–9 mppcf), there was no indication of any untoward effects of dust exposure on workers.

Exposures to relatively low concentrations of silica for a prolonged period may be capable of causing hilar node fibrosis, impairing the clearance of any silica inhaled subsequently. In one case, 30 years of exposure to $<0.1\ mg/m^3$ led to hilar node fibrosis and calcification in an exposed stonemason; subsequent exposure for 5 years to about $2\ mg/m^3$ led to rapid, progressive silicosis that proved fatal. Estimates of exposure tallied with postmortem measurement of lung burden, suggesting retention of all dust deposited in the lungs over his final period of work.[5]

In some occupations, such as sandblasting and production of silica flour, exposure to high concentrations of silica over only a few years has produced a more rapidly progressive form of the disease termed accelerated silicosis. The symptoms are those of the more chronic disease, but clinical and radiological progression is rapid.[6] An acute form of silicosis has occurred in a few workers exposed to very high concentrations of silica over periods of as little as a few weeks. The history is one of progressive dyspnea, fever, cough, weight loss, and, in severe cases, death with a year or two. In acute silicosis the nodular pattern is absent, the lungs showing a diffuse ground-glass appearance, similar to pulmonary edema.[6]

Exposure of silica has also been related to chronic airflow limitation without radiographic changes.[7] Epidemiological studies of quartz-exposed workers reported statistically significant numbers of excess deaths or cases of renal disease or subclinical renal changes.[8]

A large number of studies have been conducted in an effort to assess the role of silica exposure in the pathogenesis of lung cancer.[8–10] Some studies of mining, quarry, tunnel, and foundry workers have shown moderately raised standardized mortality ratio (SMRs) for lung cancer, ranging from 127 to 156.[11] However, the role of smoking or other contributing factors, such as radon exposure, cannot be excluded, and other large cohort studies have not found any increased risk for lung cancer.

Cohort and case control studies on registered silicotics reported excess lung cancer risks, with relative risks ranging from 1.5 to 6.0.[9] Excesses were seen across countries, industries, and time periods, and a number of studies reported exposure-response gradients, using varying indicators of exposure. Meta-analyses of the epidemiological studies of silica exposure and lung cancer reported a moderate summary risk of 1.3 for silica-exposed workers and higher summary relative risks of 2.2–2.3 for studies of silicotic workers.[8]

In animal studies, significant increases in adenocarcinomas and squamous cell carcinomas of the lung have occurred in rats after inhalation or intratracheal instillation in rats, but not in hamsters.[9] Increasing *in vitro* and *in vivo* evidence suggests that the rat lung tumor response to crystalline silica exposure is a result of marked and persistent inflammation and epithelial proliferation. However, other pathways such as a role for crystalline silica surface-generated oxidants or a direct genotoxic effect cannot be ruled out.

Silica was not mutagenic in bacterial assays; both positive and negative results have been reported in a wide variety of *in vivo* and *in vitro* genotoxic assays.[8]

The IARC has determined that there is sufficient evidence for the carcinogenicity of crystalline silica to experimental animals and to humans.[9]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for crystalline quartz silica is $0.1\ mg/m^3$ for the respirable fraction of dust.

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SILICON
CAS: 7440-21-3

Si

Synonyms: None

Physical Form. Black to gray needlelike crystals

Uses. In manufacture of transistors, silicon diodes, and similar semiconductors; for making alloys such as ferrosilicon and silicon copper

Exposure. Inhalation

Toxicology. Silicon appears to be a biologically inert material.

Little information is available on the toxicology of pure elemental silicon, which is an inert material that appears to lack the property of causing fibrosis in lung tissue.[1] Silicon dust gave an inert response on intraperitoneal injection into guinea pigs and rats.[2] Another study, however, reported minimal pulmonary lesions in rabbits after the intratracheal injection of silicon dust at a high level of 25 mg.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 10 mg/m^3, for total dust containing no asbestos and <1% crystalline silica.

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SILICON CARBIDE
CAS: 409-21-2

SiC

Synonyms: Carborundum; Crystolon; Carbonite; Carbofrax; Electrolon

Physical Form. Green to bluish-black iridescent crystals

Uses. Manufacture of abrasives and refractories, brake linings, heating elements, and thermistors

Exposure. Inhalation

Toxicology. Silicon carbide, in certain forms, may be a cause of pneumoconiosis in exposed workers.

Silicon carbide has generally been considered to be an inert dust with little adverse effect on the lungs.[1] Animal experiments have supported this view. In one study, rats injected intratracheally at 20 mg/day with silicon carbide dust for 50 exposures and observed for up to 12 months had no significant changes in the lungs.[2] Human studies, however, have reported abnormal chest radiographs compatible with pneumoconiosis and significant reductions in pulmonary functions among workers exposed to silicon carbide.[3,4] Pathologic reports of silicon carbide pneumoconiosis identified silicon carbide but no significant amounts of other fibrogenic agents.[5,6]

A recent cohort mortality study among Canadian silicon carbide workers suggested that exposure to fibers may increase the risk of malignant and nonmalignant respiratory disease.[7] The risk ratio was 1.67 for lung cancer and 4.08 for nonmalignant respiratory disease among those with the highest cumulative dust exposures.[7]

In the silicon carbide manufacturing process the major bioactive dusts identified are quartz particles and silicon carbide fibers generated in the process. In contrast to the silicon carbide fibers, silicon carbide particles were found to be inert in animal studies. Silicon carbide fibers have fibrogenic activities comparable to asbestos fibers of similar size and are likely to contribute to the pathogenesis of the interstitial lung disease of silicon carbide production workers.[3] Studies of exposure to silicon carbide whiskers (cylindrically shaped single crystals) in rats have also shown dose-related increases in the severity of alveolar, bronchiolar, and pleural wall thickening and inflammatory lesions that did not reverse after a recovery period.[8] Rats exposed 7 hours/day, 5 days a week for 1 year to silicon carbide whiskers had fibrosis and pleural mesotheliomas.[9]

These results have suggested that mineral dusts that are inert in a particulate form may have biological activity when they occur in a fibrous form. Factors affecting fiber toxicity include length, diameter, respirability, resistance to chemical dissolution in biological fluids, and durability.[10]

In vitro experiments have shown disturbances in cellular DNA content and karyotype.[10]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 10 mg/m^3 for total dust containing <1% quartz.

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SILICON TETRAHYDRIDE
CAS: 7803-62-5

SiH_4

Synonyms: Silane; monosilane

Physical Form. Colorless gas

Uses. Manufacture of solid-state devices; source of silicon for semiconductor manufacture

Exposure. Inhalation

Toxicology. Silicon tetrahydride is considered to be a skin, eye, and mucous membrane irritant.

There is no information regarding its toxicity to humans; by analogy with other tetrahydrides it is considered to be an irritant.[1,2]

Silicon tetrahydride has a low acute toxicity in experimental animals. In rats the 4-hour LC_{50} is 9600 ppm.[3] Rats exposed at 126 ppm for 1 hour were apparently unaffected.[2]

Six of eight mice died after 4-hour exposure to 10,000 ppm.[4] Acute renal tubular necrosis was observed in animals exposed at 2500 ppm or more for 4 hours. At 1000 ppm 6 hours/day, 5 days/week for 4 weeks there was mild irritation manifested as exudate and inflammatory or necrotic cells on the nasal mucosa.[5] No other changes were noted after hematologic, biochemical, or histopathologic examination. In the Ames assay silicon tetrahydride was mutagenic in some strains of bacteria with or without metabolic activation.[6]

The potential for explosion, fire, and oxygen-deficient atmospheres constitutes the major hazard with silicon tetrahydride.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 5 ppm (6.6 mg/m^3).

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SILVER (and Compounds)
CAS: 7440-22-4

Ag

Compounds: Silver nitrate; silver chloride; silver oxide; silver sulfide

Physical Form. Elemental silver is a lustrous, white solid metal.

Uses. Photographic materials; electrical and electronics products; alloys and solders; in jewelry, mirrors, flatware, and coinage

Exposure. Inhalation; oral; dermal

Toxicology. The primary effect of silver exposure is argyria, a gray-blue discoloration of the skin, eyes, nails, mucous membranes, and/or internal organs.

Argyrosis (deposition of silver in the eyes) appears to be the critical effect and is observed in workers exposed to silver compounds at concentrations in the range of 0.005–0.38 mg/m^3.[1] Disturbances with night vision and lens changes without visual impairment have been associated with argyrosis.[1]

Argyria may occur in an area of repeated or abrasive dermal contact with silver or silver compounds, or more extensively over widespread areas of skin and the conjunctiva of the eyes after long-term oral or inhalation exposure.[2] Localized argyria occurs in the skin and eyes, where gray-blue patches of pigmentation are formed without evidence of tissue reaction.[3] Generalized argyria is recognized by the widespread pigmentation of the skin; the tissue discoloration is due to the deposition of silver complexes and to a silver-induced increase in melanin and is more pronounced in the sunlight-exposed parts of the skin.[1] Argyria of the respiratory tract has been described in two workers involved in the manufacture of silver nitrate. Their only symptom was mild chronic bronchitis. Bronchoscopy revealed tracheobronchial pigmentation. Biopsy of the nasal mucous membrane showed silver deposition in the subepithelial area.[3] It has been estimated that gradually accumulated intake of from 1 to 5 g of silver will lead to generalized argyria.[3]

Upper respiratory tract irritation has been observed in humans at estimated exposure levels of between 0.04 and 0.4 mg silver/m^3 for less than 1 to greater than 10 years.[2] Irritant effects are considered to be related to the caustic properties of the various silver compounds, rather than the silver itself.

Massive exposure to heated vapor of metallic silver for 4 hours by a workman caused lung damage with pulmonary edema.[4] Ingestion of 10 g of silver nitrate is usually fatal. Large oral doses of the compound cause abdominal pain and rigidity, vomiting, convulsions, and shock.[5] Patients dying after intravenous administration of Collargol (silver plus silver oxide) showed necrosis and hemorrhage in the bone marrow, liver, and kidney.[6]

There is no historical information in humans to suggest that silver affects reproduction.[2] In an early animal study, there was no reduction in fertility or observable changes in spermatozoa after 2 years of exposure to 89 mg silver/kg/day as silver nitrate or silver chloride in the drinking water.

Although fibrosarcomas have been reported in animals after subcutaneous imbedding of silver foil, normal routes of exposure have not provided indications of carcinogenicity in animals or humans, and silver is not expected to be carcinogenic in humans.[2]

In genotoxic assays, the silver ion caused DNA strand breaks *in vitro* but silver compounds were not mutagenic in several bacterial assays.[1,2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 0.01 mg/m^3 for soluble compounds, as Ag, and 0.1 mg/m^3 for metal dust and fume.

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SOAPSTONE

$3MgO{\cdot}4SiO_2{\cdot}H_2O$

Soapstone is a soft metamorphic rock without precise mineralogical definition composed mainly of talc, dolomite, and actinolite; talc is mined as soapstone, but some forms of soapstone have as little as 50% talc.

Synonyms: Steatite; massive talc

Physical Form. Talclike material of varying composition, but generally grayish-white, fine, odorless power. It is noncombustible and insoluble in water.

Uses. Pigment in paint, varnishes; filler for paper, rubber, soap; lubricating molds and machinery; heat insulator

Exposure. Inhalation

Toxicology. The fibrous talc in soapstone dust causes fibrotic pneumoconiosis; an increased incidence of cancer of the lungs and pleura has been reported.

In the development of talc pneumoconiosis or talcosis, the subject initially is symptom-free, but cough and dyspnea develop as the disease progresses; cyanosis, digital clubbing, and cor pulmonale occur in advanced cases. The disease progresses slowly, even in the absence of continued exposure; occasionally, the disease may progress rapidly, with death occurring within a few years of a very heavy exposure.[1,2]

In an early report of 66 workers handling soapstone, no cases of pneumoconiosis were found in workers with an average dust exposure of 2.8 mg/m^3 but exposures ranging from 22 to 50 mg/m^3 caused severe cases.[3]

An epidemiological study of 260 workers with 15 or more years of exposure to commercial talc dust, containing talc, tremolite, anthophyllite, carbonate dusts, and a small amount of free silica, revealed a four times greater than expected mortality rate from cancer of the lungs and pleura; in addition, a major cause of death among these workers was cor pulmonale—a result of the pneumoconiosis.[4,5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for soapstone is 3 mg/m^3 as respirable dust containing no asbestos and <1% crystalline silica and 6 mg/m^3 as inhalable dust containing no asbestos and <1% crystalline silica.

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SODIUM FLUOROACETATE

CAS: 62-74-8

$CH_2FCOONa$

Synonyms: Compound 1080; fluoroacetic acid, sodium salt; Fratol; sodium monofluoroacetate

Physical Form. Fine white powder

Uses. Rodenticide (restricted use)

Exposure. Inhalation; ingestion

Toxicology. Sodium fluoroacetate is highly toxic and causes convulsions and ventricular fibrillation.

Fluoroacetate produces its toxic action by inhibiting the citric acid cycle.[1] The fluorine-substituted acetate is metabolized to fluorocitrate that inhibits the conversion of citrate to isocitrate. There is an accumulation of large quantities of citrate in the tissue, and the cycle is blocked. The heart and central nervous system are the most critical tissues involved in poisoning by a general inhibition of oxidative energy metabolism.[1]

Onset of symptoms after ingestion is frequently delayed for 30 minutes to 2 hours; effects are vomiting, apprehension, auditory hallucinations, nystagmus, a tingling sensation of the nose, numbness of the face, facial twitching, and epileptiform convulsions.[2,3] After a period of several hours, there may be pulsus alterans, long sequences of ectopic heartbeats (often multifocal), tachycardia, ventricular fibrillation, and death.[3,4] The lethal oral dose in humans is estimated to be approximately 5.0 mg/kg.[4,5] In a fatal case of ingestion, autopsy findings included hemorrhagic pulmonary edema and degeneration of renal tubules.[5]

A retrospective study of 38 cases of sodium fluoroacetate poisoning (including 7 deaths) concluded that hypotension and early-onset metabolic acidosis and increased serum creatinine were most often associated with poor short-term survival.[6]

Applied as a 0.1% mixture in fish meal, and widely dispersed throughout a workplace as a rat poison, sodium fluoroacetate caused several employees to become seriously ill (details not given).[7] Exposure is thought to have occurred from airborne contamination, although accidental ingestion cannot be ruled out.

In the only alleged case of chronic human poisoning, an exterminator repeatedly exposed over a period of 10 years presented with severe and progressive lesions of the renal tubular epithelium and with milder hepatic, neurological, and thyroid dysfunctions.[8]

In developmental studies in rats 0.75 mg/kg/day administered by gavage on days 6–17 of gestation caused significant reductions in maternal and fetal body weight gains, but no external fetal abnormalities were noted.[9]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for sodium fluoroacetate is 0.05 mg/m^3 with a notation for skin.

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SODIUM HYDROXIDE
CAS: 1310-73-2

NaOH

Synonyms: Caustic soda; caustic flake; lye, caustic; liquid caustic

Physical Form. White solid

Uses. Manufacture of rayon, mercerized cotton, soap, paper, aluminum, petroleum products; metal cleaning; electrolytic extraction of zinc; tin plating; oxide coating

Exposure. Skin or eye contact; inhalation

Toxicology. Sodium hydroxide is highly corrosive; it is a severe irritant of the eyes, mucous membranes, and skin.

The greatest industrial hazard is rapid tissue destruction of eyes or skin on contact either with the solid or with concentrated solutions.[1,2]

Contact with the eyes causes disintegration and sloughing of conjunctival and corneal epithelium, corneal opacification, marked edema, and ulceration; after 7–13 days, either gradual recovery begins or there is progression of ulceration and corneal opacification.[3] Complications of severe eye burns are symblepharon with overgrowth of the cornea by a vascularized membrane, progressive or recurrent corneal ulceration, and permanent corneal opacification.[1]

On the skin, solutions of 25–50% cause the sensation of irritation within about 3 minutes; with solutions of 4%, this does not occur until after several hours.[1] Under occlusion a 0.12% solution was irritating after 1 hour.[4] If not removed from the skin, severe burns with deep ulceration will occur. Exposure to the dust or mist may cause multiple small burns with temporary loss of hair.[2]

Although inhalation of sodium hydroxide is usually of secondary importance in industrial exposures, the effects from the dust or mist will vary from mild irritation of the nose at 2 mg/m^3 to severe pneumonitis, depending on the severity of exposure.[1,2]

Severe obstructive airway disease was associated with chronic exposure to sodium hydroxide mists in one reported case.[5] The worker, who for 20 years had daily exposure to boiling sodium hydroxide solutions, initially experienced tightness of chest, dyspnea, cough, and eye irritation that would resolve after leaving the exposure area. Eventually the worker began to suffer from mild exertional dyspnea and cough when not exposed. Physical examination, chest X ray, pulmonary function tests, and arterial blood gases were all compatible with severe obstructive airway disease. It is probable that the massive and prolonged occupational exposure to the sodium hydroxide mists induced a bronchial inflammatory reaction leading to irreversible increased airway resistance.

Ingestion produces immediate burning pain in the mouth and throat with severe abdominal pain. Swelling of the lips, ulcerative mucosal burns, dyspnea, vomiting of large pieces of mucosa, and shock may follow. Immediate complications include hemorrhage and perforation of the gut. Esophageal stricture and pyloric stenosis may occur as late complications. Cases of squamous cell carcinoma of the esophagus have occurred with latent periods of 12–42 years after ingestion. These cancers were undoubtedly sequelae of tissue destruction and possibly scar formation, rather than a direct carcinogenic action of sodium hydroxide itself.[1]

The ACGIH 2003 short-term excursion limit (STEL)/ceiling limit for sodium hydroxide is 2 mg/m^3.

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SODIUM METABISULFITE
CAS: 7681-57-4

$Na_2S_2O_5$

Synonyms: Disodium disulfite; sodium pyrosulfite

Physical Form. White powder or crystal with the odor of sulfur dioxide

Uses. As a preservative in food and wine; as an antioxidant in pharmaceuticals.

Exposure. Ingestion; inhalation

Toxicology. Sodium metabisulfite may cause bronchospasm, oculonasal symptoms, and urticaria in sulfite-sensitive individuals; irritation of mucous membranes may occur from inhalation of the dust.

Two workers died while applying dry sodium metabisulfite in a ship hold.[1] Postmortem examination showed diffuse pulmonary edema consistent with death secondary to asphyxia and visceral congestion.

Sodium metabisulfite can trigger bronchoconstriction in asthmatic subjects. In one study, 30 asthmatic subjects inhaled sodium metabisulfite in concentrations of 6.2, 12.5, 50, and 100 mg/ml.[2] All the asthmatic subjects responded with decline in FEV_1. The response occurred within 1 minute, and most subjects recovered to baseline after 30 or 40 minutes. Neither enhanced sensitivity to subsequent histamine inhalation nor refractoriness to subsequent sodium metabisulfite inhalation was found. None of the nonasthmatic, nonatopic subjects responded to sodium metabisulfite, but inhalation of high doses may cause mild bronchoconstriction in these individuals.

The mechanism of action of may involve the liberation of sulfur dioxide gas from sodium metabisulfite that in turn acts on the parasympathetic nerves in the lung.[2]

In mice exposed to aerosols of sodium metabisulfite there was sensory irritation of the upper respiratory tract.[3]

A low order of systemic toxicity was found in chronic feeding studies with rats. Administered in the diet for 2 years 0.215% sodium metabisulfite caused no adverse effects.[4] Reproductive parameters were not affected in three-generation feeding studies in rats at concentrations up to 13 mmol/kg/day.[4]

Sodium metabisulfite was genotoxic in mice *in vivo* as determined by chromosomal aberration, micronucleus, and sperm shape assays.[5] It was not mutagenic in bacterial assays.[6]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for sodium metabisulfite is 5 mg/m^3.

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STIBINE
CAS: 7803-52-3

SbH_3

Synonyms: Antimony hydride; hydrogen antimonide

Physical Form. Colorless gas

Sources. Produced accidentally as a result of the generation of nascent hydrogen in the presence of antimony; formed when acid solutions of antimony compounds are treated with reducing agents

Exposure. Inhalation

Toxicology. Stibine is a hemolytic agent in animals; it is expected that the same effect will occur in humans.

No clear-cut case of fatal stibine poisoning in humans has been reported.[1-4] Acute exposures to humans would be expected to cause rapid destruction of red blood cells, hemoglobinuria, anuria, jaundice, and death. Workers exposed to a mixture of gases (concentrations unmeasured) of stibine, arsine, and hydrogen sulfide developed headache, weakness, nausea, abdominal and lumbar pain, hemoglobinuria, hematuria, and anemia.[1] Although these signs and symptoms are clearly manifestations of acute hemolytic anemia, it is not possible to determine the relative contribution of arsine, which is also a hemolytic agent. By analogy to other effects caused by arsine, additional signs of stibine poisoning may be leukocytosis and jaundice.

Guinea pigs exposed to 65 ppm of stibine for 1 hour developed hemoglobinuria followed within a few days by profound anemia.[5] Stibine is also a pulmonary irritant in animals, causing pulmonary congestion and edema and, ultimately, death in cats and dogs after a 1-hour exposure at 40–45 ppm.[5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for stibine is 0.1 ppm (0.51 mg/m^3).

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STODDARD SOLVENT
CAS: 8052-41-3

15–20% Aromatic hydrocarbons
80–85% Paraffin and naphthenic hydrocarbons

Synonyms: White spirits; safety solvent; varnoline

Physical Form. Colorless liquid

Uses. Dry cleaning; degreasing; paint thinner

Exposure. Inhalation

Toxicology. Stoddard solvent is a mild central nervous system depressant and a mucous membrane irritant.

Stoddard solvent is a mixture of predomi-

nantly C9 to C11 hydrocarbons of which 30–50% are straight- and branched-chain paraffins, 30–40% naphthenes, and 10–20% aromatic hydrocarbons.[1] Although uses may differ, Stoddard solvent is chemically similar to mineral spirits and the terms have been used interchangeably.[1]

One of six volunteers exposed to 150 ppm of Stoddard solvent for 15 minutes had transitory eye irritation; at 470 ppm (2700 mg/m^3) all subjects had eye irritation and two had slight dizziness.[2] Eight volunteers exposed at 4000 mg/m^3 for 50 minutes had some changes in simple reaction time tests but not in perceptual speed, short-term memory, or manual dexterity compared with pre- and postexposure self controls.[3]

Studies involving painters with long-term exposure to Stoddard solvent have found increased incidences of memory impairment, fatigue, impaired concentration, irritability, dizziness, headache, and reduced cognitive function.[4]

Reports of Stoddard solvent as an etiologic agent in the development of aplastic anemia are of questionable validity.[1] Skin exposure may cause dermatitis and sensitization.[1]

Rats exposed to Stoddard solvent at a level of 1400 ppm for 8 hours exhibited eye irritation, bloody exudate around the nostrils, and slight loss of coordination. Exposure of a dog resulted in increased salivation at 3 hours, tremor at 4 hours, and clonic spasms after 5 hours; 1700 ppm caused tremors, convulsions, and finally death in cats after 2.5–7.5 hours.[2] No significant effects were observed in dogs exposed 6 hours/day for 65 days to 330 ppm; there was elevated blood urea nitrogen levels and marked tubular regeneration in the kidneys of rats similarly exposed.[2] Renal effects noted in rats are consistent with a mechanism that appears to be unique to male rats (i.e., interactions with α2u-globulin), and it is not known whether Stoddard solvent would cause similar effects in humans.[5]

Stodddard solvent was not genotoxic in a variety of assays including *Salmonella typhimurium*, a mouse lymphoma mutation assay, rodent bone marrow cytogenic tests, and rodent dominant lethal tests.[4,5]

The odor threshold is 0.9 ppm; the odor and irritative properties probably do not provide adequate warning of dangerous concentrations.[2]

The 2003 ACGIH threshold limit value-time-weighted average TLV-TWA for Stoddard solvent is 100 ppm (525 mg/m^3).

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STRYCHNINE
CAS: 57-24-9

$C_{21}H_{22}N_2O_2$

Synonym: Stricnina

Physical Form. White crystalline powder

Use. Rodenticide

Exposure. Inhalation; ingestion

Toxicology. Strychnine is a potent convulsant.

Strychnine poisoning occurs from accidental and intentional ingestion and from misuse as a therapeutic agent.[1] Doses of 5–7 mg cause muscle tightness, especially in the neck and jaws, and twitching of individual muscles, especially in the little fingers.[1]

The lethal oral dose in humans is probably around 100, but doses as low as 16 mg have reportedly been fatal whereas doses of 2000 mg have been survived.[1,2] After ingestion, effects usually occur within 10–30 minutes and include stiffness of the face and neck muscles and increased reflex excitability.[3] Strychnine acts by altering nerve impulses in the spinal cord, resulting in a decreased threshold for stimulation, and, hence, a hyperexcitable state. Any sensory stimulus may produce a violent motor response that, in the early stages of intoxication, tends to be a coordinated extensor thrust and, in later stages, may be a tetanic convulsion with opisthotonos; anoxia and cyanosis develop rapidly. Between convulsions, muscular relaxation is complete, breathing is resumed, and cyanosis lessens.[1] Because sensation is unaffected, the convulsions are painful and lead to overwhelming fear. As many as 10 convulsions separated by intervals of 10–15 minutes may be experienced, but death often occurs after the second to fifth convulsion, and even the first convulsion may be fatal if sustained; death is commonly due to asphyxia.[2,3] If recovery occurs, it is remarkably prompt and complete despite the violence of the illness; muscle soreness may persist for a number of days.[1]

In fatal cases, the pathologic findings are entirely nonspecific. They usually consist of petechial hemorrhages and congestion of the organs, indicating combined action of severe convulsions and anoxia.[1] Compression fractures and related injury may be found in cases with violent tetany.[1]

Strychnine poisoning may also occur from dermal exposure. In one recent case report a women experienced marked pain in the lower limbs, dermal sensitivity, and stiffness in her jaw 24 hours after cleaning up a strychnine spill. Strychnine was confirmed in the plasma and urine by gas chromatography-mass spectrometry.[4]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for strychnine is 0.15 mg/m^3.

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STYRENE, MONOMER
CAS: 100-42-5

$C_6H_5CHCH_2$

Synonyms: Vinylbenzene; phenylethylene; styrene monomer; cinnamene

Physical Form. Colorless to yellowish oily liquid

Uses. Solvent for synthetic rubber and resins; intermediate in chemical synthesis; manufacture of polymerized synthetic materials

Exposure. Inhalation; skin absorption

Toxicology. Styrene is an irritant of the skin, eyes, and mucous membranes and is neurotoxic.

Humans exposed to 376 ppm experienced eye and nasal irritation within 15 minutes; after 1 hour at 376 ppm, effects were headache, nausea, decreased dexterity and coordination, and other signs of transient neurological impairment.[1] Subjective complaints, including

headache, fatigue, and concentration difficulty, have been reported after 90-minute experimental exposures at concentrations as low as 50 ppm.[2] Subtle but significant changes involving neurobehavioral performance and peripheral nervous function were detected in workers exposed to styrene at a mean dose of 22 ppm.[3]

Alterations in electroencephalographs and nerve conduction velocities have also been reported.[4] Studies of effects of styrene on the hematopoietic and immune systems, liver, and kidney in exposed workers have not revealed consistent changes.

The rate of absorption of the liquid through the skin of the hand and the forearm in humans was 9–15 mg/cm^2/hour.[5] Prolonged or repeated exposure may lead to dermatitis due to defatting action on the skin.[6]

Rats and guinea pigs exposed to 10,000 ppm became comatose in a few minutes and died after 30–60 minutes of exposure.[7] Animals exposed to 2500 ppm showed weakness and stupor, followed by incoordination, tremor, coma, and death in 8 hours.[7] Rats and guinea pigs showed signs of eye and nasal irritation after exposure to 1300 ppm for 8 hours/day, 5 days/week for 6 months.[6]

Although high-level experimental exposure to animals has resulted in evidence of liver damage, there is no clear-cut evidence of human liver toxicity from industrial exposures.[2] Liver enzymes and serum bile acid concentrations among 34 workers with average 30 to 40 ppm styrene exposures for a mean of 5.1 years did not differ significantly from a control group of unexposed workers.[8]

Some epidemiological studies have suggested increased risks for lymphatic and hematopoietic neoplasms. However, the risks are generally small, statistically unstable, and often based on subgroup analyses. The possibility that the observations are the results of confounding by other occupational exposures cannot be ruled out.[9–12]

In an inhalation study in mice there was an increase in the incidence of pulmonary adenomas.[12]

The IARC has determined that there is limited evidence in experimental animals and in humans for the carcinogenicity of styrene.[12]

An increased incidence of chromosome aberrations and micronuclei in peripheral lymphocytes have been reported in occupationally exposed workers. Additional studies have found a slight increase in the incidence of sister chromatid exchanges, whereas no increase has been found in several other studies.[12] Sister chromatid exchange and chromosomal aberrations were induced in vivo in rodents and in vitro in human lymphocytes. Both DNA and protein adducts are formed in humans after styrene exposure.

Limited studies of the effects of styrene on reproduction are available, including conflicting reports of association between exposure and birth defects and fetal loss. In one report, women who worked at the most highly exposed jobs had offspring with adjusted birth weights of 4% less than the offspring of unexposed women.[13] Decreased pup weight, postnatal developmental delays, as well as neurobehavioral and neurochemical abnormalities have been reported in rats exposed to styrene during pre- or postnatal development.[12]

The odor threshold is 0.1 ppm; the disagreeable odor and the eye and nose irritation make the inhalation of seriously acute toxic quantities unlikely, although the warning properties may not be sufficient for prolonged exposures.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for styrene is 50 ppm (213 mg/m^3) with a short-term excursion limit (STEL) of 100 ppm (426 mg/m^3) and a notation for skin absorption.

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STYRENE OXIDE

CAS: 96-09-3

C_8H_8O

Synonyms: Epoxyethylbenzene; epoxystyrene; phenylethylene oxide; phenyloxirane; styrene-7,8-oxide

Physical Form. Colorless to pale straw colored liquid

Uses. Used as an intermediate in the production of styrene glycol and its derivatives; as a reactive dilutent in the epoxy resin industry; as a chemical intermediate for making β-phenethyl alcohol, a fragrance material

Exposure. Inhalation; skin

Toxicology. Styrene oxide is a skin and eye irritant and may produce skin sensitization; it is carcinogenic in experimental animals.

Tests with human subjects indicate that styrene oxide is capable of causing moderate skin irritation and skin sensitization.[1] These effects may result from single or repeated contact with the undiluted liquid and with solutions as dilute as 1%. Experience indicates that persons who have become sensitized may react severely to contact with the vapor as well as with the liquid material.

In rats, exposure to 1000 ppm was lethal to two of six animals within 4 hours.[2] Repeated 7-hour exposures at 300 ppm were rapidly fatal to 40% of female rats, and extensive mortality occurred in rats receiving prolonged exposure to 100 ppm.[3] Toxicity also was marked in the rabbit, with prolonged and repeated exposures at 15–50 ppm producing mortality.[3] Histopathologic changes in rats and rabbits included metaplasia and hyperplasia of the lungs.

Inhalation exposure during gestation by rats and rabbits produced reproductive and developmental toxicity as well as maternal toxicity.[3] Exposure to 15 or 50 ppm for 7 hours/day on days 1–24 of gestation resulted in maternal toxicity (increased mortality, decreased food consumption, and weight gain) and increased the frequency of resorptions in rabbits. Exposure of rats to 100 ppm on days 1–19 of gestation decreased fecundity by significantly increasing preimplantation loss. Fetal size, including crown-rump length and weight, also tended to be decreased by exposure in both species. It has not been established whether the developmental effects are direct effects or are the result of maternal toxicity.

The liquid is slowly absorbed by the skin and may reach toxic levels in rabbits over a 24-hour period with an LD_{50} of 2.8 g/kg.[1]

Intraperitoneal injection has been associated with hepatic damage in rats, causing a decrease in the activities of mixed function oxidases and in cytochrome P-450 content.[4]

In a long-term bioassay, styrene oxide administered to rats by gavage (250 or 50 mg/kg daily for 1 year) produced a high incidence of tumors in the forestomach (papillomas, acanthomas, and in situ and invasive squamous cell carcinomas).[5] Styrene oxide also increased the incidence of squamous cell papillomas and carcinomas of the forestomach in mice when administered by gavage at doses of 375 or 750 mg/kg for 2 years.[6]

Prenatal exposure followed by postnatal oral administration of 96 weekly doses of 100–150 mg/kg also produced a significantly increased incidence of forestomach tumors, including papillomas and carcinomas in rats.[7]

No increase in the incidence of skin tumors was observed in two mice studies after topical application.[2,8]

Both positive and negative findings have been reported in genotoxic assays of styrene oxide. It has induced gene mutations in bacteria and rodent cells *in vitro* and caused chromosomal aberrations and sister chromatid exchange both *in vivo* and *in vitro*.[9]

Styrene oxide forms covalent adducts with DNA in humans, rats, and mice.

The IARC has determined that there is sufficient evidence for the carcinogenicity of styrene oxide to experimental animals and that, although there is inadequate evidence for the carcinogenicity to humans, it should be regarded as probably carcinogenic to humans.[9]

The ACGIH has not determined a threshold limit value (TLV) for styrene oxide.

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SULFOLANE
CAS: 126-33-0

$C_4H_8SO_2$

Synonyms: 1,1-Dioxidetetrahydrothiofuran; 1,1-dioxothiolan; cyclotetramethylene sulfone; dioxothiolan; sulfoxaline; tetrahydrothiophene 1,1-dioxide; tetramethylene sulfone; thiocyclopentane dioxide; thiophane dioxide

Physical Form. Colorless, oily liquid (solid at 15°C)

Uses. Process solvent for extractions of aromatics and for purification of acid gases

Toxicology. Sulfolane is a convulsant in animals.

Sulfolane is not highly toxic. Oral LD_{50} values in the rat range from 1846 to 2500 mg/kg.[1] Symptoms of neurotoxicity have been observed in rats, dogs, and monkeys after ingestion, injection, inhalation, or dermal application. Effects included convulsions, hyperactivity, tremor, and ataxia.[2] In acute inhalation studies, no rats died in the 2 weeks after 4-hour exposure to levels as high as 12,000 mg/m^3.[2] Dogs exposed continuously to 200 mg/m^3 for 7 days experienced convulsions.

The liquid is not irritating to the skin and is mildly irritating to the eyes.[3] It was not a sensitizer in the guinea pig.[4,5]

Sulfolane was not mutagenic in bacterial assays with or without metabolic activation.[6]

A threshold limit value (TLV) has not been established for sulfolane.

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SULFUR DIOXIDE

CAS: 7446

SO_2

Synonyms: Sulfurous anhydride; sulfurous oxide

Physical Form. Colorless gas

Uses. Intermediate in the manufacture of sulfuric acid and sulfite pulp; casting of nonferrous metal; used in the food industry as a biocide and a preservative

Exposure. Inhalation

Toxicology. Sulfur dioxide is a severe irritant of the eyes, skin, and upper airways of the respiratory tract.

The irritant effects of sulfur dioxide are due to the rapidity with which it forms sulfurous acid on contact with moist membranes.[1,2] Approximately 90% of all sulfur dioxide inhaled is absorbed in the upper respiratory passages, where most effects occur; however, it may produce respiratory paralysis and may also cause pulmonary edema.[2] In fatal cases, histopathologic examination of the lungs has revealed pulmonary edema and alveolar hemorrhage.[3]

Exposure to concentrations of 10–50 ppm for 5–15 minutes causes irritation of the eyes, nose, and throat; rhinorrhea, choking; cough, and, in some instances, reflex bronchoconstriction with increased pulmonary resistance.[2]

The phenomenon of adaptation to irritating concentrations is a recognized occurrence in experienced workers.[2] Workers repeatedly exposed to 10 ppm experienced upper respiratory irritation and some nosebleeds, but the symptoms did not occur at 5 ppm. In another study, initial cough and irritation did occur at 5 ppm and 13 ppm but subsided after 5 minutes of exposure.[4]

In a human experimental study with the subjects breathing through the mouth, brief exposure to 13 ppm caused a 73% increase in

pulmonary flow resistance, 5 ppm resulted in a 40% increase; and 1 ppm produced no effects.[4]

Studies of individuals with mild asthma have demonstrated much greater sensitivity to low levels of sulfur dioxide exposure, particularly during exercise. Exposures to concentrations of 0.5–0.1 ppm during exercise resulted in significant increases in airway resistance in these subjects.[5] At rest, exposures to 1 ppm resulted in significant increases in airway resistance in mild asthmatics.[6]

Epidemiological studies of workers chronically exposed to sulfur dioxide, as in copper smelters, have yielded conflicting results regarding excessive occurrence of chronic respiratory disease, chronic bronchitis, or decrements in pulmonary function. Such studies are plagued by the confounding effect of smoking and difficulties in exposure assessment. Overall, the evidence for chronic effects in humans including carcinogenicity is quite limited.[3,7]

In one animal study, a significant increase in lung tumors was observed in female mice exposed by inhalation.[3] Available data indicate a genotoxic potential for sulfur dioxide.[8] Increases in chromosome aberrations and sister chromatid exchanges have been detected in occupationally exposed workers.[8] The IARC has determined that there is limited evidence for the carcinogenicity of sulfur dioxide in experimental animals and inadequate evidence in humans.

Although a variety of environmental exposures involving sulfur dioxide have been linked to human reproductive effects, there is no clear relationship between sulfur dioxide concentrations and adverse reproductive outcomes.[3]

Exposure of the eyes to liquid sulfur dioxide from pressurized containers causes corneal burns and opacification resulting in a loss of vision.[2] The liquid on the skin produces skin burns from the freezing effect of rapid evaporation.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for sulfur dioxide is 2 ppm (5.2 mg/m^3) with a short-term excursion limit (STEL) of 5 ppm (13 mg/m^3).

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SULFUR HEXAFLUORIDE
CAS: 2551-62-4

SF_6

Synonyms: Sulfur fluoride

Physical Form. Colorless, odorless gas

Uses. Dielectric for high-voltage equipment

Exposure. Inhalation

Toxicology. Sulfur hexafluoride is an agent of low toxicity; at extremely high levels it has a mild effect on the nervous system.

In humans, inhalation of 80% sulfur hexafluoride and 20% oxygen for 5 minutes produced peripheral tingling and a mild excitement stage, with some altered hearing in most subjects.[1] According to the ACGIH, the chief hazard, as with other inert gases, would be asphyxiation as a result of the displacement of air by this heavy gas.[2]

Rats exposed for many hours to an atmosphere containing 80% sulfur hexafluoride and 20% oxygen gave no perceptible indications of intoxication, irritation, or other toxicological effects.[3] Electrical discharges and high temperatures will cause sulfur hexafluoride decomposition.[2,4] Although some decomposition products are highly toxic, the concentrations produced and practical significance under usual working conditions are undetermined.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for sulfur hexafluoride is 1000 ppm (5970 mg/m^3).

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SULFUR MONOCHLORIDE

CAS: 10025-67-9

S_2Cl_2

Synonyms: Sulfur chloride; sulfur subchloride; disulfur dichloride

Physical Form. Nonflammable, light amber to yellowish-red fuming, oily liquid

Uses. Intermediate and chlorinating agent in manufacture of organics, sulfur dyes, insecticides, and synthetic rubber

Exposure. Inhalation

Toxicology. Sulfur monochloride is an irritant of the eyes, mucous membranes, and skin.

On contact with water, it decomposes to form hydrogen chloride and sulfur dioxide; because this occurs rapidly, it acts primarily as an upper respiratory irritant and does not ordinarily reach the lungs.[1] However, exposure to high concentrations may cause pulmonary edema.[2]

Concentrations of 2–9 ppm are reported to be mildly irritating to exposed workers.[3] Splashes of the liquid in the eyes will produce severe immediate damage, which may result in permanent scarring.[2] The liquid on the skin will produce irritation and burns if not removed.[2]

Exposure of mice to 150 ppm for 1 minute is fatal.[1] In cats, some deaths occurred after a 15-minute exposure to 60 ppm.

The 2003 ACGIH short-term excursion limit (STEL)/ceiling limit for sulfur monochloride is 1 ppm (5.5 mg/m^3).

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SULFUR PENTAFLUORIDE

CAS: 5714-22-77

S_2F_{10}

Synonym: Disulfur decafluoride

Physical Form. Colorless liquid

Source. Production by-product of synthesis of sulfur hexafluoride

Exposure. Inhalation

Toxicology. Sulfur pentafluoride is a severe pulmonary irritant in animals; severe exposure is expected to cause the same effect in humans.

Exposure of rats to 1 ppm for 16–18 hours was fatal; 0.5 ppm caused pulmonary edema and hemorrhage; 0.1 ppm caused irritation of the lungs; 0.01 ppm had no effect.[1] Nonfatal exposure of rats to 10 ppm for 1 hour caused pulmonary hemorrhage.[1]

The ACGIH 2003 short-term excursion limit (STEL)/ceiling limit for sulfur pentafluoride is 0.01 ppm (0.10 mg/m^3).

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SULFUR TETRAFLUORIDE

CAS: 7783-60-0

SF_4

Synonyms: None

Physical Form. Colorless gas with odor similar to sulfur dioxide

Uses and Sources. As a fluorinating agent in the production of water- and oil-repellant materials and lubricity improvers; found as a degradation product of sulfur hexafluoride

Exposure. Inhalation

Toxicology. Sulfur tetrafluoride is extremely irritating and corrosive to the respiratory tract, skin, and eyes.

Six workers were exposed to degradation products of sulfur hexafluoride during electrical repair work.[1] One degradation product, sulfur tetrafluoride, was identified from work-site measurements. Unprotected exposure totaling approximately 6 hours occurred over a 12-hour period in an underground enclosed space. Workers initially noticed a burning battery-like odor and experienced eye irritation with tears, dry and burning throat, and chest tightness. The workers went above ground, and symptoms abated after approximately 15 minutes. Subsequent underground visits resulted in a recurrence of symptoms. Repair work was stopped after workers experienced chest tightness, shortness of breath, headache, fatigue, nosebleed, nausea, and vomiting. Most symptoms resolved within a week of exposure with some intermittent epistaxis persistent up to a month. Radiographic evidence of multilobar atelectasis was present in one worker, whereas a second worker developed chest tightness on exposure to cold air and transitory changes on pulmonary function tests. Examination of the workers 1 year later did not reveal any persistent adverse consequences.

At the time of the incident work site measurements qualitatively identified sulfur tetrafluoride in the air samples. It was suggested that intense heat caused sulfur hexafluoride to decompose to sulfur tetrafluoride, which escaped as a pipe was opened at the work site. Subsequent to this incident, it has been noted that because sulfur hexafluoride is an odorless gas, any odors present in areas containing heated sulfur hexafluoride must be considered to be coming from decomposition products, which are significant health hazards.

In animal studies a 4-hour exposure at 19 ppm was lethal to one of two rats.[2] Eye irritation and irregular breathing were observed, and there was evidence of pulmonary edema at necropsy. Rats exposed at 4 ppm 4 hours/day for 10 days had dyspnea, weakness, and nasal discharge.

The 2003 ACGIH ceiling threshold limit value (TLV-C) for sulfur tetrafluoride is 0.1 ppm (0.44 mg/m^3).

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SULFURIC ACID
CAS: 7664-93-9

H_2SO_4

Synonyms: Oil of vitriol; sulphuric acid

Physical Form. Colorless liquid

Uses. Fertilizer manufacturing; metal cleaning; manufacture of chemicals, plastics, and explosives; petroleum refining; pickling of metal

Exposure. Inhalation

Toxicology. Sulfuric acid is a severe irritant of the respiratory tract, eyes, and skin; contact with the teeth causes dental erosion; cancer of the respiratory tract has been associated with chronic exposure.

Sulfuric acid is a direct irritant that results in adverse effects at the site of contact.[1] The concentration of acid is the determinant of effect because a small amount of concentrated sulfuric acid will cause significant damage in contact with tissue, whereas the same amount of acid sufficiently diluted will have no effect. Changes in pH are thought to be responsible for toxicity rather than sulfate itself. If enough acid-neutralizing capacity is available at the site of contact, there will be no effects.[1]

In human subjects, concentrations of about 5 mg/m^3 were objectionable, usually causing cough, with an increase in respiratory rate and impairment of ventilatory capacity.[2]

In a study of 248 workers, no significant association was found between exposure to vapor concentrations of up to 0.42 mg/m^3 (2.6–10 µg mass median diameter) and symptoms of cough, phlegm, dyspnea, and wheezing.[3] However, the FVC in the highest-exposure group was reduced compared with that of a low-exposure group. Repeated exposure of workers to unspecified sulfuric acid concentrations reportedly has caused chronic conjunctivitis, tracheobronchitis, stomatitis, and dermatitis.[4]

The dose-effect relationship for chronic exposure is difficult to determine because of the number of factors that influence toxicity, including the particle size of the mist, presence of particulates, synergistic and protective agents, and humidity.[5] In regard to particle size, the smallest aerosol particles appear to cause the greatest alteration in pulmonary function and more microscopic lesions because of their ability to penetrate deeply into the lungs.[4] Larger particles that deposit in the upper lung may be more acutely harmful because reflexive bronchoconstriction occurs. Very large particles that only penetrate the nasal passages and upper respiratory tract would not lead to either effect. Adsorbed onto other particulates sulfuric acid may be carried farther into the respiratory tract.[5] Synergism has been demonstrated between sulfuric acid and ozone, sulfur dioxide, and metallic aerosols.[5] Increased ammonia concentration in expired air affords protection. Because of the hygroscopic nature of sulfuric acid, humidity directly affects particle size and, hence, toxicity.[5]

In guinea pigs, aerosols of larger, but still respirable, size were more lethal than those of

smaller size.[6] For 8-hour exposures, the LC_{50} was 30 mg/m^3 for mists of 0.8 µm and was greater than 109 mg/m^3 for 0.4-µm mists.[6] Animals that died from exposure to the larger mists had hyperinflated lungs, whereas those that died from the smaller mists also had hemorrhage and transudation. Changes in pulmonary function, however, were more severe for aerosols of smaller diameter.[7] The concentration producing a 50% increase in pulmonary flow resistance was 0.3 mg/m^3 for 0.3-µm particles, 0.7 mg/m^3 for 1 µm, 6 mg/m^3 for 3.4 µm, and 30 mg/m^3 for 7 µm. Long-term exposure of monkeys at concentrations between 0.1 and 1 mg/m^3, regardless of particle size, produced slight but increasingly severe microscopic pulmonary lesions.[8] Impairment of pulmonary ventilation occurred above 2.5 mg/m^3.

The corrosive effects of sulfuric acid on teeth with chronic exposure are well established.[4] The damage, etching of dental enamel followed by erosion of enamel and dentine with loss of tooth substance, is limited to the parts of the teeth that are exposed to direct impingement of acid mist upon the surface. Although etching typically occurs after years of occupational exposure, in one case exposure to an average of 0.23 mg/m^3 for 4 months was sufficient to initiate erosion.[3]

Splashed in the eye, the concentrated acid causes extremely severe damage, often leading to blindness, whereas dilute acid produces more transient effects, from which recovery may be complete.[9] Chemical burns are the most commonly encountered occupational hazard. Initially, the zone of contact is bleached and turns brown before the formation of a clearly defined ulcer on a light red background. The wounds are long in healing, and scarring may result in functional inhibition. Severe burns have been fatal. A worker sprayed in the face with liquid fuming sulfuric acid suffered skin burns of the face and body, as well as pulmonary edema from inhalation.[4] Sequelae were pulmonary fibrosis, residual bronchitis, and pulmonary emphysema; in addition, necrosis of the skin resulted in marked scarring.[4] The threshold sulfuric acid concentrations resulting in skin and eye irritation are unclear, with some studies reporting severe ocular and skin effects at 10% whereas others report no effects at this concentration.[1] Although ingestion of the liquid is unlikely in ordinary industrial use, the highly corrosive nature of the substance will produce serious burns of the mouth and the esophagus.[4]

A number of studies have indicated that exposures to sulfuric acid or to acid mist in general are associated with laryngeal cancer.[10–13] In a nested case-referent study, a 13-fold excess risk of laryngeal cancer was found among chemical refinery workers with the highest levels of sulfuric acid exposure compared with those least exposed; a fourfold risk for moderately exposed workers versus those least exposed also was found.[10] Fourteen cases of laryngeal cancer were identified (vs. 6.4 expected) in 1031 steelworkers exposed to acid mists for an average of 9.2 years, with an average first year of exposure of 1949.[11] Exposure levels averaged about 0.2 mg/m^3, and the average duration of exposure was 9.5 years. Excess risks for laryngeal cancer were also found in a Swedish study of a cohort of workers in steel pickling.[12] In a population-based case-referent report from Canada, there was an association between exposure to sulfuric acid in the workplace, particularly at higher concentrations and over longer periods of time, and the development of laryngeal cancer.[13] More recently, sulfuric acid mist exposure has also been associated with gastric cardia cancer and nasopharyngeal carcinoma.[14, 15]

It has been postulated that sulfuric acid may produce tumors by direct genotoxic effects of lowered pH or may promote carcinogenesis by inducing chronic tissue irritation.[1] IARC has determined that there is sufficient evidence that occupational exposure to strong inorganic acid mists containing sulfuric acid is carcinogenic to humans.[16]

Significant increases in the incidences of sister chromatid exchange, micronucleus formation, and chromosomal aberrations in peripheral lymphocytes were observed in a single study of workers engaged in the manufacture of sulfuric acid.[16]

Sulfuric acid mist was not teratogenic in mice or rabbits exposed 7 hours/day to 20 mg/m^3 during the period of major organogenesis.[17]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for sulfuric acid is 1 mg/m^3 with a short-term excursion level (STEL/ceiling) of 3 mg/m^3.

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SULFURYL FLUORIDE
CAS: 2699-79-8

SO_2F_2

Synonyms: Sulfuric oxyfluoride; sulfuryl difluoride; Vikane

Physical Form. Colorless gas

Uses. Insect fumigant

Exposure. Inhalation

Toxicology. Sulfuryl fluoride is a central nervous system depressant and a pulmonary irritant in animals.

A worker exposed to an undetermined concentration of a mixture of sulfuryl fluoride and 1% chloropicrin for 4 hours developed nausea, vomiting, abdominal pain, and pruritis;

physical examination revealed conjunctivitis, rhinitis, pharyngitis, and paresthesia of the right leg, all of which rapidly subsided.[1] The role of sulfuryl fluoride in this case is not known, but the signs and symptoms are those expected of chloropicrin overexposure.

Two fatalities occurred after reentry of a home fumigated with sulfuryl fluoride.[2] The male experienced severe dyspnea and cough, followed by generalized seizure and cardiopulmonary arrest within 24 hours. The female initially had weakness, nausea, and repeated vomiting; within 4 days, there was severe hypoxemia and diffuse pulmonary infiltrates. Ventricular fibrillation and death occurred on day 6. The concentration of sulfuryl fluoride gas was not available, and the difference in time of death for the two individuals was not explainable.

Evaluation of workers occupationally exposed to sulfuryl fluoride found no effects attributable to exposure in a series of psychological and neurological tests compared with individuals with no history of exposure.[3]

Acute exposure of rats to high concentrations (up to 40,000 ppm) has resulted in convulsions, pulmonary edema, respiratory arrest, and death.[4] In rats repeatedly exposed at 600 ppm, death was attributed to renal papillary necrosis; renal toxicity was not present in rabbits similarly exposed. Exposure of rabbits to 300 or 600 ppm resulted in convulsions and hyperactivity, moderate inflammation of nasal tissues, and some inflammation of the trachea or bronchi. Subchronic studies found that rats exposed at 300 ppm had mottled incisor teeth, minimal renal effects, pulmonary histiocytosis, inflammation of nasal tissues, and cerebral vacuolation.

Exposure to sulfuryl fluoride was not teratogenic in either rats or rabbits exposed to levels up to 225 ppm during periods of major organogenesis; fetotoxic effects in the form of reduced body weights were only observed in rabbits at levels that produced maternal weight loss.[5] No treatment-related effects on reproductive or fertility indices, gross pathology or histopathology of the reproductive organs, or pup survival was observed in rats exposed at 5, 20, or 150 ppm 6 hours/day by inhalation for two generations.[6] Parental toxicity occurred in the high-dose group as evidenced by decreased body weight gain, dental fluorosis, and an increased incidence of aggregates of alveolar macrophages in the lungs and was accompanied by decreased pup weights in the F_1 and F_2 litters.

There are no warning properties of overexposure because the gas is odorless and colorless.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) of sulfuryl fluoride is 5 ppm (21 mg/m^3) with a short-term excursion limit (STEL)/ceiling of 10 ppm (42 mg/m^3).

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TALC (Nonasbestos Form)
CAS: 14807-96-6

$Mg_3Si_4O10(OH)_2$

Synonym: Nonfibrous talc

Physical Form. Talc as a pure chemical compound is hydrous magnesium silicate. Talc is

usually crystalline, flexible, and soft. The purity and physical form of any sample of talc depend on the source of the talc and on the minerals found in the ore body from which it is refined.

Uses. For clarifying liquid by filtration; pigment; for lubricating molds and machinery; electric and heat insulator; in cosmetics

Exposure. Inhalation

Toxicology. The nonasbestos form of talc, also termed nonfibrous or pure talc, has not been proven to cause the effects produced by exposure to fibrous talc, namely, fibrotic pneumoconiosis and an increased incidence of cancer of the lungs and pleura.

Although there are a number of contradictory reports regarding the effects of talc, the contradiction has been ascribed to the differences in mineral composition of the various talcs, which include pure talc, talc associated with silica and other nonasbestiform minerals, and talc containing asbestiform fibers such as tremolite and anthophyllite.[1]

In a study of 20 workers exposed for 10–36 years to talc described as "pure," at levels ranging from 15 to 35 mppcf, no evidence of pneumoconiosis was found.[2,3] In another study that compared the pulmonary function of workers exposed to either fibrous or nonfibrous talc, it was concluded that although the fibrous form was the more pathogenic type, both talcs produced pulmonary fibrosis; no data were presented to document the types of talc involved.[4]

A study of 260 workers with 15 or more years of exposure to commercial talc dust (containing not only talc, but also tremolite, anthophyllite, carbonate dusts, and a small amount of free silica) revealed a 40-fold greater than expected proportional mortality from cancer of the lungs and pleura. In addition, a major cause of death was cor pulmonale, a result of the pneumoconiosis; the effects were likely due to the asbestos-form contaminants.[5,6] The role of nonfibrous talc in these disease states could not be assessed.

In a study of 80 talc workers, there was an excess prevalence of productive cough and of criteria of chronic obstructive lung disease (COLD) compared with 189 nonexposed workers.[7] The increase in COLD and wheezing occurred only among smokers. Those talc workers with more than 10 years of exposure had significantly decreased FEV_1; none of the talc workers had chest X rays definitely consistent with classic talc pneumoconiosis.[7] Exposure had been to talc of industrial grade with less than 1% silica and less than two fibers of asbestos/ml at levels of 0.51–3.55 mg/m^3, with most of the workers being exposed to less than 1 mg/m^3 (or 2 mppcf).

A mortality study of 392 miners and millers of nonasbestos talc in Vermont showed an excess of deaths due to nonmalignant respiratory disease among millers and an excess of lung cancer mortality among miners.[8] The fact that the excess lung cancer mortality was observed for miners and not millers, despite probable higher dust exposure, led the investigators to conclude that other etiologic agents either alone or in combination with talc dust affected the miners.[8]

Another historical cohort study of 655 workers in a New York talc mine and mill revealed no significant differences in death rates from all causes, from cancer of the respiratory system, or from nonmalignant respiratory disease for the period from 1948 to 1978.[9] However, workers with previous occupational histories were found to have excessive mortality from lung cancer and from nonmalignant respiratory tract disease, again suggesting another etiologic agent. No excess cancer risk or cause-specific mortality was found in a cohort mortality study of 94 talc miners and 295 talc millers from Norway who were exposed to a nonasbestiform talc with low quartz content.[10]

A 1-year follow-up of 103 miners and millers of talc ore free from asbestos and silica showed an association between exposure and small opacities on chest radiographs; the annual loss in FEV_1 and FVC was greater than expected and could not be wholly attributed to cigarette smoking.[11] However, effects on pulmonary function in nonsmokers was not associated with lifetime or current talc exposure.[11]

In inhalation studies with hamsters exposed to 8 mg/m^3 at a cumulative dust dose

ranging from 15 to 6000 mg/m^3 no talc-induced lung lesions were found.[12] However, Italian talc, containing some quartz, was fibrogenic in specified pathogen-free rats exposed to a respirable dust concentration of 10.8 mg/m^3, the cumulative dust doses being approximately 4100, 8200, and 16,400 mg/m^3 for 3-, 6-, and 12-month exposures.[13] There was some evidence of progression of the fibrosis after exposure to talc had been discontinued in the animals exposed the longest period of time. The IARC has determined that there is inadequate evidence for carcinogenicity of talc to experimental animals; there is inadequate evidence for the carcinogenicity to humans of talc not containing asbestiform fibers, whereas there is evidence for carcinogenicity to humans of talc containing asbestiform fibers.[14]

In a subsequent National Toxicology Program study, rats exposed to dust levels of 18 mg/m^3 (with occasional higher excursions) were found to have impaired respiratory function, increased lung weights, inflammatory and proliferative processes in the lungs, interstitial fibrosis, hyperplasia of the alveolar epithelium, and occasionally squamous metaplasia.[15] Incidences of alveolar/bronchiolar adenomas and carcinomas were significantly higher in females but not males, and pheochromocytomas of the adrenal medulla occurred in both sexes. Mice similarly exposed had inflammation in the lungs but no hyperplasia, fibrosis, or pulmonary neoplasms. It has been suggested that the high doses used in this study may have overwhelmed the bronchopulmonary clearance mechanism, leading to the fibrotic tissue response.[1] Under conditions that do not overload the lung, natural defense mechanisms such as macrophages and mucociliary clearance can ordinarily cope with the lung burden without lesion development.

In vitro assay of a number of respirable talc specimens of high purity demonstrated a modest but consistent cytotoxicity to macrophages; the investigators conclude that the talcs would be expected to be slightly fibrogenic in vivo.[16]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for talc (containing no asbestos fibers) is 2 mg/m^3.

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TANTALUM
CAS: 7440-25-7

Ta

Synonyms: None

Physical Form. Solid (powder)

Uses. Manufacture of capacitors and other electronic components; chemical equipment and corrosion-resistant tools

Exposure. Inhalation

Toxicology. Tantalum has a low order of toxicity but has produced transient inflammatory lesions in the lungs of animals.

Surgical implantation of tantalum metal products such as plates and screws has not shown any adverse tissue reaction, thus demonstrating its physiological inertness.[1]

Intratracheal administration to guinea pigs of 100 mg of tantalum oxide produced transient bronchitis, interstitial pneumonitis, and hyperemia, but it was not fibrogenic.[2] There were some slight residual sequelae in the form of focal hypertrophic emphysema and organizing pneumonitis around metallic deposits, and there was slight epithelial hyperplasia in the bronchi and bronchioles. Doses as high as 8000 mg/kg given orally produced no untoward effects in rats.[3]

There was no mutagenic enhancement detected in the sera of animals implanted with tantalum pellets.[4]

The 2003 threshold limit value-time-weighted average (TLV-TWA) for tantalum metal and oxide dusts, as Ta, is 5 mg/m^3.

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TELLURIUM
CAS: 13494-80-9

Te

Synonyms: None

Physical Form. Grayish-white, lustrous, brittle, crystalline solid or dark gray to brown amorphous powder

Uses. Coloring agent in chinaware, porcelains, glass; reagent in producing black finish on silverware; rubber manufacturing; component of many alloys

Exposure. Inhalation

Toxicology. Tellurium causes garlic odor of the breath and malaise in humans.

Serious cases of tellurium intoxication have not been reported from industrial exposure. Iron foundry workers exposed to concentrations between 0.01 and 0.1 mg/m^3 complained of garlic odor of the breath and sweat, dryness of the mouth and metallic taste, somnolence, anorexia, and occasional nausea; urinary concentrations ranged from 0 to 0.06 mg/l. Somnolence and metallic taste in the mouth did not appear with regularity until the level of tellurium in the urine was at least 0.01 mg/l.[1] Skin lesions in the form of scaly itching patches and loss of sweat function occurred in workers exposed to tellurium dioxide in an electrolytic lead refinery.[2]

Hydrogen telluride has caused pulmonary irritation and hemolysis of red blood cells in animals; this gas is very unstable, however, and its occurrence as an actual industrial hazard is unlikely.[1,3]

In animals, acute tellurium intoxication results in restlessness, tremor, diminished reflexes, paralysis, convulsions, somnolence, coma, and death.[4] Administration to pregnant rats of 500–3000 ppm tellurium in the diet resulted in a high incidence of hydrocephalic offspring.[5] Weanling rats fed elemental tellurium at a level of 1% (10,000 ppm) in the diet developed a neuropathy characterized by segment demyelination; remyelination and functional recovery occurred despite continued administration of tellurium.[6] Both skeletal and soft tissue malformations (primarily hydrocephalus) were noted in the offspring of rats exposed to 3000 or 15,000 ppm in the diet on days 6–15 of gestation, but significant maternal toxicity was also noted.[7] Similarly, skeletal delays and nonspecific abnormalities occurred in the offspring of rabbits only at dosages (5250 ppm in the diet) well in excess of levels that produced significant maternal toxicity.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for tellurium, and compounds as Te, is 0.1 mg/m^3.

See separate monograph on tellurium hexafluoride.

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TELLURIUM HEXAFLUORIDE
CAS: 7783-80-4

TeF_6

Synonyms: None

Physical Form. Gas

Source. By-product of ore refining

Exposure. Inhalation

Toxicology. Tellurium hexafluoride is a strong irritant, and death may occur from pulmonary edema.

Human exposure has caused headache and dyspnea.[1,2] Two subjects accidentally exposed to tellurium hexafluoride after leakage of 50 g into a small laboratory experienced garlic breath, fatigue, a bluish-black discoloration of the webs of the fingers, and streaks on the neck and face.[3] Complete recovery occurred without treatment.

Rodents exposed to 1 ppm for 1 hour had increased respiratory rates, whereas a 4-hour

exposure at this concentration caused pulmonary edema.[4] However, repeated exposure at 1 ppm 1 hour/day for 5 days produced no effect; 5 ppm for 4 hours was fatal.

The 2003 threshold limit value (TLV) for tellurium hexafluoride is 0.02 ppm (0.10 mg/m^3) as Te.

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TERPHENYLS
CAS: 26140-60-3
84-15-1 o-terphenyl
92-06-8 m-terphenyl
92-94-4 p-terphenyl

$C_{18}H_{14}$

Synonyms: Phenylbiphenyls; diphenylbenzenes; triphenyls; *o*-terphenyl; *m*-terphenyl; *p*-terphenyl

Physical Form. Colorless or light yellow solids

Uses. Coolant for heat exchange in nuclear reactors

Exposure. Inhalation

Toxicology. Terphenyls are irritants of the eyes, mucous membranes, and skin.

There are no well-documented studies showing the effects of terphenyls on humans. Clinical studies of an exposed group of workers showed no ill effects from prolonged exposure to 0.1–0.9 mg/m^3.[1] Workers have experienced eye and respiratory irritation at levels above 10 mg/m^3.[2] As a class of compounds, organic coolants (including terphenyls) have caused transient headache and sore throat.[1] In addition, there have been cases of dermatitis attributed to skin contact with organic coolant compounds.[1]

Inhalation by rats of relatively high concentrations (660–3390 mg/m^3) of mixed and single isomers for periods of 1 hour for up to 14 days caused tracheobronchitis, pulmonary edema, and death at the higher concentrations.[3] In rats, the oral LD_{50} for *o*-terphenyl was 1.9 g/kg; for *m*-terphenyl it was 2.4 g/kg; and for *p*-terphenyl, it was greater than 10 g/kg.[4]

Transient morphologic changes in mitochondria of pulmonary cells were found in rats exposed to 50 mg/m^3 terphenyls 7 hours/day for up to 8 days.[5] The number of vacuolated mitochondria increased with days of exposure.[5]

The 2003 ACGIH ceiling-threshold limit value (C-TLV) for terphenyls is 0.53 ppm (5 mg/m^3).

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1,1,2,2-TETRACHLORO-1,2-DIFLUOROETHANE
CAS: 76-12-0

$C_2Cl_4F_2$

Synonyms: TCDF; Refrigerant 112

Physical Form. Colorless solid or liquid

Uses. As a refrigerant; solvent extractant; as a blowing or foaming agent

Exposure. Inhalation

Toxicology. At high concentrations, 1,1,2,2-tetrachloro-1,2-difluoroethane affects the nervous system and causes pulmonary edema in animals; it is expected that severe exposure in humans will produce the same effects.

There are no reports of adverse effects in humans.

Rats exposed to 30,000 ppm died within 1 hour after onset of exposure with severe pulmonary hemorrhage.[1] At 15,000 ppm, rats exhibited excitability, incoordination, coma, rapid respiration, tremor, and convulsions; three of four died in 3 hours with pulmonary edema and hyperemia of the lungs and liver.[2] Exposure at 5000 ppm for 18 hours caused coma, pulmonary damage, and death.[1] Rats survived 10 exposures of 4 hours each at 3000 ppm with rapid, shallow respiration, hyperresponsiveness, and slight incoordination; recovery was immediate after exposure.[2] Decreased leukocyte count occurred in female rats exposed to 1000 ppm 6 hours/day for 31 days.[2]

Gavage administration of 0.62 or 1.24 mmol/kg/day to rats for 21 days did not cause clinical signs of toxicity or microscopic effects in either the liver or kidney.[3] The inability to produce hyalin droplet nephropathy suggests that kidney neoplasms would not occur in rats in 2-year studies.[3]

1,1,2,2-Tetrachloro-1,2-difluoroethane was mildly irritating to rabbit eyes and guinea pig skin.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 1,1,2,2-tetrachloro-1,2-difluoroethane is 500 ppm (4170 mg/m^3).

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1,1,2,2-TETRACHLOROETHANE
CAS: 79-34-5

$CHCl_2CHCl_2$

Synonyms: Acetylene tetrachloride; sym-tetrachloroethane; 1,1-dichloro-2,2-dichloroethane

Physical Form. Heavy, clear liquid

Uses. Intermediate in the production of trichloroethylene, tetrachloroethylene, and 1,2-dichloroethylene; previously used as a solvent, insecticide and fumigant

Exposure. Inhalation; skin absorption

Toxicology. 1,1,2,2-Tetrachloroethane is toxic to the liver and causes central nervous system depression and gastrointestinal effects.

Reports of industrial experience indicate that cases of intoxication most commonly have presented symptoms of gastrointestinal irri-

tation (nausea, vomiting, abdominal pain, anorexia) and liver involvement (enlarged and tender liver, jaundice, bilirubinuria).[1,2] Jaundice sometimes progressed to cirrhosis and was often accompanied by delirium, convulsions, coma, and death. Other cases have primarily been characterized by central nervous system effects (dizziness, headache, irritability, nervousness, insomnia, paresthesia, and tremors).[1,2]

In one study, exposure of two men at 116 ppm for 20 minutes caused dizziness and mild vomiting; at 146 ppm, dizziness occurred after 10 minutes, mucosal irritation at 12 minutes, and fatigue within 20 minutes.[2] Concentrations up to 335 ppm produced the same symptoms with shorter exposure times. Occupational exposure to concentrations ranging from 1.5 to 247 ppm caused signs of liver injury such as hepatomegaly and increased serum bilirubin. These signs were still found after air concentrations had been reduced below 36 ppm.[2] Among a group of workers in India exposed to 20–65 ppm, effects were nausea, vomiting, and abdominal pain and a high incidence of tremor of the fingers.[3]

Oral ingestion of 3 ml caused coma or impaired consciousness in eight adult patients mistakenly administered tetrachlorethane.[2] Dermal absorption has been suspected in some poisoning cases.[2] Skin exposure may also produce dermatitis due to defatting action; in rare cases, the dermatitis may be caused by hypersensitivity to the substance.[4]

Treatment of mice during gestation caused embryotoxic effects and a low incidence of malformations.[5] Administration of 3.2 mg/kg/day to rats for 27 weeks caused irreversible histopathologic changes in the testes.[6]

In short-term renal toxicity studies in rats gavage administration of 1,1,2,2-tetrachloroethane caused renal toxicity as evidenced by an increased renal tubule cell labeling index, indicating replicative DNA synthesis.[7] In 2-year studies 1,1,2,2-tetrachloroethane administered by gavage produced an increased incidence of hepatocellular carcinomas in mice but not in rats.[8] In one epidemiological study of exposed army workers there was a slight increase in deaths due to genital cancer and leukemia.[8] Exposure levels were not available, and other confounding factors may have been present, so that no definite conclusions could be drawn from the study.[9] The IARC has determined that there is limited evidence of carcinogenicity for 1,1,2,2-tetrachloroethane in experimental animals and that it is not classifiable as to its carcinogenicity to humans.[10]

In *in vivo* genetic assays tetrachloroethane bound covalently to mice DNA.[10] It induced sister chromatid exchanges and cell transformation, but not chromosomal aberrations or unscheduled DNA synthesis, in rodent cells in vitro.

Tetrachloroethane has a mild, sweetish odor detectable at 3 ppm that may not provide sufficient warning of dangerous levels because of olfactory fatigue.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 1,1,2,2-tetrachloroethane is 1 ppm (6.9 mg/m^3) with a notation for skin absorption.

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TETRACHLORONAPHTHALENE

CAS: 1335-88-2

$C_{10}H_4Cl_4$

Synonym: Halowax

Physical Form. Solid

Uses. Synthetic wax; dielectrics in capacitors; wire insulation

Exposure. Inhalation; skin absorption

Toxicology. Tetrachloronaphthalene may cause liver injury.

Experiments on human volunteers showed tetrachloronaphthalene to be nonacneigenic as opposed to the penta- and hexachloro-derivatives that produce very severe chloracne.[1]

Rats exposed 16 hours/day to 10.97 mg/m^3 of tri- and tetrachloronaphthalene vapor for up to 4.5 months had slight liver injury.[2] When a mixture of tetra- and pentachloronaphthalene was fed to rats at a dose of 0.5 mg/day for 2 months, definite liver injury and some mortality occurred.[2]

Tetrachloronaphthalene was not mutagenic in the *Salmonella* Ames test.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for tetrachloronaphthalene is 2 mg/m^3.

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TETRAETHYL LEAD

CAS: 78-00-2

$Pb(C_2H_5)_4$

Synonyms: Lead tetraethyl; TEL; tetraethylplumbane

Physical Form. Colorless liquid

Uses. Gasoline additive to prevent "knocking" in motors

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Tetraethyl lead (TEL) affects the nervous system and causes mental aberrations, including psychosis and mania, convulsions, and death.

Of approximately 150 reported fatal cases of TEL poisoning, most have been related

to early production methods, to cleaning of leaded gasoline storage tanks without protective equipment, and to suicidal or accidental ingestion.[1] Milder cases of intoxication have been caused by exposures to leaded gasoline in the workplace.[1]

The absorption by humans of a sufficient quantity of TEL, either briefly at a high rate (100 mg/m^3 for 1 hour) or for prolonged periods at a lower rate, causes intoxication.[2] The interval between exposure and the onset of symptoms varies inversely with dose and may last 1 hour to several days.[1] This clinical latency is related to the time it takes for TEL to be absorbed, distributed, and metabolized to triethyl lead before toxic action develops.[1]

The signs and symptoms of TEL intoxication differ in many respects from those of inorganic lead intoxication and are often vague and easily missed. The initial or prodromal symptoms are nonspecific and include asthenia, weakness, fatigue, headache, nausea, vomiting, diarrhea, and anorexia.[1] Insomnia is usually present, and any sleep is light, usually with nightmares. Signs of nervous system involvement may then develop (ataxia, tremor, hypotonia) as well as bradycardia and hypothermia, referred to as the TEL triad.[1]

More severe intoxication causes recurrent or nearly continuous episodes of disorientation, hallucinations, facial contortions, and intense hyperactivity, which requires that the individual be restrained. Such episodes may convert abruptly into maniacal or violent convulsive seizures, which may terminate in coma and death.[2] Autopsy reports from humans who succumbed to TEL poisoning confirm that the brain is the critical target organ, and both focal and generalized damage have been described. For survivors of TEL poisoning, recovery may take many weeks or months.[1] There is some question as to whether or not all changes are reversible after heavy or long-term exposures.[1]

During intoxication, there is a striking elevation of the rate of excretion of lead in the urine, but only a negligible or slight elevation of the concentration of lead in the blood.[2,3] In severe intoxication, the urine lead is rarely less than 350 µg/l of urine, whereas the blood lead is rarely more than 50 µg/100 g of blood.[2,3] There is also a total absence of morphologic or chemical abnormalities in the erythrocytes—in sharp contrast to intoxication caused by inorganic lead.[2]

A cohort of gasoline depot workers exposed to a mean external TEL concentration of 84.8 µg/m^3 (as Pb) had a statistically increased frequency of appearance of tremor and sinus bradycardia (vs. controls).[4] No clinical neurological or neurobehavioral findings were found after long-term exposure at a chemical manufacturing plant where TEL exposures ranged from 0.6 to 43.1 µg/m^3 (as Pb).[5]

In a mortality study of 592 workers, the mean exposure time to TEL was 17.9 years and urinary lead levels during this period did not exceed 180 µg/liter. The incidence of death in this group and in a control group of employees was less than that expected in the general population, and there were no peculiarities in the specific causes of death in either group.[6] In a similar study of a different cohort of these exposed workers, there were no significant health differences compared with a control group.[7] A recent case-control study of TEL manufacturing workers found an increased incidence of rectal cancer (odds ratio = 3.7) and sigmoid colon cancer (odds ratio = 3.5).[8] With both of these cancers, an exposure-response relationship was observed; odds ratios showed a nearly fourfold increase at the high to very high cumulative exposure level.

Of 41 female Swiss mice that survived for 36 weeks after a single subcutaneous injection of 0.6 mg, 5 developed malignant lymphomas during the next 15 weeks; the significance of the study cannot be evaluated, because this tumor occurs spontaneously with a variable incidence in the mouse strain used.[9,10]

TEL is not an irritant, and no unpleasant sensations are related to skin contact or inhalation.[1] The ability to penetrate skin makes reliance on airborne concentrations impractical.[2] Teratogenic effects have not been observed after exposure to maximally tolerated doses in mice or rats.[1] Rodent embryos may serve as a poor model for human fetuses because the hepatic microsomal metabolizing

enzymes do not develop until after birth in rodents whereas these enzymes develop early in humans.

The 2003 time-weighted average-threshold limit value (TWA-TLV) is 0.1 mg/m^3, as Pb, with a notation for skin absorption.

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TETRAETHYL PYROPHOSPHATE

CAS: 107-49-3

$C_8H_{20}O_7P_2$

Synonyms: Ethyl pyrophosphate; phosphoric acid tetraethyl ester; TEPP; Tetron; NIFOS; TEP

Physical Form. Colorless, odorless liquid (pure); amber liquid (crude)

Uses. Insecticide

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Tetraethyl pyrophosphate (TEPP) is a highly toxic anticholinesterase agent.

Signs and symptoms of overexposure are caused by the inactivation of the enzyme cholinesterase, which results in the accumulation of acetylcholine at synapses in the nervous system, skeletal and smooth muscle, and secretory glands.[1–3] The sequence of the development of systemic effects varies with the route of entry.[2] The onset of signs and symptoms is usually prompt but may be delayed for up to 12 hours.[1,2] After inhalation, respiratory and ocular effects are the first to appear, often within a few minutes of exposure. Respiratory effects include tightness in the chest and wheezing due to bronchoconstriction and excessive bronchial secretion; laryngeal spasms and excessive salivation may add to the respiratory distress; cyanosis may also occur. Ocular effects include miosis, blurring of distant vision, tearing, rhinorrhea, and frontal headache.

After ingestion, gastrointestinal effects such as anorexia, nausea, vomiting, abdominal cramps, and diarrhea appear within 15 minutes and muscular fasciculations in the immediate area occur usually within 15 minutes to 4 hours. The lowest lethal oral dose in humans was approximately 1.4 g/kg; oral doses of 0.3 mg/kg have caused abnormal muscle

contractions, gastrointestinal upset, and wakefulness.[4]

Skin absorption is somewhat greater at higher ambient temperatures and is increased by the presence of dermatitis.[1,2]

With severe intoxication by all routes, an excess of acetylcholine at the neuromuscular junctions of skeletal muscle causes weakness aggravated by exertion, involuntary twitchings, fasciculations, and, eventually, paralysis.[2] The most serious consequence is paralysis of the respiratory muscles; in fatal cases death usually occurs within 24 hours.[2] Effects on the central nervous system include giddiness, confusion, ataxia, slurred speech, Cheyne–Stokes respiration, convulsions, coma, and loss of reflexes. The blood pressure may fall to low levels, and cardiac irregularities including complete heart block may occur.[1]

In nonfatal cases, recovery usually occurs within 1 week, but increased susceptibility to anticholinesterase agents persists for up to several weeks after exposure.[2] Daily exposure to concentrations that are insufficient to produce symptoms after a single exposure may result in the onset of symptoms. Continued daily exposure may be followed by increasingly severe effects.[1]

Mild intoxication was reported in 15 people exposed to a dust of 1% TEPP; the predominant symptom was shortness of breath, which occurred after breathing the dust-laden air for 30 minutes. Symptoms rapidly abated after exposure was terminated.[5]

Eye exposure can produce visual disturbances without affecting blood cholinesterase levels. Exposed crop duster pilots, unable to judge distances, have been involved in accidents. Volunteers instilled with 2 drops of 0.1% TEPP 30 minutes apart experienced maximal miosis without any change in blood cholinesterase.[6]

TEPP inactivates cholinesterase by phosphorylation of the active site of the enzyme to form the diethylphosphoryl enzyme. Over the following 24–48 hours, there is a process, termed aging, of conversion to the monoethylphosphoryl enzyme. Aging is of clinical interest in the treatment of poisoning because cholinesterase reactivators such as pralidoxime (2-PAM, Protopam) chloride are ineffective after aging has occurred.

The 2003 ACGIH time-weighted average-threshold limit value (TWA-TLV) for Tetraethyl pyrophosphate (TEPP) is 0.004 ppm (0.047 mg/m^3) with a notation for skin absorption.

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TETRAHYDROFURAN
CAS: 109-99-9

$(C_2H_4)_2O$

Synonyms: Cyclotetramethylene oxide; diethylene oxide; THF; tetramethylene oxide

Physical Form. Colorless liquid

Uses. Widely used as an industrial solvent, especially for plastic resins; as a reaction medium; in a coating agent used in the production of audio- and videotapes; in the fabri-

cation of articles for packaging, transporting, and storing of foods

Exposure. Inhalation

Toxicology. Tetrahydrofuran (THF) is an upper respiratory tract irritant; at high concentrations it is a central nervous system depressant; it causes liver tumors in female mice.

Two workers, who had been exposed to glue containing THF for up to 8 hours in a confined space, had nausea, headache, dizziness, dyspnea, and chest pain.[1] Clinical examination disclosed conjunctival irritation and alteration in liver enzymes. Symptoms disappeared within a few hours after exposure ceased, and liver enzymes returned to normal within 2 weeks.

Administered to mice, 49,000 ppm for 51 minutes resulted in narcosis, muscular hypotonia, disappearance of corneal reflexes, then coma followed by death.[2] The LC_{50} was estimated to be 21,000 ppm in rats exposed for 3 hours.[3] Repeated exposure of rats to concentrations ranging from 100 to 5000 ppm for 12 weeks caused a dose-related increase in irritation of the mucous membranes. At the 5000 ppm level there was marked edema or opacity of the cornea, salivation, and discharge or bleeding in the nasal mucosa.

In subchronic studies mice and rats were exposed at 0, 66, 200, 600, 1800, and 5000 ppm 6 hours/day, 5 days/week for 13 weeks.[4] Rats were ataxic at the high dose, and mice exposed to 1800 or 5000 ppm appeared to be in a state of narcosis. A minimal to mild centrilobular hepatocytomegaly also occured in the mice exposed at 5000 ppm. Stomach lesions, limited to the rats, were thought to occur from direct contact of THF ingested during the inhalation exposure period.

In 2-year inhalation studies (0, 200, 600 or 1800 ppm) there was some evidence of carcinogenicity in male rats based on increased incidences of renal tubule adenoma or carcinoma and clear evidence of carcinogenicity in female mice based on increased incidences of hepatocellular neoplasms.[5]

Exposure of pregnant CD-1 mice 6 hours/day on days 6–17 of gestation was embryotoxic at 1800 and 5000 ppm as indicated by a reduction in the number of live fetuses per litter (95% resorptions in the 5000 ppm group).[6] These doses were also maternally toxic, producing narcosis in dams at 1800 ppm and significant lethality at 5000 ppm. There were no statistically significant differences in the incidences of malformations or variations. In rats similarly exposed, maternal and fetal body weights were significantly reduced at the 5000 ppm exposure level.

THF showed little evidence of mutagenic activity in a variety of *in vitro* and *in vivo* assays.[5]

Studies have suggested that measurement of THF concentration in the urine may be a useful biological indicator of occupational exposure to THF, whereas exhaled breath and blood analyses may be less suitable.[7]

The liquid has an ethereal odor similar to acetone and a pungent taste.

The 2003 ACGIH time-weighted average-threshold limit value (TWA-TLV) for tetrahydrofuran is 200 ppm (590 mg/m^3) with a short-term exposure limit (STEL) of 250 ppm (737 mg/m^3).

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TETRALIN
CAS: 119-64-2

$C_{10}H_{12}$

Synonyms: 1,2,3,4-tetrahydronaphthalene; tetraline; tetranap; benzocyclohexane

Physical Form. Colorless liquid

Uses. As a solvent for fats and oils and as an alternative to turpentine in polishes and paint; insecticide

Exposure. Inhalation

Toxicology. Tetralin is an irritant to the skin, eyes, and mucous membranes and may cause neurological disturbances at high concentrations.

The hallmark for tetralin exposure in humans is the production of green urine.[1] Two painters who used tetralin-containing varnishes in a poorly ventilated area had intense irritation of the mucous membranes, profuse lacrimation, headache, stupor, and the characteristic green urine. Hospital patients on a ward whose floor had been waxed with a tetralin-based polish experienced similar symptoms including eye irritation, headache, nausea, diarrhea, and green urine. Asthenia also was observed in subjects who had slept in rooms waxed with a tetralin-based polish.

In a human case involving ingestion of approximately 1–1.5 mg/kg, effects consisted of nausea, vomiting, and green-gray urine.[2] Clinical changes included proteinuria and elevated serum levels of bilirubin, creatine, alkaline phosphatase, lactic dehydrogenase, and glutamic oxaloacetic transaminase. All signs and symptoms returned to normal within 2 weeks.

Exposure to tetralin-saturated vapor for 8 hours was lethal to rats.[3] Nephrotoxicity, evidenced as increased cytoplasmic hyalin droplets in proximal convoluted tubular epithelial cells, occurred in male but not female rats exposed intragastrically for 2 weeks.[4]

Acute intoxication of guinea pigs, exposed orally (0.25 ml/day), percutaneously (by application to 6 cm^2 of shaved skin), or by inhalation (1.42 mg/l for 8 hours/day), produced loss of weight, tremors, paralysis of the hindquarters, and difficult respiration.[3]

Tetralin has caused cataracts in guinea pigs and rabbits but not rats after oral or inhalation exposure; differences in the susceptibility of different species to cataractogenic effects have been attributed to differences in their metabolism of the compound.[5]

Applied to the skin of guinea pigs, the liquid caused erythema, drying, and defatting.

In rabbits, the irritant dermal and ocular dose was 500 mg and the dermal LD_{50} was 17.3 g/kg.[3]

An ACGIH threshold limit value-time-weighted average (TLV-TWA) has not been established for tetralin.

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TETRAMETHYL LEAD
CAS: 75-74-1

$Pb(CH_3)_4$

Synonyms: Lead tetramethyl; TML

Physical Form. Colorless liquid

Uses. Gasoline additive, especially to aviation and premium grades with high aromatic content

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Tetramethyl lead (TML) affects the nervous system in animals.

Accidental human exposure to a high level of TML liquid for approximately 5 minutes caused no signs or symptoms of lead poisoning. Significant exposure was corroborated by high levels of urinary lead, averaging almost 1000 μg/24 hour for the first 4 days after exposure.[1] By comparison, urinary lead levels of less than 750 μg/24 hour after tetraethyl lead (TEL) exposure have been associated with confusion, agitation, and acute toxic delirium.[1]

In a plant, 21 workers were exposed at different times to TEL and then to TML under similar conditions for similar periods of time. TML had three times the airborne level found during TEL production, yet the urinary lead levels were nearly the same in both cases; this suggests that TML is absorbed more slowly then TEL.[2] No signs or symptoms of toxicity were noted.

In rats, the approximate oral LD_{50} for TML is 108 mg/kg vs. 17 mg/kg for TEL. Effects were tremor, hyperactivity, and convulsions.[3] Inhalation studies on rats showed TML to have less than one-tenth the toxicity of TEL.[4] In dogs and mice, however, the reverse is true, with TML being more potent than TEL.[5]

Prudent practice suggests that TML be treated as if it were TEL.[5] Further caution is indicated by recent reports that the degradation product of TML, trimethyllead, acts differently from higher-trialkylated compounds, inducing lipid peroxidation.[6] This difference indicates a potential for more severe chronic toxicity from TML exposure.

TML was not mutagenic in a number of bacterial strains with or without metabolic activation.[7]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for tetramethyl lead is 0.15 mg/m^3 as Pb with a notation for skin absorption.

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TETRAMETHYL SUCCINONITRILE
CAS: 3333-52-6

$C_8H_{12}N_2$

Synonyms: TMSN; tetramethylsuccinic acid dinitrile

Physical Form. Crystalline solid

Source. Breakdown product of azobisisobutyronitrile used as a blowing agent for the production of vinyl foam; by-product of a polymerization catalyst in photocopier toner

Exposure. Inhalation; skin absorption

Toxicology. Tetramethyl succinonitrile (TMSN) is a convulsant.

Exposure involving TMSN occurred in a group of 16 workers using azoisobutryonitrile over an 18-month period in the production of polyvinyl chloride foam.[1] There were five cases of convulsions and unconsciousness. Other symptoms reported included headache, dizziness, nausea, and vomiting. Although an unknown concentration of TMSN was the suspected etiologic agent, it was noted that exposure to a number of other substances also occurred. All symptoms subsided after installation of improved ventilation in the work area.

Exposure of rats to the vapor at 60 ppm for 2–3 hours, or to 6 ppm for 30 hours, caused death.[1] Mice exposed to 22 ppm had muscle spasms and died within 2–3 hours.[1,2] Rats, guinea pigs, rabbits, and dogs administered TMSN by a variety of routes developed violent convulsions and asphyxia, which eventually led to death from 1 minute to 5 hours after convulsions.[1] In a variety of species, LD_{50} values for intravenous, intraperitoneal, subcutaneous, and oral administration ranged from 17.5 to 30 mg/kg.[1] Administration of a quick-acting barbiturate followed by phenobarbital reduced the toxicity of TMSN given in doses up to 50 mg/kg.[1,2]

Increased renal weights and tubular nephrosis were found in male rats but not females treated for 90 days at 10 or 3 mg/kg/day by intubation.[3] Increased kidney weights were also noted in male rats exposed to 5 or 10 ppm in the drinking water for 90 days. The only effects in dogs administered 1.0 or 3.0 mg/kg/day by capsule for 90 days were slight depressions of body weight gain and, at the higher dose, a small increase in blood thiocyanate.[3]

Parental injection of TMSN caused some fetal malformation and embryonic death but only at doses that caused severe maternal toxicity.[4]

The 2003 ACGIH time-weighted average-threshold limit value (TWA-TLV) for tetramethyl succinonitrile is 0.5 ppm (2.8 mg/m^3) with a notation for skin absorption.

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TETRANITROMETHANE
CAS: 509-14-8

$C(NO_2)_4$

Synonym: TNM

Physical Form. Pale yellow liquid

Uses. Oxidizer in rocket propellants; explosive in admixture with toluene; reagent for

detecting presence of double bonds in organic compounds

Exposure. Inhalation

Toxicology. Tetranitromethane vapor is a severe irritant of the eyes and respiratory tract; it can cause mild methemoglobinemia.

In workers, various studies showed that exposure caused irritation of the eyes, nose, and throat; dizziness; headache; chest pain; dyspnea; and, rarely, skin irritation.[1]

Severe exposure may be expected to cause the formation of methemoglobin and resultant anoxia with cyanosis (especially evident in the lips, nose, and earlobes); other effects are weakness, dizziness, and severe headache.[2–4] Concentrations in excess of 1 ppm cause lacrimation and upper respiratory irritation, whereas 0.4 ppm may cause mild irritation.[2] The liquid on the skin may cause mild burns.[2]

The LC_{50} for rats was 1230 ppm for 36 minutes; effects included lacrimation, rhinorrhea, gasping, and cyanosis. Pulmonary edema was present at autopsy.[1] At 300 ppm, all rats died within 40–90 minutes, whereas exposure to 33 ppm caused deaths in 3–10 hours.[1] Exposure to 6.35 ppm 6 hours/day, 5 days/week, for 6 months resulted in death of 11 of 19 rats; similar exposure in dogs caused mild symptoms the first 2 days, followed by complete recovery.[1] In three species of animals, intravenous injection caused methemoglobinema, anemia, damage to the central nervous system, and pulmonary edema.[1]

Rats and mice were exposed 6 hours/day, 5 days/week for 2 years at 2 or 5 ppm or 0.5 or 2 ppm, respectively.[5,6] Tetranitromethane was found to cause mild irritation and hyperplastic lesions in the nasal passages. Nearly all animals exposed at the higher dose levels developed alveolar/bronchiolar adenoma or carcinoma; squamous cell neoplasms of the lung also occurred in exposed rats. The carcinogenic activity of tetranitromethane appears to be the result of chronic epithelial irritation mitotic stimulation and ensuing hyperplastic response.[6]

Tetranitromethane was genotoxic in a number of assays inducing chromosomal aberrations and sister chromatid exchanges in Chinese hamster ovary cells.[6]

The IARC has determined that there is sufficient evidence for the carcinogenicity of tetranitromethane in experimental animals and that it is possibly carcinogenic to humans.[7]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for tetranitromethane is 0.005 ppm (0.04 mg/m^3) with an A2-suspected human carcinogen designation.

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TETRASODIUM PYROPHOSPHATE
CAS: 7722-88-5

$Na_4P_2O_7$

Synonyms: Sodium pyrophosphate; tetrasodium diphosphate; TSPP

Physical Form. White crystalline powder

Uses. As a water softener; as a metal cleaner; as a dispersing and emulsifying agent

Exposure. Inhalation

Toxicology. Tetrasodium pyrophosphate (TSPP) is of low toxicity, but the dust may be irritating to the eyes, upper respiratory tract, and skin.

Mild to moderate skin and eye irritation have occurred with acute exposure to the dust.

In rats the oral LD_{50} ranges between 1 and 3 g/kg.[1] Applied to rabbit eyes it can cause severe irritation and corneal injury. There were no adverse effects in rats fed 50 mg/kg/day for 1 year.

Injected into chick embryos TSPP produced terata.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for tetrasodium pyrophosphate is 5 mg/m^3.

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TETRYL
CAS: 479-45-8

$C_7H_5N_5O_8$

Synonyms: 2,4,6-Trinitrophenylmethylnitramine; tetralite; nitramine; *N*-methyl-*N*-2,4,6-tetranitroaniline

Physical Form. Yellow crystals

Uses. Once widely used as a military explosive but no longer manufactured or used in the United States

Exposure. Inhalation; skin absorption

Toxicology. Tetryl causes contact and sensitization dermatitis and irritation of the upper respiratory tract.

Contact with tetryl causes a bright yellow staining, most often seen on the palms, face, and neck and in the hair.[1] The irritant effects on the upper respiratory tract are variously localized from the nostrils to the bronchi and cause burning, itching, sneezing, nasal discharge, epistaxis, and cough. The symptoms may begin the first day of exposure or as late as the third month; on removal from exposure the symptoms typically regress over 2–4 weeks.[1]

Dermatitis in workers may appear as early as the first week of exposure to the dust, with itching of and around the eyes; there is a progression to erythema and edema occurring most often on the nasal folds, cheeks, and neck; papules and vesicles may develop; the remainder of the body is rarely affected.[1] The severest forms show massive generalized edema with partial obstruction of the trachea due to swelling of the tongue and require hospitalization; exfoliation usually occurs after the edema subsides.[1] The majority of these effects occur between the 10th and 20th days of exposure; on cessation of exposure, there is rapid abatement of the mild symptoms and, after 3–10 days, disappearance of physical signs.[1]

Some individuals have become sensitized to tetryl and developed a rash in response to recontact with even small amounts of the substance.[2]

Other effects reported in tetryl workers are irritability, fatigue, malaise, headache, lassitude, insomnia, nausea, and vomiting.[1] Anemia, of either the marrow depression or deficiency type, has been observed among tetryl workers.[1] Conjunctivitis may be caused by rubbing the eyes with contaminated hands or by airborne dust; keratitis and iridocyclitis have occurred.[3] Tetryl has been reported to cause irreversible liver damage and death after chronic heavy exposure.[4] However, complicat-

ing medical conditions and/or coexposure to other toxic chemicals could be contributing factors in the deaths.[2]

A number of *in vitro* genotoxic assays in bacteria and fungi suggest that tetryl is a direct-acting genotoxin.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for tetryl is 1.5 mg/m^3.

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THALLIUM
CAS: 7440-28-0

Tl

Compounds. Thallium acetate; thallium chloride

Physical Form. Bluish-white, very soft, inelastic, easily fusible heavy metal

Uses. In the semiconductor industry for the production of switches and closures; the pharmaceutical industry for cardiac imaging; manufacture of optical glass; formerly used as a rodenticide and insecticide until banned in the US in 1972.

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Thallium is one of the most toxic of the heavy metals; it primarily affects the nervous system and gastrointestinal tract and causes hair loss.

The lethal oral dose of thallium acetate for humans is estimated to be about 12 mg/kg body weight.[1] Although symptoms may be nonspecific owing to multiorgan toxicity, gastroenteritis, polyneuropathy, and hair loss are the dominant clinical features of poisoning.[2] In fatal cases, however, death has been regularly attributed to cardiac or respiratory failure, which may overshadow the characteristic manifestation of neuropathy.[3] A latent period of hours to 1–2 days may follow acute exposure.[2] Nausea, vomiting, diarrhea, abdominal pain, and gastrointestinal hemorrhage are common initial complaints. These symptoms are followed or accompanied by ptosis and strabismus; peripheral neuritis; pain, weakness, and paresthesias in the legs; tremor; and retrosternal tightness and chest pain.[1,4] Severe and abrupt alopecia is pathognomonic of the toxic effects of thallium and usually, but not always, occurs after 2–3 weeks.[4,5]

Severe intoxication has resulted in prostration, tachycardia, blood pressure fluctuations, convulsive seizures, choreiform movements, and psychosis. Recovery may be complete, but permanent residual effects such as ataxia, optic atrophy, tremor, mental abnormalities, and footdrop have been reported.[4] In cases of fatal intoxication, typical autopsy findings include pulmonary edema, necrosis of the liver, nephritis, and degenerative changes in peripheral axons.[1]

Prolonged ingestion of thallium produces a variable clinical picture, which includes stomatitis, tremor, cachexia, polyneuropathy, alopecia, and emotional disturbance.[4] Alopecia may be the best known effect of chronic poisoning, with epilation beginning about 10 days after ingestion and complete hair loss occurring in about 1 month.[2]

In a study of 15 workers who had handled solutions of organic thallium salts over a 7.5-year period, 6 workers suffered thallium intoxication. Chief complaints were abdominal pain, fatigue, weight loss, pain in the legs, and nervous irritability; three of the workers had albuminuria, and one had hematuria.[6]

In another cohort study, no statistically significant clinical effects were found, even though urinary concentrations ranging up to 236 µg/liter indicated exposures above the threshold limit value (TLV) of 0.1 mg/m^3.[7] A urine thallium concentration of 100 µg/l corresponds approximately to a 40 hour/week exposure at 0.1 mg/m^3, and normal values range between 0.6 and 2.0 µg/l.[7]

Several mechanisms have been postulated to account for thallium's toxicity, including ligand formation with sulfhydryl groups of enzymes and transport proteins, inhibition of cellular respiration, interaction with riboflavin and riboflavin-based cofactors, alteration of the activity of K^+-dependent proteins, and disruption of intracellular calcium homeostasis.[2]

In six cases of thallium intoxication of pregnant women during their first trimester, no congenital abnormalities were observed.[7] Fetal mortality was reported in one case where the mother was severely affected; maternal signs included dyesthesias in the hands and feet, difficulty in walking, vertigo, and alopecia.[8]

Exposure of pregnant mice, rabbits, or rats produced slight embryotoxic effects at maternally toxic doses.[9]

Administered in the drinking water to male rats for 60 days, 0.7 mg thallium/day, as thallium sulfate, caused abnormalities in testicular morphology, function, and biochemistry.[10] Effects included increased epididymal sperm with increased numbers of immature cells, decreased sperm motility, and reduced testicular β-glucuronidase.

Thallium was genotoxic in a variety of assays inducing single-strand breaks in mouse cell cultures, dominant lethals in male rats *in vivo*, and DNA damage in bacterial systems.[3]

Cytogenic evaluation of 13 thallium-poisoned people revealed increased chromosomal aberrations and an increase in single-strand breaks.[11] Long-term studies of carcinogenicity in humans or animals are not available.[12]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for thallium and soluble compounds is 0.1 mg/m^3, as Tl, with a notation for skin absorption.

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THIAZOLES—RUBBER COMPONENTS
CAS: Mercaptobenzothiazol 149-30-4

$C_7H_5NS_2$

Synonyms: MBT; 2-Benzothiazolethiol; Captax; Kaptax; Royal MBT; Vulkacit Mercapto

Physical Form. Yellow to tan brown crystalline powder.[1]

Uses. Vulcanization accelerator for type of rubber usually used in the production of household rubber gloves rather than medical rubber gloves; corrosion inhibitor in metal-working fluids, detergents, antifreeze, and photographic emulsions.

Exposure. Dermal

Toxicology. Thiazoles cause allergic skin reactions of type IV [delayed-type hypersensitivity (DTH)].[2–3]

The most important contact allergen in the thiazole group is mercaptobenzothiazol (MBT).[2] Studies thus far suggest that men are more often affected than women.[3–4]

A retrospective study was performed of 3851 patients who presented at a clinic with suspected allergic contact dermatitis over a 5-year period.[5] Workup of each case included standard patch tests for delayed-type sensitivity. Of the 3851 patients, 145 had type IV allergies to one or more rubber constituents. Five of the 145 were positive to MBT.

In 2-year gavage studies, there was some evidence of carcinogenic activity of MBT based on increased incidences of mononuclear cell leukemia, pancreatic acinar cell adenomas, adrenal gland pheochromocytomas, and preputial gland adenomas or carcinomas (combined) in male rats and increased incidences of adrenal gland pheochromocytomas and pituitary gland adenomas in female rats.[6] There was no evidence of carcinogenic activity for male mice and equivocal evidence of carcinogenic activity for female mice, indicated by increased incidences of hepatocellular adenomas or carcinomas (combined).

In a cohort study of workers at a rubber chemicals plant, exposure to MBT did not seem to increase the risk of most cancers, including cancers of the lung and prostate.[7]

MBT was not mutagenic in Ames bacterial assays, but it induced chromosomal damage in mammalian cells in culture.[6]

Reproductive effects were not observed in two-generation studies of rats treated with up to 15,000 ppm MBT in the diet.[8]

An ACGIH threshold limit value (TLV) has not been established for mercaptobenzothiazol.

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THIOACETAMIDE
CAS: 62-55-5

CH_3CSNH_2

Synonyms: Acetothioamide; ethanethioamide; TAA

Physical Form. Colorless crystals

Uses. Laboratory reagent used as a substitute for hydrogen sulfide

Exposure. Inhalation; skin absorption

Toxicology. Thioacetamide can cause liver and pulmonary damage; it is carcinogenic to experimental animals.

Exposure to high concentrations may cause irritation of the nose, throat, and lungs; even higher exposure may result in pulmonary edema. High exposure can also cause liver injury severe enough to cause death.[1]

In female Wistar rats, administration of 50 mg/kg twice weekly for 30 weeks resulted in hepatic necrosis.[2] Slight to moderate cirrhosis was observed in male albino rats fed 0.005% or 0.01% in the diet for 18 months; one of six survivors developed hepatic cell adenoma.[3] Thioacetamide induced liver cell tumors in mice and liver and bile duct tumors in rats after chronic administration of 0.03% in the diet. Cirrhosis, neoplastic nodules, cholangiofibromas, hepatocarcinomas, and cholangiocarcinomas occurred in male ACI rats fed 0.035% in the diet for 1 year.[4] In hamsters, 2.5 mg given by gavage once a week for 30 weeks was not carcinogenic.

In a wide variety of genotoxic assays thioacetamide has given inconsistent and contradictory results.[5] Although the carcinogenicity of thioacetamide may be related to its genotoxic properties, cytotoxic effects maybe more critical.[5,6] Cytotoxicity leads to regenerative cell proliferation, and this may be involved in the pathogenesis of the neoplasm.[6] Furthermore, epigenetic agents may either pose no risk to humans because their effects are specific to rodents or pose a risk only at high exposures, where they produce the same cellular effects in humans that are the basis of their carcinogenic activity in rodents.[6]

The IARC has determined that there is sufficient evidence for the carcinogenicity of thioacetamide to animals; no data were available in humans.[7]

The ACGIH has not established a threshold limit value (TLV) for thioacetamide.

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4,4′-THIOBIS(6-*tert*-BUTYL-*m*-CRESOL)
CAS: 96-69-5

$C_{22}H_3O_2S$

Synonyms: 4,4′-thio-bis(3-methyl-6-*tert*-butylphenol); bis(3-*tert*-butyl-4-hydroxy-6-methylphenyl)sulfide; TBBC

Physical Form. Fine white to gray powder

Uses. As an antioxidant in the rubber and plastics industry; as a stabilizer in polyethylene and polyolefin packaging materials for foodstuffs

Exposure. Ingestion; inhalation

Toxicology. 4,4′-Thiobis(6-*tert*-butyl-*m*-cresol) (TBBC) is of low systemic toxicity in animals; allergic contact dermatitis has been reported in humans.

Allergic contact dermatitis developed on the hands and face of two patients after exposure to latex examination gloves.[1] Both patients were patch test negative to the usual rubber allergens, but both had a positive test reaction to TBBC.

In 15-day feeding studies, groups of rats and mice were fed diets containing 1000, 2500, 5000, 10,000, or 25,000 ppm TBBC.[2] All 25,000 and some 10,000 ppm rats died; rats in the 5000 and 10,000 ppm group consumed less food than controls and had significant weight loss and diarrhea. Renal papillary and tubule necroses were the principle lesions attributed to TBBC exposure in the 10,000 ppm group. Focal necrosis of the glandular stomach also occurred in some 10,000 ppm rats. Some mice did not survive exposure at 5000 and 10,000 ppm, and 25,000 ppm was lethal to all. Weight loss, diarrhea, and renal tubule necrosis were similar to that observed in rats.

Histopathologic findings in rats fed 2500 or 5000 ppm for 13 weeks included hypertrophy of Kupffer cells, bile duct hyperplasia, and individual cell necrosis of hepatocytes; pigmentation and degeneration of the renal cortical tubule epithelial cells was also present.[2] In male rats exposed at 1000 ppm and above hematocrit and hemoglobin concentrations and mean erythrocyte volume were significantly lower than controls. Mice survived exposures up to 2500 ppm in their diets for 13 weeks. Body weights were significantly lower in the high-dose groups and corresponded with reduced feed consumption. Kupffer cell hypertrophy, bile duct hyperplasia, increased spleen weights, and an increase in size and number of macrophages in mesenteric lymph nodes were present in the 2500 ppm-treated mice.

Two-year studies of rats administered up to 2500 ppm and mice administered up to 1000 ppm in the diet was associated with Kupffer cell hypertrophy, cytoplasmic vacuolization, and mixed cell foci in the liver of rats but no significant pathologic findings in mice. There was no evidence of carcinogenic activity in either species.

TBBC was not mutagenic in *Salmonella typhimurium* strains with or without metabolic activation. In Chinese hamster ovary cells, TBBC induced an increase in sister chromatid exchanges but there were no increases in chromosomal aberrations.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 4,4′-thiobis(6-*tert*-butyl-*m*-cresol) is 10 mg/m^3.

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THIOGLYCOLIC ACID
CAS: 68-11-1

$C_2H_4O_2S$

Synonyms: Mercaptoacetic acid; thiovanic acid; thioglycollic acid

Physical Form. Colorless liquid

Uses. In the formulations of permanent wave solutions and depilatories; in pharmaceutical manufacture; as a stabilizer in vinyl plastics

Exposure. Inhalation; skin absorption

Toxicology. Thioglycolic acid is corrosive to the skin, eyes, and mucous membranes on contact.

In one reported case, thioglycolic acid accidentally splashed onto the eyes, face, legs, and arms caused second-degree burns of the skin.[1] Within 2 hours the corneas became clouded and the conjunctivae was edematous. Over the course of several months the cornea cleared and necrotic conjunctiva regenerated and vascularized, leaving slightly impaired vision.

In rats the oral LD_{50} is less than 50 mg/kg.[2] Applied to the skin of guinea pigs, 5 ml/kg of a 10% solution caused weakness, gasping, convulsions, and death.

Whole body exposure of rats for 4 hours to 0.172 or 0.338 mg/l resulted in some mortality; clinical signs of irritative respiratory toxicity during exposures included wetness about the eyes and mouth, abnormal respiration, restlessness, and hunched posture.[3] Abnormal respiration, brown-stained snout, sensitivity to touch, and reduced food and water consumption were noted during the 14-day observation period. Microscopic evaluation of decedent rats and rats surviving 2-week recovery found lung congestion among study lethalities only.[3]

Two drops of a 10% solution instilled in rabbit eyes caused immediate pain, and the epithelium turned gray within seconds; the conjunctivae were hyperemic with moderate discharge and corneas were opaque at 2 days.[2] Corneal clouding gradually, but not completely, cleared with in 6 weeks.

Thioglycolic acid was not mutagenic in a number of *Salmonella typhimurium* strains with or without metabolic activation.[4]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for thioglycolic acid is 1 ppm (3.8 mg/m^3) with a notation for skin absorption.

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THIONYL CHLORIDE

CAS: 7719-09-7

$SOCl_2$

Synonyms: Sulfurous oxychloride; thionyl dichloride

Physical Form. Colorless to pale yellow liquid with a suffocating odor

Uses and Sources. In the manufacture of lithium batteries; in the synthesis of herbicides, surfactants, drugs, vitamins, and dyestuffs

Exposure. Inhalation

Toxicology. Thionyl chloride may cause severe irritation of the skin, eyes, and mucous membranes as well as potentially serious lung injury.

Two cases of accidental thionyl chloride exposure resulting in lung injury that varied from relatively mild and reversible interstitial lung disease to a severe form of bronchiolitis obliterans have recently been reported.[1] In the first case a 30-year-old worker was exposed when a thionyl chloride tank burst in an open space. The worker was asymptomatic until dyspnea gradually developed 2 weeks after his exposure. The patient was mildly dyspneic with 22 respirations per minute, and lung function

tests showed moderate restrictive dysfunction. After treatment by salbutamol inhalations, oral aminophylline, and prednisone 60 mg, the patient's condition improved within 2 weeks, and prednisone dosage was tapered to 20 mg/day. This, however, was followed by a relapse that was treated successfully by doubling the prednisone dose and slowly tapering off over a total period of 6 months.

In the second case a 23-year-old worker suffered short-term exposure to thionyl chloride fumes in an enclosed space. Acute effects included second-degree chemical burns on the ankle, wrist, tongue, nasal septum, and corneas. The patient was not dyspneic, and chest radiographs were normal. Arterial blood gases showed mild, partially compensated metabolic acidosis with a lower partial pressure of oxygen, and lung function tests showed mild restrictive change. Hydrocortisone treatment (300 mg/day intravenously) was initiated to prevent or minimize the risk of lung injury. The dose was reduced to 50 mg/ day after 3 days, and on discharge a regimen of 10 mg/day of prednisone was prescribed. After a latent, clinically asymptomatic phase of over 2 weeks the patient was readmitted with acute respiratory failure. Chest radiographs showed bilateral hyperinflated lungs with verticalization of the heart. Lung function tests showed a severe mixed restrictive and obstructive pattern that was unresponsive to bronchodilators. A clinical diagnosis of bronchiolitis obliterans secondary to the inhalation of thionyl chloride fumes was made. Other complications included spontaneous pneumothorax and bronchopleural fistula. The patient ultimately survived but was left permanently disabled.

The clinicians noted that although the first patient responded well to steroid therapy, steroids may be less useful in more severe cases of bronchiolitis obliterans. Specifically, steroid treatment should be stopped if no improvement is seen during the first days because this treatment may increase the risk of lung infection in the presence of a denuded lung epithelium.

In an earlier report a worker exposed to an unknown concentration of thionyl chloride for approximately 6 minutes after a battery cell exploded succumbed to fulminant pulmonary edema 3 hours after the accident.[2]

The toxicity of thionyl chloride is attributed to the formation of sulfur dioxide and hydrogen chloride in contact with water. The reaction of one molecule of thionyl chloride with one molecule of water yields two molecules of hydrogen chloride and one of sulfur dioxide. Therefore, 1 ppm of thionyl chloride produces a total irritant gas concentration equivalent to 3 ppm.[3]

The LD_{50} for thionyl chloride, which was completely hydrolyzed to sulfur dioxide and hydrogen chloride gases when evaporated in air, was 500 ppm for a 1-hour exposure in rats; the acute toxicity of the hydrolyzed mixture was comparable to a theoretical calculation for additive effects of the mixture.[4]

The 2003 ACGIH threshold limit value-ceiling (TLV-C) for thionyl chloride is 1 ppm (4.9 mg/m^3).

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THIRAM
CAS: 137-26-8

$C_6H_{12}N_2S_4$

Synonyms: Tetramethylthiuram disulfide; TMTD; tetramethylthioperoxydicarbonic diamide; bis(dimethylthiocarbamyl)disulfide

Physical Form. White or yellow crystals

Uses. Agricultural fungicide; rubber accelerator

Exposure. Inhalation

Toxicology. Thiram is an irritant of the eyes, mucous membranes, and skin and causes sensitization dermatitis; adverse reproductive effects have been reported in experimental animals.

Thiram is the methyl analog of disulfiram or Antabuse, a drug used to establish a conditioned reflex of fear of alcohol in the treatment of alcoholism.[1] Ingestion of even a small amount of alcohol while undergoing Antabuse therapy is followed by distressing and occasionally dangerous symptoms including, flushing, palpitations, headache, nausea, vomiting, and dyspnea. The systemic "Antabuse-alcohol" syndrome is apparently rare in thiram-exposed workers, but it has been reported.[2] In one case, a man became ill and died 4 days after treating seed with thiram. Although he received substantial exposure over 10 hours, it is unclear whether he received enough thiram to produce death without associated alcohol ingestion.[2] A skin reaction, without other systemic effects, is said to occur in chronically exposed workers after ingestion of alcohol. The response of the skin is rapid and takes the form of flushing, erythema, pruritis and urticaria.[1] Thiram without alcohol can produce dermatitis but only in a few susceptible people. Sensitization dermatitis in the form of eczema has occurred on the hands, forearms, and feet.[1,3]

In mice and male rats, the oral LD_{50} was approximately 4 g/kg; symptoms of toxicity were ataxia and hyperactivity followed by inactivity, loss of muscular tone, labored breathing, clonic convulsions, and death within 2–7 days.[4]

Daily administration of 132 mg/kg body weight in the diet for 13 weeks decreased the fertility of CD rats; 14 days at 96 mg/kg altered the estrous cycle of females.[5] In female rats 50 mg/kg injected intraperitoneally on the day of proestrus delayed ovulation and resulted in a lower fertility rate, a reduction of live fetuses, an increase in resorptions, and a slower rate of fetal development.[6] Gavage doses in rats of 25 mg/kg/day for 90 days produced a significant increase in relative testes weight and mild pathomorphological changes indicative of testicular dysfunction.[7] A significant increase in the frequency of abnormal sperm was found in mice after a single subcutaneous dose of 1000 mg/kg or five repeated doses at 250 mg/kg body weight.[8]

Thiram was teratogenic at maternally toxic doses, causing primarily skeletal malformations in hamsters given a single oral dose of 250 mg/kg during the period of organogenesis and in mice given oral doses of 5–30 mg per animal daily between days 6 and 17 of pregnancy.[9,10]

A dietary level of 1000 ppm for 2 years produced weakness, ataxia, and varying degrees of paralysis of the hind legs of rats.[2]

In a chronic feeding study, rats were administered 3, 30, or 300 ppm in the diets for up to 2 years and dogs were given 0.4, 4, or 40 mg/day for up to 2 years.[11] Rats of the high-dose group had retarded growth and females had anemia, regressive changes of the sciatic nerve, and atrophy of the calf muscle. Dogs in the high-dose group had severe toxic signs, including vomiting, salivation, and clonic convulsions and did not survive the first year of treatment. Ophthalmological changes included fundal hemorrhage, miosis, and desquamation of the retina. At the mid-dose range dogs had liver failure and females also had kidney damage. There were no increased incidences of any tumors.

Thiram also was not carcinogenic in rats by gavage or in mice by single subcutaneous injection.[2,5] In skin painting studies in mice thiram had tumor-initiating and -promoting activity but was not a complete carcinogen.[12]

The IARC has noted, however, that thiram can react with nitrite under mildly acidic conditions, simulating those in the human stomach, to form *N*-nitrosodimethylamine, which is carcinogenic in a number of species.[5] Dietary administration of 500 ppm thiram plus 2000 ppm sodium nitrite for 2 years caused a high incidence of nasal cavity tumors in rats vs. no tumors in controls or in animals given only one compound.[13]

The IARC has determined that there is inadequate evidence in experimental animals

and in humans for the carcinogenicity of thiram.

Thiram was genotoxic to insects, plants, fungi, and bacteria: it induced sister chromatid exchange and unscheduled DNA synthesis in cultured human cells. Despite established genotoxicity *in vitro*, it showed no clastogenic and/or aneugenic activity in vivo after oral administration to mice at the maximum tolerated dose.[14]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for thiram is 1 mg/m^3.

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TIN (Inorganic Compounds)
CAS: 7440-31-5

Sn

Compounds: Stannic oxide; tin tetrachloride; stannic chloride; stannous chloride; stannous sulfate; sodium stannate; potassium stannate

Physical Form. Solid

Uses. Protective coatings and alloys; glass bottle manufacture

Exposure. Inhalation

Toxicology. Inorganic tin salts are irritants of the eyes and skin.

No systemic effects have been reported from industrial exposure. Some inorganic tin compounds can cause skin or eye irritation because of acid or alkaline reaction produced with water. Tin tetrachloride, stannous chloride, and stannous sulfate are strong acids; sodium and potassium stannate are strong

alkalies.[1] Glass bottle makers exposed to a hot mist of stannic chloride (0.10–0.18 mg/m^3) and hydrogen chloride (5 ppm) had an excess of symptoms of respiratory irritation over workers exposed predominantly to hydrogen chloride in the same plant.[2] Exposure to dust and fume of tin oxide results in stannosis, a rare benign pneumoconiosis.[3]

Ingested inorganic tin exhibits only moderate toxicity, probably because of poor absorption and rapid tissue turnover. However, consumption of food and fruit juices heavily contaminated with tin compounds in the range of 1400 ppm or more results in symptoms of gastrointestinal irritation, including nausea, abdominal cramps, vomiting, and diarrhea.[4]

In animals, high doses of soluble tin salts induce neurological disturbances.[4] Subcutaneous injection of animals with sodium stannous tartrate at a daily dose of 12.5 mg/kg was fatal. Death was preceded by vomiting, diarrhea, and paralysis with twitching of the limbs.[5] Daily administration to a dog of stannous chloride in milk at a level of 500 mg/kg produced paralysis after 14 months.[1]

Administration of 1 and 3 mg Sn/kg body weight to rats resulted in inhibition of various enzymes, including hepatic succinate dehydrogenase and the acid phosphatase of the femoral epiphysis. Tin also appears to interact with the absorption and metabolism of biological essential metals such as copper, zinc, and iron and to influence heme metabolism.[4]

Limited animal testing with stannous chloride has not revealed evidence of carcinogenic potential.[6] Mixed results have been observed in genotoxic assays.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for tin (metal, oxide, and inorganic compounds except SnH_4) is 2 mg/m^3.

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TIN (Organic Compounds)
CAS: 7440-31-5

Sn

Synonyms: Triethyltin iodide; dibutyltin chloride; tributyltin chloride; triphenyltin acetate; bis(tributyltin) oxide; triphenyltin chloride

Physical Form. Solids and liquids

Uses. Stabilizers in polymers; biocides, catalysts

Exposure. Inhalation; skin absorption

Toxicology. Organotin compounds cause irritation of the eyes, mucous membranes, and skin; some produce cerebral edema and others cause hepatic necrosis.

The most toxic of the organotin compounds are the trialkyltins, followed by the dialkyltins and monoalkyltins.[1] The tetraalkyltins are metabolized to their trialkyltin homologs; their effects are those of the trialkyltins, with severity of effects dependent on the rate of metabolic conversion. In each major organotin group, the ethyl derivative is the most toxic.[1]

Triethyltin: Oral administration of a French medication (Stalinon, containing diethyltin diiodide and isolinoleic esters) for treatment of

human furunculosis resulted in 217 cases of poisoning of which 102 were fatal.[1,2] The capsules were found to be contaminated with triethyltin and other organotin compounds. After a latent period of 4 days, effects were severe, persistent headache, vertigo, visual disturbances (including photophobia), abdominal pain, vomiting, and urinary retention. The more severe cases showed transient or permanent paralysis and psychic disturbances. Residual symptoms in those who recovered included persistent headache, diminished visual acuity, paresis, focal anesthesia, and, in four severe cases, flaccid paraplegia with incontinence. The most significant lesion found at autopsy was cerebral edema.

Tributyltin: Workers exposed to the vapor or fume of tributyltin compounds developed sore throat and cough several hours after exposure.[3] When a worker was splashed in the face with a tributyltin compound, lacrimation and severe conjunctivitis appeared within minutes, despite immediate lavage, and persisted for 4 days. At the end of 7 days, the eyes appeared normal.[3] Chemical burns may result after only brief contact with the skin. Pain is usually moderate, and itching is the chief symptom. Healing is usually complete within 7–10 days.[3]

Triphenyltin Acetate: Liver damage has occurred from occupational exposure to triphenyltin acetate.[1] In two cases, both developed hepatomegaly; one had slightly elevated SGPT and SGOT activity. Occupational exposure to a 20% solution produced skin irritation 2–3 days after prolonged contact with contaminated clothing. Other nonspecific effects of exposure have included headache, nausea, vomiting, diarrhea, and blurred vision.[1]

Trimethyltin: Induction of overt neurological and behavioral changes in rodents, including aggression, hyperexcitability, tremor, spontaneous seizures, and hyperreactivity, by trimethyltin compounds are well documented.[4]

Bis(Tributyltin) Oxide (TBTO): TBTO is an irritant of the eyes and respiratory tract.[1]

In chronic rodent studies, no evidence of carcinogenicity was found in studies with triphenyltin acetate, triphenyltin hydroxide, or dibutyltin acetate.[5] Tributyltin oxide was associated with an increased incidence of benign pituitary and pheochromocytomas in rats that was attributed a direct action on the endocrine glands rather than a carcinogenic effect.[5] Results from most genotoxicity assays for organic tin have been negative.

Developmental effects including decreased fetal weights and increased incidences of cleft palate have occurred in mice at doses of TBTO that also produce maternal toxicity.[5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for tin (organic compounds) is 0.1 mg/m^3, as Sn, with a short-term excursion limit (STEL) of 0.2 mg/m^3 and a notation for skin absorption.

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TITANIUM DIOXIDE
CAS: 13463-67-7

TiO_2

Synonyms: Unitane; rutile; anatase; octahedrite; brookite

Physical Form. White powder

Uses. Widely used in paints, paper, plastics, ceramics, rubber, and inks; in sunscreens and cosmetics

Exposure. Inhalation

Toxicology. Titanium dioxide is a mild pulmonary irritant and is generally regarded as a nuisance dust.

Three of 15 workers who had been exposed to titanium dioxide dust, three showed radiographic signs in the lungs resembling "slight fibrosis," but disabling injury did not occur. The magnitude and duration of exposure were not specified.[1,2] In the lungs of three workers involved in processing titanium dioxide pigments, deposits of the dust in the pulmonary interstitium were associated with cell destruction and slight fibrosis; the findings indicated that titanium dioxide is a mild pulmonary irritant.[3]

Cohort and case control analyses of 1576 workers found no statistically significant associations between titanium dioxide exposure and risk of lung cancer, chronic respiratory disease, and chest roentgenogram abnormalities.[4] No cases of pulmonary fibrosis were observed among titanium dioxide-exposed employees.

Rats exposed 6 hours/day for 5 days to 50 mg/m^3 and examined at various intervals after exposure showed no pulmonary response to titanium dioxide as determined by bronchoalveolar lavage fluid parameters or histopathology.[5] Repeated exposure of rats to concentrations of 10–328 mppcf of air for as long as 13 months caused small focal areas of emphysema, which were attributed to large deposits of dust. There was no evidence of any specific lesion being produced by titanium dioxide.[6]

In a 2-year inhalation bioassay exposure to 250 mg/m^3 titanium dioxide resulted in the development of squamous cell carcinomas in 13 of 74 female rats and in 1 of 77 male rats, as well as an increase in bronchioloalveolar adenomas. No excess tumor incidence was observed at 50 mg/m^3.[7] Given the extremely high concentration exposures, the unusual histology and location of the tumors, and the absence of metastases, the authors questioned the biological relevance of these tumors to humans.[7] There was no evidence that titanium dioxide-coated mica produced either toxicological or carcinogenic results when administered in the diet of F344 rats for 130 weeks at concentrations as high as 5%.[8]

Titanium dioxide was not mutagenic in bacterial assays, but it did increase the frequency of sister chromatid exchanges and micronuclei in Chinese hamster ovary cells.[8,9] In another report titanium dioxide was not genotoxic in a number of *in vitro* assays, but irradiation with UV/visible light caused significant photogenotoxicity in a single-cell gel assay and a chromosomal aberration assay.[10]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for titanium dioxide is 10 mg/m^3.

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TOLUENE
CAS: 108-88-3

$C_6H_5CH_3$

Synonyms: Toluol; methylbenzene; phenylmethane

Physical Form. Colorless liquid

Uses. Manufacturing of benzene and other chemicals; solvent for pains and coatings; component of gasoline

Exposure. Inhalation; skin absorption

Toxicology. Toluene causes central nervous system depression.

Exposure to extremely high concentrations of toluene (5000–30,000 ppm) may cause mental confusion, loss of coordination, and unconsciouness within a few minutes. Controlled exposure of human subjects to 200 ppm for 8 hours produced mild fatigue, weakness, confusion, lacrimation, and paresthesias of the skin. At 600 ppm for 8 hours other effects included euphoria, headache, dizziness, dilated pupils, and nausea. At 800 ppm for 8 hours, symptoms were more pronounced and aftereffects included nervousness, muscular fatigue, and insomnia persisting for several days.[1–4]

Subjects exposed to 100 ppm of toluene for 6 hours complained of eye and nose irritation and, in some cases, headache, dizziness, and a feeling of intoxication. However, no significant difference in performance on a variety of neurobehavioral tests were noted. No symptoms were noted at 10 or 40 ppm.[5]

Chronic organic brain dysfunction, associated with cerebral and cerebellar atrophy, has been described after long-term inhalational abuse of toluene among glue sniffers exposed to very high concentrations. Several studies of workers repeatedly exposed to toluene or mixtures of toluene and other solvents have suggested minor abnormalities on neuropsychological testing or differences in performance on such testing compared with unexposed controls, hearing loss, changes in visual-evoked brain stem potentials and color vision impairment.[6] In contrast, a study of 43 rotogravure printers exposed to estimated mean levels of 117 ppm for a mean of 22 years failed to demonstrate significant clinical neuroradiological, neurophysiological, or neuropsychological differences when compared with a control group of 31 unexposed printers.[7]

Severe but reversible liver and kidney injury occurred in a person who was a glue sniffer for 3 years. The chief component of the inhaled solvent was toluene (80% vol/vol); other ingredients were not listed.[3] In workers exposed for many years to concentrations in the range of 80–300 ppm, there was no clinical or laboratory evidence of altered liver function.[3]

Toluene exposure does not result in the hematopoietic effects caused by benzene. The myelotoxic effects previously attributed to toluene are judged by more recent investigations to be the result of concurrent exposure to benzene present as a contaminant in toluene solutions.[3] Most of the toluene absorbed from inhalation is metabolized to benzoic acid, conjugated with glycine in the liver to form hippuric acid, and excreted in the urine. The average amount of hippuric acid excreted in the urine by persons not exposed to toluene is approximately 0.7–1.0 g/l of urine.[3]

There are a number of reports that women exposed to toluene have an increased risk of spontaneous abortions; however, a causal relationship is difficult to establish because of confounding exposures, lack of exposure data, and small sample sizes.[6]

Chronic maternal inhalation abuse of toluene during pregnancy has been associated with teratogenic effects in a number of case reports. Manifestations include microcephaly,

central nervous system dysfunction, attentional deficits, developmental delay with language impairment, and growth retardation.[8] Phenotypic abnormalities may include a small midface, short palpebral fissures with deep-set eyes, low-set ears, flat nasal bridge with a small nose, micrognathia, and blunt fingertips. Interpretation of these human results may be confounded by the contribution of multiple chemical exposures.[9] Furthermore, it has been noted that only excessively high doses, possibly on the order of 30,000 ppm, that produce maternal toxicity have been associated with developmental effects.

Results from a number of animal studies indicate that exposure to levels of toluene that begin to produce maternal toxicity can cause fetal effects, including reduced fetal survival and retardation of growth and skeletal development toxicity.[6] Rat studies also suggest that exposure in utero can impair behavioral development.[6] Exposure to 2000 ppm 6 hours/day, for 80 days before mating and through lactation, produced no significant maternal toxicity but caused retardation of both fetal and postnatal development in rats.[9]

A chronic inhalation study found no evidence of carcinogenic activity in rats exposed at concentrations of 600 ppm or 1200 ppm for 2 years, or in mice exposed at 120, 600, or 1200 ppm for the same duration.[10] Epidemiological findings of various cancer (stomach, lung, and colorectal) increases with toluene exposure are not strong enough to conclude an association because of multiple exposure circumstances and weak consistency of findings.[11]

The IARC has determined that there is evidence for the lack of carcinogenicity of toluene in experimental animals and that there is inadequate evidence for carcinogenicity in humans.[11] Results of in vitro assays generally indicate that toluene is not genotoxic.[6] Reports of increased incidences of sister chromatid exchanges and chromatid breaks in exposed workers are confounded by concurrent exposure to other organic chemicals.[6]

The liquid splashed in the eyes of two workers caused transient corneal damage and conjunctival irritation; complete recovery occurred within 48 hours.[3] Repeated or prolonged skin contact with liquid toluene has a defatting action, causing drying, fissuring, and dermatitis.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for toluene is 50 ppm (188 mg/m^3) with a notation for skin absorption.

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TOLUENE-2,4-DIISOCYANATE
CAS: 584-84-9

$CH_3C_6H_3(NCO)_2$

Synonyms: TDI; toluene diisocyanate

Physical Form. Colorless liquid; aerosol

Uses. Production of polyurethane foams and plastics; used in polyurethane paints and wire coatings; the most commonly used material is a mixture of 80% 2,4 isomer and 20% 2,6 isomers

Exposure. Inhalation

Toxicology. Toluene-2,4-diisocyanate (TDI) is a strong irritant of the eyes, mucous membranes, and skin and is a potent sensitizer of the respiratory tract.

Exposure of humans to sufficient concentrations causes irritation of the eyes, nose, and throat; a choking sensation; and a productive cough of paroxysmal type, often with retrosternal soreness and chest pain.[1,2] If the breathing zone concentration reaches 0.5 ppm, the possibility of respiratory response is imminent.[3] Depending on length of exposure and level of concentration above 0.5 ppm, respiratory symptoms will develop with a latent period of 4–8 hours.[3] Higher concentrations produce a sensation of oppression or constriction of the chest. There may be bronchitis and severe bronchospasm; pulmonary edema may also occur. Nausea, vomiting, and abdominal pain may complicate the presenting symptoms. On removal from exposure, the symptoms may persist for 3–7 days.

Although the acute effects of TDI may be severe, their importance is overshadowed by respiratory sensitization in susceptible persons; this has occurred after repeated exposure to levels of 0.02 ppm TDI and below.[2] The onset of symptoms of sensitization may be insidious, becoming progressively more pronounced with continued exposure over a period of days to months. Initial symptoms are often nocturnal dyspnea and/or nocturnal cough with progression to asthmatic bronchitis.[1] Immediate, late, and dual patterns of bronchospastic response to laboratory exposure to TDI in sensitized individuals have been observed, confirming the clinical findings of nocturnal symptoms in some exposed workers. The time from initial employment to the development of symptoms suggestive of asthma has been reported to vary from 6 months to 20 years.[4,5]

In another pattern of sensitization response, a worker who has had only minimal upper respiratory symptoms or no apparent effects from several weeks of low-level exposure may suddenly develop an acute asthmatic reaction to the same or a slightly higher level. The asthmatic reaction may be severe, sometimes resulting in status asthmaticus, which may be fatal if exposure continues.[1]

Susceptibility to TDI-induced asthma does not require a prior history of atopy or allergic conditions, and sensitization may not be any more common in atopics.[6] Given sufficient exposure, it appears that virtually any person may become sensitized. The proportion of individuals with TDI asthma in working populations has varied from 4.3% to 25%.[7] There is some evidence that this percentage decreases with decreasing air concentrations. Exposure to spills of TDI appear to increase the risks of sensitization. The pathophysiology of TDI-induced asthma is unknown; both immunologic and nonimmunologic pharmacologic mechanisms have been postulated. Amines may play a causative role in TDI-induced asthma.[8] It is clear, however, that TDI-induced asthma is not solely mediated by a type I hypersensitivity response associated with IgE antibody.[6]

Several studies have provided evidence of cross-shift and progressive annual declines in FEV_1 and FEF 25% to 75% among asymptomatic workers, without evidence of TDI asthma, exposed to low levels of TDI (below

0.02 ppm and as low as 0.003 ppm). The annual declines were two- to threefold greater than expected, appeared to be dose related, and correlated with observed cross-shift declines. Workers, in general, exhibited no acute or chronic symptoms related to these exposures or pulmonary function decrements.[9,10]

The diagnosis of TDI-induced asthma relies primarily on the clinical history in a worker with known exposure, recognizing that symptoms (wheezing, dyspnea, cough) may develop at night long after the end of the shift. Serial measurement of peak flow rates by the worker may aid in making the diagnosis.[11] Nonspecific bronchial hyperreactivity to histamine or methacholine is frequently, but not invariably, present in patients with TDI-induced asthma. Its absence may reflect that the asthma is quiescent owing to no recent exposure and re-exposure may lead to hyperreactivity. Failure to demonstrate nonspecific hyperreactivity on a single test does not exclude the diagnosis of TDI-induced asthma.[12] RAST testing for IgE antibodies against *p*-tolyl monoisocyanate antigens is probably not useful because of the occurrence of false-positive (in exposed but asymptomatic workers) and false-negative results.[13] Specific bronchoprovocation challenge with TDI is a definitive way to make the diagnosis but is often not practical because of the need for prolonged observation for late reactions and the risk of severe reactions.

After removal from exposure, some patients have had resolution of symptoms. The early detection of TDI-induced occupational asthma and the prompt removal of sensitized workers from exposure may increase the chances of remission.[14] However, there is evidence from several studies that individuals with TDI-induced asthma may continue to have symptoms of dyspnea and wheezing and bronchial hyperreactivity for 2 or more years after cessation of exposure.[15–17] In one study, patients with TDI-induced asthma who continued to have exposure to TDI for 2 more years had, as a rule, marked abnormal decreases in spirometric parameters and increases in nonspecific hyperreactivity.[15] In another study, 6 of 12 workers with a convincing history of TDI-induced asthma had positive responses to specific bronchial provocation testing with low concentrations of TDI (up to 0.02 ppm) at a mean of 4.5 years after cessation of exposure. These persons had persistent respiratory symptoms requiring daily treatment for asthma and persistent airway hyperreactivity.[16] Once sensitized, it is clear that patients can react to concentrations of 0.005 ppm or less.[7]

Bronchial biopsies of subjects with occupational asthma induced by TDI revealed pathologic features such as increased number of inflammatory cells in the airway mucosa and thickening of subepithelial collagen.[18]

Splashes of TDI liquid in the eye cause severe conjunctival irritation and lacrimation. On the skin, the liquid produces a marked inflammatory reaction. Sensitization of the skin occurs but is uncommon because of proper work practices. There seems to be little relation between skin sensitivity and respiratory sensitivity to TDI.[1]

Commercial-grade TDI consisting of 80% 2,4-TDI and 20% 2,6-TDI was administered by gavage to female rats and mice at doses of 60 or 120 mg/kg, whereas male rats received 30 or 60 mg/kg and male mice received 120 or 240 mg/kg.[19] The major nonneoplastic lesions observed in rats were dose-related increases in acute bronchopneumonia, and in mice there was cytomegaly of the renal tubular epithelium in males. Despite early mortality in all groups, TDI was carcinogenic to both species, causing pancreatic acinar cell adenomas in male rats, pancreatic islet cell adenomas, neoplastic nodules of the liver, and mammary gland tumors in female rats and subcutaneous fibromas and fibrosarcomas in both sexes. In female mice there was an increase in hemangiomas and hepatocellular adenomas. The pattern of multiple tumor sites was similar to that found with 2,4-diaminotoluene. Metabolic studies have shown that common metabolites are produced from the 2,4-TDI isomer and from 2,4-diaminotoluene, suggesting that the 2,4-isomer in the commercial-grade TDI was responsible for the carcinogenic activity. No strong association or consistent pattern of carcinogenicity has emerged in limited human epidemiological studies involving isocyanate exposure.[20]

The IARC has determined that there is inadequate evidence for the carcinogenicity of toluene diisocyanates in humans and sufficient evidence in experimental animals.[20]

In genotoxic assays, TDI has produced chromosomal aberrations, base pair substitution, frameshift mutations, and DNA stand breaks of human white blood cells *in vitro*.[21] It induced gene mutation and sister chromatid exchanges but not DNA damage or chromosomal aberrations in cultured rodent cells.[20] It did not induce micronuclei in mammalian erythrocytes *in vivo*.

Biological monitoring of TDI exposure levels has been accomplished with postshift analysis of urinary toluene.[22]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for toluene-2,4-diisocyanate is 0.005 ppm (0.036 mg/m^3) with a short-term excursion limit (STEL) of 0.02 ppm (0.14 mg/m^3).

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TOLUIDINE

o-Toluidine CAS: 95-53-4

m-Toluidine CAS: 108-44-1

p-Toluidine CAS: 106-49-0

$CH_3C_6H_4NH_2$

Synonyms: Aminotoluene; 1 methyl-2-aminobenzene; 2-methyl-aniline

Physical Form. Clear to light yellow liquid

Uses. Dye intermediate

Exposure. Inhalation; skin absorption

Toxicology. *ortho*-Toluidine causes anoxia due to the formation of methemoglobin and hematuria; *asis*-toluidine hydrochloride is carcinogenic in experimental animals. The *meta*- and *para*-isomers are assumed to produce comparable toxic effects; however, *meta*-toluidine seems to have no carcinogenic activity.

Signs and symptoms of overexposure are due to the loss of oxygen-carrying capacity of the blood. The earliest manifestations of poisoning in humans are headache and cyanosis of the lips, the mucous membranes, the fingernail beds, and the tongue.[1] Minor degrees of hypoxia may lead to a temporary sense of well-being and exhilaration. As the lack of oxygen increases, however, there is growing weakness, dizziness, and drowsiness, leading to stupor, unconsciousness, and even death if treatment is not prompt. Exposure to 10 ppm for more than a short time may lead to symptoms of illness, and 40 ppm for 60 minutes may cause severe toxic effects.[2] Transient microscopic hematuria has been observed in *o*-toluidine workers, presumably of renal origin, because no alterations in the bladder mucosa were observed by cystoscopy.[3]

In general, higher ambient temperatures increase susceptibility to cyanosis from exposure to methemoglobin-forming agents.[4]

Rats survived an 8-hour exposure to concentrated vapor.[5] Animals exposed to from 6 to 23 ppm for several hours developed mild methemoglobinemia.[6] In the eye of a rabbit, the liquid caused a severe burn.[5] Excessive drying of the skin may result from repeated or prolonged contact.[1] The *meta*- and *para*-isomers of toluidine show the same toxicity profile and dose range as *ortho*-toluidine; similar effects from exposure are expected, although these isomers have not been tested as extensively as *o*-toluidine.[7]

Ortho-toluidine hydrochloride was carcinogenic in mice fed diets containing 1000 or 3000 mg/kg for 2 years, producing hepatocellular carcinomas or adenomas in females and hemangiosarcomas at multiple sites in males.[8] In another strain of mice fed diets of 16,000 ppm for 3 months and then 8000 ppm for an additional 15 months or 32,000 ppm for 3 months followed by 16,000 ppm for 15 months, there were significant dose-dependent increases in the incidences of vascular tumors.[9] It was also carcinogenic in rats fed a 0.028 mol/kg diet for 72 weeks, producing tumors of multiple organs.[10] *p*-Toluidine was carcinogenic to mice after oral administration, producing liver tumors; *meta*-toluidine was not carcinogenic in any reports.[7]

A number of epidemiological studies have observed a high excess of bladder tumors among *o*-toluidine-exposed workers, but in all studies there was concomitant exposure to various other potential bladder carcinogens.[11] It has been noted, however, that the coexposures differed between studies, and in cases with data on duration of exposure, the highest risk was observed in the subgroup with the longest duration of exposure. In one report, 13

cases of bladder cancer were observed (vs. 3.61 expected) among 1749 chemical workers exposed to *o*-toluidine and aniline.[12] Increased risk of bladder cancer was strongly associated with duration of employment in the department where *o*-toluidine and aniline were used. The investigators suggested that because *o*-toluidine was a more potent animal bladder carcinogen than aniline, it was more likely to be the etiologic agent responsible for the bladder cancer excesses in this plant.

The IARC has determined that there is sufficient evidence for carcinogenicity of *o*-toluidine hydrochloride in animals and that it should be regarded as though it presents a carcinogenic risk to humans.[11,13]

In genotoxic assays *o*-toluidine induced sister chromatid exchanges and chromosomal aberrations *in vitro*, and *in vivo* it enhanced sister chromatid exchanges but gave equivocal results for micronuclei and sperm morphology.[11]

Skin absorption of toluidines is considered to be a potential hazard. Recent estimations of workplace exposures have included individual dermal badges and surface wipes in addition to airborne monitoring.[14]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for the toluidines is 2 ppm (8.8 mg/m^3) with a notation for skin absorption; the *ortho* and *para* isomers have an A2-suspected human carcinogen designation.

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TOXAPHENE
CAS: 8001-35-2

$C_{10}H_{10}Cl_8$ *(approximate)*

Synonyms: Chlorinated camphene; polychlorocamphene; octachlorocamphene

Physical Form. Yellow waxy solid

Use. Formerly used as an insecticide

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Toxaphene is a central nervous system stimulant; it is carcinogenic in experimental animals.

Toxaphene is a mixture of at least 670 chlorinated camphenes; differences in toxicity have been observed for various toxaphene fractions or components.[1]

Most fatal cases of poisoning have been due to accidental ingestion, resulting in convulsions and death due to respiratory arrest.[1–4] The lethal oral dose for humans is estimated to be 2–7 g.[2]

Symptoms of acute intoxication are salivation, hyperexcitability, behavioral changes, and in severe cases convulsions and death.[1] Convulsions may be preceded by nausea, vomiting, and muscle spasms or may begin without antecedent symptoms.[2] Onset of symptoms occurs within 4 hours, with death occurring from 4 to 24 hours after exposure. Nonfatal poisoning has been characterized by nausea, mental confusion, jerking of the arms and legs, and convulsions.[3,4]

One proposed mechanism for toxaphene-induced neurotoxicity is that it acts as a noncompetitive γ-aminobutyric acid (GABA) antagonist at the chloride channel in brain synaptosomes. Substances that bind to the GABA-regulated chloride channel induce convulsions by inhibiting chloride flux thus allowing brain cells to depolarize and fire spontaneously.[1,5]

Few cases of intoxication due to occupational exposure have been reported, and, of these, two cases of pneumonitis in insecticide sprayers are of dubious validity.[6] In one acute study, 25 volunteers were exposed to 500 mg/m^3 for 30 minutes for 10 days.[7] After a 3-week respite, the exposure was repeated for 3 days. Each subject was thought to have absorbed 1 mg/kg/day. Physical examination and blood and urine tests revealed no toxic manifestations.

In subchronic animal studies, rats fed diets containing 4, 20, 100, or 500 ppm of the compound showed no clinical signs of toxicity; dose-dependent histologic changes were observed in the kidney, thyroid, and liver.[8] For dogs administered 0.2, 2.0, and 5.0 mg/kg/day for 13 weeks by capsule, there were mild to moderate dose-dependent histologic changes in the liver and thyroid, but no clinical signs of toxicity were observed.[8]

Toxaphene is less toxic when applied to the skin as compared with oral administration.[1] Dermal LD_{50} values ranging from 7.8 to 45 g/kg have been obtained in laboratory animals. Applied to rabbit skin for 4 hours toxaphene was mildly irritating; a 0.5% solution was nonirritating to the forearms and faces of volunteers.

No fetal anatomic defects were observed in rats and mice at doses ranging from 0.05 to 75 mg/kg/day.[1] Adverse developmental effects, such as impaired righting reflexes, have been observed in rats at doses below those required to produce maternal toxicity.[9]

There was no evidence that toxaphene interfered with fertility or pup survival and growth when male and female rats were fed toxaphene in their diet at concentrations as high as 25 mg/kg/day and then mated.[10]

Toxaphene caused a dose-related increase of hepatocellular carcinomas in mice fed 98 or 198 ppm for 80 weeks. In rats, there was a significantly increased incidence of neoplastic thyroid lesions at the high dose.[11] The IARC has determined that there is sufficient evidence in experimental animals for the carcinogenicity of toxaphene and that it is possibly carcinogenic to humans.[12]

Toxaphene has been found to be genotoxic in a number of assays.[1] It was mutagenic in *Salmonella typhimurium*, and increased the frequency of sister chromatid exchanges in cell culture. In one study toxaphene-exposed individuals had a higher incidence of chromosomal aberrations in lymphocytes than controls. However, *in vivo* toxaphene did not bind to DNA or produce dominant lethal mutations.[12]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for toxaphene is 0.5 mg/m^3 with a short-term

excursion limit (STEL) of 1 mg/m^3 and a notation for skin absorption.

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TRIBUTYL PHOSPHATE
CAS: 126-73-8

$(C_4H_9)_3PO_4$

Synonyms: TBP; phosphoric acid tributyl ester

Physical Form. Colorless liquid

Uses. Antifoaming agent; plasticizer for cellulose esters, lacquers, plastic, and vinyl resins; component in hydraulic fluids for aircraft control systems

Exposure. Inhalation

Toxicology. Tributyl phosphate (TBP) is an irritant of the eyes, mucous membranes, and skin; it causes pulmonary edema in animals, and severe exposure is expected to cause the same effect in humans.

Workers exposed to unspecified concentrations of vapor complained of headache and nausea; hot vapor was severely irritating to the eyes and throat.[1] The liquid on the skin is said to be irritating.[2]

In rats, 123 ppm for 6 hours caused respiratory irritation.[2] The oral LD_{50} for rats was 3 g/kg; effects included weakness, dyspnea, pulmonary edema, and muscle twitching.[2]

In contrast to earlier reports, more recent studies suggest that TBP has negligible risk of causing organophosphorus compound-induced delayed neurotoxicity.[3] Two oral doses of 1500 mg/kg TBP separated by a 21-day interval did not produce delayed neurotoxicity in hens; neither neurological deficits nor histopathologic changes characteristic of organophosphorus compound-induced delayed neurotoxicity were observed. Although some electrophysiological and histopathologic changes have been reported in rat peripheral nerve after doses of 6000 mg/kg

over 2 weeks, the damage is not considered characteristic of delayed neuropathy.

Administered by gavage to rats 5 days/week for 18 weeks, doses of 0.20 g and above caused diffuse hyperplasia of the urinary bladder epithelium.[4] After chronic administration of TBP at levels of 200, 700, and 3000 ppm in the feed of rats for 2 years there was a dose-related increase in the severity of urinary bladder hyperplasia and the incidence of urinary bladder papillomas in the two highest groups; transitional cell carcinomas were present in 6 of 49 males in the 3000 ppm group.[5] In a parallel study in mice receiving 150, 1000, and 3500 ppm in feed, increased relative and absolute liver weights were observed in the mid- and high-dose groups; hepatocellular adenomas were increased in the high-dose males.[6] TBP was not genotoxic in a variety of *in vivo* and *in vitro* assays.[7] It has been suggested that the carcinogenic effects of TBP are species- and organ specific. The necrotic actions of TBP (or a metabolite) on rat urinary bladder epithelium may induce chronic repair processes that cause the normal epithelium to be transformed into its metaplastic and neoplastic forms.[8]

TBP was not teratogenic when administered to rats and rabbits during gestation; fetotoxic effects (delayed ossification and reduced fetal body weights) occurred in rats at doses that caused severe maternal toxicity.[9] There was no evidence of reproductive toxicity or reproductive organ pathology in two-generation studies in rats fed TBP in the diet.[10]

The liquid has a mildly irritating effect on the rabbit eye and skin.[8]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 0.2 ppm (2.2 mg/m^3).

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TRICHLOROACETIC ACID

CAS: 76-03-9

CCl_3COOH

Synonyms: TCA; trichloroethanoic acid

Physical Form. Crystals

Uses. As a reagent for albumin detection; in making herbicides. It is found as a by-product after chlorination of water containing humic materials.

Exposure. Ingestion; skin contact

Toxicology. Trichloroacetic acid (TCA) is corrosive to the skin and eyes.

There is little information available concerning the general toxicity of TCA. It is a relatively strong acid; the medical reports of acute exposure show mild to moderate skin and eye burns.

In animal studies, 500 mg/kg was fatal to mice by intraperitoneal administration and the reported oral LD_{50} values were 3.3 g/kg for rats and 5.0 g/kg for mice.[1]

Current concern regarding TCA arises from chronic low-level exposure via chlorinated drinking water. In 90-day subchronic studies, 5000 ppm in the drinking water caused increased liver- and kidney-to-body weight ratios in rats.[2] Increased hepatic peroxisome activity and histopathologic changes in the liver and kidneys were also observed.

Administered in the drinking water of mice for 61 weeks 2 or 5 g/l TCA caused hepatocellular carcinomas and adenomas. After a single intraperitoneal injection of ethylnitrosourea, TCA (2 or 5 g/l in the drinking water for 61 weeks) increased the tumor incidence from 5% to 48%.[3] TCA was not carcinogenic in rats.[4]

Repeated administrations of TCA induced cell proliferation in the livers of mice but reduced cell proliferation in the livers of rats.[5] It causes hepatic peroxisome proliferation in both rats and mice but not humans.[5]

TCA was not mutagenic in bacterial assays.[5] Neutralized TCA was not clastogenic in human lymphocytes in vitro or in the mouse bone marrow micronucleus test.[6]

Developmental studies have evaluated the effects of TCA in the rat; animals were dosed by oral intubation on gestation days 6–15 with 330, 800, 1200, or 1800 mg/kg/day.[7] There were no maternal deaths associated with toxicity, but weight gain during treatment was reduced at levels of 800 mg/kg and above. Maternal spleen and kidney weights also increased in a dose-dependent manner. The mean percentage of resorbed implants per litter was 34%, 62%, and 90% at 800, 1200, and 1800 mg/kg, respectively. Live fetuses showed dose-dependent reductions in weight and length. The mean frequency of soft tissue malformations (primarily in the cardiovascular system) ranged from 9% at the low dose to 97% at the high dose. Skeletal malformations were found only at the two highest doses and were principally in the orbit. The authors considered TCA to be developmentally toxic in the rat at doses of 330 mg/kg and above, which also caused slight maternal toxicity.

The IARC has determined that there is limited evidence for the carcinogenicity of TCA in experimental animals and that it is not classifiable as to its carcinogenicity to humans.[5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for trichloroacetic acid is 1 ppm (6.7 mg/m^3).

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1,2,4-TRICHLOROBENZENE
CAS: 120-82-1

$C_6H_3Cl_3$

Synonyms: Unsymmetrical trichlorobenzene

Physical Form. Colorless liquid

Uses. As a dye carrier, an herbicide intermediate, a heat transfer medium, a dielectric fluid in transformers and a lubricant

Exposure. Inhalation; skin absorption

Toxicology. 1,2,4-Trichlorobenzene may cause eye and throat irritation; at high concentrations it may produce hepatic toxicity.

In certain individuals eye and throat irritation may occur at 3–5 ppm.[1]

The single oral LD_{50} value was 756 mg/kg in rats and 766 mg/kg in mice.[2] The dermal LD_{50} was 11 g/kg in rats.[2] Repeated exposures at 70 and 200 ppm 6 hours/day for 15 days caused lethargy and reduced body weight gain in animals.[3] Male rats, rabbits, and monkeys were exposed at 0, 25, 50, or 100 ppm 7 hours/day, 5 days/week for 26 weeks.[4] No differences were seen in body weight measurements, hematology, serum biochemistry, pulmonary function, or eye examination between any of the animals and their controls. Microscopic changes were observed in the rat liver and kidney parenchyma after 4 or 13 weeks of exposure but not after 26 weeks.

Topical application to rabbit ears three times/week for 13 weeks caused some local dermal irritation due to defatting action.[5]

Embryonic effects were only observed at treatment levels associated with severe maternal toxicity.[6] Administered to rats on days 9–13 of gestation 360 mg/kg/day caused retarded embryonic development in the form of reduced head length, crown-rump length, somite number, and protein content; maternal deaths (2/9 rats) and significantly decreased body weight gain were also seen.

In a multigeneration study in rats, 400 ppm in the drinking water caused a significant increase in adrenal gland weights of the F_0 and F_1 generations.[7]

The 2003 ACGIH ceiling threshold limit value (C-TLV) for 1,2,4-trichlorobenzene is 5 ppm (37 mg/m^3).

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1,1,1-TRICHLOROETHANE
CAS: 71-55-06

CH_3CCl_3

Synonyms: Methylchloroform; methyltrichloromethane; trichloromethylmethane; α-trichloroethane

Physical Form. Colorless liquid

Uses. Solvent to clean metals, plastic molds, motors, electronic gear, and semiconductors;

extraction solvent; aerosol propellant; dry cleaning solvent

Exposure. Inhalation; skin absorption

Toxicology. 1,1,1-Trichloroethane causes central nervous system depression.

Human deaths after inhalation exposure have been attributed to respiratory failure secondary to central nervous system depression and to cardiac arrhythmias.[1,2] Lethal arrhythmias may result from sensitization of the heart to epinephrine.

Based on effects caused in monkeys and rats, the following are expected in humans: 20,000 ppm for 60 minutes, coma and possibly death; 10,000 ppm for 30 minutes, marked incoordination; 2000 ppm for 5 minutes, disturbance of equilibrium.[3] Human subjects exposed to 900–1000 ppm for 20 minutes experienced light-headedness, incoordination, and impaired equilibrium; transient eye irritation has also been reported at similar concentrations.[1] Impairments in psychomotor task performance such as reaction time, perceptual speed, and manual dexterity have been demonstrated at levels around 350 ppm.[4,5] Other studies at similar exposure levels have failed to show any impairment, but the type of task chosen to test behavioral effects and the times at which behavioral measures were sampled during the course of exposure may explain the variations from study to study.[4]

Some case reports have associated chronic long-term exposure with peripheral sensory neuropathy and toxic encephalitis.[6,7] In one instance, a woman with daily exposure to 1,1,1-trichloroethane and considerable potential of dermal exposure developed perioral tingling accompanied by discomfort in her hands and feet; the oral and hand symptoms disappeared after removal from exposure.[6] In another report, a group of 28 workers with long-term repetitive high exposures to 1,1,1-trichloroethane had significant deficits in memory, intermediate memory, rhythm, and speed as determined by a neuropsychological battery of tests.[7] Evidence of long-term central nervous system damage has also been suggested from animal studies. Gerbils exposed at 210 and 1000 ppm for 3 months had increased glial fibrillary acid protein, which is considered to be a marker for astrogliosis and is associated with brain injury.[8]

An epidemiological study of 151 matched pairs of exposed textile workers revealed no evidence of cardiovascular, hepatic, renal, or other effects as a function of exposure; for some workers, exposures exceeded 200 ppm, and duration of exposure ranged from several months to 6 years.[9]

A few scattered reports have indicated mild kidney and liver injury in humans from severe exposure; animal experiments have confirmed the potential for liver, but not kidney, injury.[1,10]

The liquid is mildly irritating when applied to the skin or instilled directly into the eyes.[2]

In a carcinogenicity study, rats and mice were given the liquid orally at two different dose levels, 5 days a week for 78 weeks.[11] Both female and male test animals exhibited early mortality compared with untreated controls, and a variety of neoplasms were found in both treated animals and controls. Although rats of both sexes demonstrated a positive dose-related trend, no relationship was established between the dosage groups and the species, sex, type of neoplasm, or sites of occurrence. The IARC concluded that an evaluation of the carcinogenicity of 1,1,1-trichloroethane could not be made.[12] In a subsequent study, rats exposed at 1500 ppm 6 hours/day, 5 days/week for 2 years showed no oncogenic effects.[13]

Inhalation exposure of female rats before mating and during pregnancy at 2100 ppm caused an increased incidence of skeletal and soft tissue variation in the offspring, indicative of developmental delay; no persistent detrimental effects were found in the offspring at 12 months of age.[14]

The genotoxic data are largely negative, although 1,1,1-trichloroethane was mutagenic in some *Salmonella* assays and induced chromosomal aberrations in Chinese hamster ovary cells and cell transformation in mammalian systems.[2]

The odor threshold has been described by various investigators as ranging from 16 to 400 ppm.[1]

The 2003 ACGIH threshold limit value-time weighted average (TLV-TWA) is 350 ppm (1910 mg/m^3) with a short-term excursion level (STEL) of 450 ppm (2460 mg/m^3).

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1,1,2-TRICHLOROETHANE

CAS: 79-00-5

$C_2H_3Cl_3$

Synonyms: Vinyl trichloride; ethane trichloride; β-trichloroethane; TCE

Physical Form. Colorless liquid

Uses. Intermediate in the production of vinylidene chloride; solvent

Exposure. Inhalation; skin absorption

Toxicology. In animals, 1,1,2-trichloroethane is a central nervous system depressant and causes liver and kidney damage; it is expected that severe exposure will produce the same effects in humans.

No cases of human intoxication or systemic effects from industrial exposure have been reported.[1]

The lethal concentration for rats was 2000 ppm for 4 hours, with the deaths occurring during a 14-day observation period.[2] An 8-hour exposure to 500 ppm was also lethal to about half of the exposed rats.[3] Rats exposed to 250 ppm for 4 hours survived but showed liver and kidney necrosis.[4] Repeated exposure to

30 ppm resulted in minor liver changes in female rats.

Application of 0.5 ml to the skin of guinea pigs was lethal to all animals within 3 days, whereas 0.25 ml was fatal to 5 of 20 animals.[5] No effects were observed with repeated application of 0.1 ml to the forearm of a volunteer. However, the liquid caused stinging, burning, and whitening of the skin when placed under occlusion for 5 min.[6] The liquid is considered a slight eye irritant when instilled in rabbit eyes.

Mice treated by intraperitoneal injection with anesthetic doses showed moderate hepatic and renal dysfunction. At autopsy, findings were centrilobular necrosis of the liver and tubular necrosis of the kidneys; the 24-hour LD_{50} for intraperitoneal injection was 0.35 mg/kg.[7] The LC_{50} values for 1,1,2-trichloroethane administered by a single gavage dose to male and female mice were 378 and 491 mg/kg, respectively.[8] Above 450 mg/kg, animals became sedated within an hour, and deaths from central nervous system depression occurred within 24 hours. Necropsies showed irritation of the upper gastrointestinal tract, pale liver, and some lung damage. Dose-dependent alterations in hepatic microsomal enzyme activities and serum enzyme levels were found in mice given 1,1,2-trichloroethane in their drinking water for 90 days.[8]

Administered orally to pregnant mice, 1,1,2-trichloroethane caused no reduction in neonate survival or in neonatal weight at doses that were maternally toxic.[9]

A significant increase in hepatocellular carcinomas occurred in mice given 195 or 390 mg/kg/day by gavage for 78 weeks.[10] Adrenal pheochromocytomas were also increased for the high-dose female mice. No neoplasms were observed at statistically significant incidences in rats given up to 92 mg/kg/day.

The IARC has determined that there is limited evidence that 1,1,2-trichloroethane is carcinogenic in experimental animals and that 1,1,2-trichloroethane is not classifiable as to its carcinogenicity to humans.[11]

1,1,2-Trichloroethane bound to DNA, RNA, and protein in vivo and induced DNA damage and micronuclei in human lymphocytes in vitro. It showed some evidence of mutagenicity in bacteria.[11]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 1,1,2-trichloroethane is 10 ppm (55 mg/m^3) with a notation for skin absorption.

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TRICHLOROETHYLENE

CAS: 79-01-6

C_2HCl_3

Synonyms: TCE; 1,1,2-Trichloroethylene; trichloroethene, 1,1-dichloro-2-chloroethylene; acetylene trichloride; ethylene trichloride

Physical Form. Colorless liquid

Uses. Degreasing solvent; dry cleaning and extraction; chemical intermediate; limited use as an anesthetic and analgesic

Exposure. Inhalation

Toxicology. Trichloroethylene (TCE) is primarily a central nervous system (CNS) depressant. Although it is carcinogenic at high doses in experimental animals, it is not considered to be a human carcinogen at low exposure levels.

Inhalation of concentrations in the range of 5000–20,000 ppm have been used to produce light anesthesia.[1] Recovery from unconsciousness is usually uneventful, but ventricular arrhythmias and death from cardiac arrest have occurred rarely. Exposure of volunteers to 500–1000 ppm has resulted in some symptoms of CNS disturbance such as dizziness, lightheadedness, lethargy, and impairment in visual-motor response tests. In general, no significant signs of toxicity or impaired performance have been noted in subjects acutely exposed to 300 ppm or less.

Prenarcotic symptoms, including visual disturbances and feelings of inebriation, occurred in workers exposed to mean levels of 200–300 ppm. Some evidence of mild liver dysfunction has occurred in workers exposed to levels sufficient to produce marked CNS effects. Prolonged exposure at toxic levels may also result in hearing defects.

Workers exposed to average levels of TCE estimated to be 100–200 ppm have reported increased incidence of fatigue, vertigo, dizziness, headaches, memory loss, and impaired ability to concentrate. Other effects noted at about 100 ppm and above include paresthesia, muscular pains, and gastrointestinal disturbances.

Intolerance to alcohol, presenting as a transient redness affecting mainly the face and neck (trichloroethylene flush) has frequently been observed after repeated exposure to TCE and alcohol ingestion. It has been suggested that ingestion of alcohol may potentiate the effect of TCE intoxication.[2]

TCE is mildly irritating to the skin; repeated contact may cause chapping and erythema due to defatting.[1] Direct eye contact produces injury to the corneal epithelium; recovery usually occurs within a few days.[1]

Breath analysis for TCE has provided a more accurate index of exposure than the measurement of metabolites (trichloroethanol and trichloroacetic acid) in the urine.[3]

Technical-grade TCE (later shown to be contaminated with other chemicals) has been found to cause liver cancer in B6C3F$_1$ mice but not in Osborne-Mendel rats in an NCI study.[4] Intragastric administration of 2.4 g/kg, five times per week for 78 weeks resulted in hepatocellular carcinomas in 31 of 48 male mice. At 1.2 g/kg, 26 of 50 males were affected, whereas male controls had a 5% liver cancer rate. Among female mice, 11 of 47 developed liver hepatocellular carcinomas, whereas only 1 of 80 control animals did.[4] In a second gavage bioassay using epichlorohydrin-free reagent-grade TCE, results paralleled the NCI study; significantly elevated incidences of hepatocellular adenomas and carcinomas occurred in mice administered 1.0 g/kg for 2 years.[5] An increase in renal adenocarcinomas was also found in male rats.[5]

Mice, rats, and hamsters inhaling up to 500 ppm 6 hours/day 5 days/week for 18 months showed no increase in tumor formation except for an increased incidence of malignant lymphomas in female MRI mice.[6] This strain normally has a high spontaneous incidence of

lymphomas, and the significance of TCE exposure is unclear. ICR mice exposed at 150 and 450 ppm for 107 weeks developed a 16% and 15% incidence of adenocarcinomas of the lungs vs. 2% for controls.[7] Rats did not show a higher incidence at any site.

Although a number of epidemiological studies have been reported, limitations have included short latency period, young age of cohort, no direct data on exposure levels, exposure to other chemicals, and possible inclusion of unexposed workers. However, in 1995 the IARC considered three cohort studies particularly relevant for the evaluation of TCE carcinogenicity.[8] Overall, the most important observations were the elevated risk for cancer of the liver and biliary tract (23 observed cases vs. 12.87 expected) and the modestly elevated risk for non-Hodgkin lymphoma (27 observed vs. 18.9 expected) in all three of the most informative cohort studies. A more recent analysis of the epidemiological studies suggests a stronger association of TCE exposure with kidney and liver cancers and some support for Hodgkin disease and non-Hodgkin lymphoma.[9] There is also a possible association of cervical cancer.

The IARC has stated that there is sufficient evidence in experimental animals and limited evidence in humans for the carcinogenicity of TCE and that it is possibly carcinogenic to humans.[8]

TCE carcinogenesis may require exposure to high doses sufficient to cause cellular necrosis.[10] Repeated cycles of necrosis and regeneration would occur with the emergence of hyperplasia and then neoplasia. Low exposures commonly encountered in human studies are not sufficient to initiate the carcinogenic process.

Results from genotoxic studies suggest that TCE is a very weak indirect mutagen.[11]

No evidence of teratogenic effects have been seen in rodent assays.[1] At 1800 ppm, 6 hours/day on days 0–20 of gestation, there were some fetotoxic effects, including incomplete ossification of the sternum in rats.[12] Rats administered 600 ppm by inhalation on days 6–20 of gestation showed maternal toxicity as evidenced by significant decreased body weight gain, but there were no indications of developmental toxicity.[13] In humans, there is no evidence of an increased incidence of adverse effects in the offspring of female TCE-exposed workers. An increased incidence of menstrual disorders in women workers and decreased libido in males has been reported in workers exposed to levels sufficient to produce marked CNS disturbances.[1] Chronic TCE exposure was significantly and negatively correlated with testosterone levels in male electronics factory workers.[14]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for trichloroethylene is 50 ppm (269 mg/m^3) with a short-term excursion level (STEL) of 100 ppm (537 mg/m^3).

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TRICHLOROFLUOROMETHANE

CAS: 75-69-4

$FCCl_3$

Synonyms: Freon 11; fluorotrichloromethane; fluorocarbon 11

Physical Form. Colorless liquid

Uses. Aerosol propellant; refrigerant and blowing agent; solvent for cleaning and degreasing

Exposure. Inhalation

Toxicology. Trichlorofluoromethane is toxic by several mechanisms: It can sensitize the myocardium to catecholamines, resulting in ventricular arrhythmias; it can have an anesthetic effect on the central nervous system (CNS), resulting in narcosis; and because it is heavier than air, it may displace oxygen, resulting in asphyxiation.

Exposure of volunteers to 250, 500, or 1000 ppm for up to 8 hours did not produce adverse effects.[1] Chronic exposure 6 hours/day for 20 days to 1000 ppm caused a slight but insignificant decrement in cognitive tests; there were no changes in pulmonary function or cardiac rhythm.[1] Workmen near a large area of spilled trichlorofluoromethane experienced narcotic effects, including loss of consciousness; prolonged tachycardia was also observed in one of those exposed.[2] Accidental ingestion caused necrosis and multiple perforations of the stomach.[2]

Sudden deaths from "sniffing" aerosols have been associated with a number of chlorofluorocarbons. The deaths are thought to be due to ventricular fibrillation following cardiac sensitization.[3]

Individuals may become sensitized to certain chlorofluorocarbons applied repeatedly to the skin surface.[2]

Exposure of rats to 500,000 ppm for 1 minute, 150,000 ppm for 8 minutes, or 100,000 ppm for 30 minutes was always fatal.[4] At 66,000 ppm, one of four rats died within 2 hours, but all survived 4 hours at 36,000 ppm.[2] Symptoms at the higher dose levels included rapid or labored breathing, twitching, unresponsiveness, or unconsciousness.

No symptoms were observed in rats, guinea pigs, monkeys, or dogs continuously exposed to 1000 ppm for 90 days or exposed to 10,250 ppm 8 hours/day for 6 weeks.[5]

Cardiac arrhythmias have been provoked in a number of species. Inhalation of 3500–6100 ppm by dogs for 5 minutes caused ventricular fibrillation and cardiac arrest after injection of epinephrine.[3] The minimal concentration that elicited cardiac arrhythmias in the anesthetized monkey was 50,000 ppm.[6]

Cardiac sensitization is unlikely to occur in humans in the absence of any effects on the CNS, and dizziness should act as an early warning that a dangerous concentration is being reached.[7]

Administered by gavage, 3925 mg/kg/day for 78 weeks, trichlorofluoromethane was not

carcinogenic to mice; results from rats are inconclusive because of poor survival rates.[8] It was not genotoxic in a number of in vitro assays.[2]

The 2003 ACGIH TLV-ceiling limit for trichlorofluoromethane is 1000 ppm (5620 mg/m^3).

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TRICHLORONAPHTHALENE
CAS: 1321-65-9

$C_{10}H_5Cl_3$

Synonyms: 1,4,5-Trichloronaphthalene; 1,4,6-trichloronaphthalene

Physical Form. White solid

Uses. Electric wire insulation; lubricants

Exposure. Inhalation; skin absorption

Toxicology. Trichloronaphthalene is moderately toxic to the liver.

Industrial exposure to trichloronaphthalene (usually mixed with tetrachloronaphthalene) has been relatively free of untoward effects compared with the more highly chlorinated naphthalenes.[1] No fatal cases of liver injury have been reported, but one instance of toxic hepatitis supposedly resulted from exposure to 3 mg/m^3.[2] Although there are several reports of chloracne from exposure to trichloronaphthalene, they do not stand up well to critical analysis.[1] Experiments on human volunteers showed that the mist was entirely nonacneigenic as opposed to the penta- and hexachloro derivatives, which produce severe chloracne.[3]

Rats exposed to 11 mg/m^3 of trichloronaphthalene, containing some tetrachloronaphthalene, 16 hours/day for 2.5 months showed slightly swollen liver cells with granular cytoplasm.[4]

The higher-chlorinated naphthalenes show a much greater toxicity.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for trichloronaphthalene is 5 mg/m^3 with a notation for skin absorption.

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2,4,6-TRICHLOROPHENOL

CAS: 88-06-2

$C_6H_3Cl_3O$

Synonyms: Dowicide 2S, Omal, Phenachlor

Physical Form. Yellow flakes

Uses. Wood preservative; disinfectant; fungicide, herbicide, defoliant

Exposure. Inhalation, skin absorption

Toxicology. In experimental animals, 2,4,6-trichlorophenol causes toxic effects to the liver and hematologic system and cancer. There is no reliable information regarding exposure and toxic effects in humans.

The acute intraperitoneal LD_{50} in rats is 276 mg/kg.[1] Signs of toxicity before death included sluggishness, hypotonia, elevated body temperature, labored breathing, altered respiratory rate, and central nervous system effects, including convulsions, tremors, coma, excited behavior, and incoordination.[2] It has been suggested that 2,4,6-trichlorophenol acts by interfering with mitochondrial oxidative phosphorylation and inhibition of cytochrome P450-dependent mixed function oxidases.[1]

Hepatic and splenic lesions were observed after subchronic oral studies in rodents.[3] Rats exposed to 2300 mg/kg/day in the diet for 7 weeks experienced a "moderate to marked" increase in splenic hematopoiesis.[3] A high incidence of bone marrow hyperplasia and leukocytosis occurred in rats after chronic exposure to about 1300 mg/kg/day in the diet.

No developmental effects were noted in offspring of female rats exposed to 2,4,6-trichlorophenol throughout gestation or in the offspring of treated males and untreated females.[4,5] Reduced mean litter size was observed in rats after exposure to 42 mg/kg/day in drinking water, but not at 4.2 mg/kg/day.[5] Reproductive function and litter size were not affected in rats administered as much as 1000 mg/kg/day by gavage.[4]

A statistically significant increase in monocytic leukemia was observed in male rats chronically administered either 250 or 650 mg/kg/day.[3] In addition, there was a statistically significant increase in hepatocellular tumors in male (both dose levels) and female (high dose only) mice. Although there is limited evidence supporting the carcinogenicity of chlorophenols as a general class of chemicals to humans, there are no data from which to evaluate the possible carcinogenicity of 2,4,6-trichlorophenol, specifically, in humans.[6] The EPA has classified 2,4,6-trichlorophenol as a probable human carcinogen based on the animal data.[7]

2,4,6-Trichlorophenol has been evaluated for genotoxicity in a variety of *in vivo* and *in vitro* assays, and results are inconclusive.[7] Although a majority of the studies reported negative results, some positive results in bacteria, yeast, and mammalian cells suggest that 2,4,6-trichlorophenol may have some genotoxic potential.[7] In contrast to earlier studies, 2,4,6-trichlorophenol was found to induce chromosome aberrations in Chinese hamster ovary (CHO) and V79 cells; variations in protocol were thought to account for the contradictory findings.[8]

An ACGIH threshold limit value-time-weighted average (TLV-TWA) has not been established for 2,4,6-trichlorophenol.

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2,4,5-TRICHLOROPHENOXYACETIC ACID

CAS: 93-76-5

$C_8H_5Cl_3O$

Synonym: 2,4,5-T

Physical Form. Solid

Uses. Formerly used as an herbicide in brush control. Production was terminated in the United States in 1979 when the Environmental Protection Agency, in an emergency action, suspended all uses because of contamination with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). In October 1983, all registrations for use of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) were cancelled by the US Department of Agriculture because of concerns over the potential of dioxin contamination to produce birth defects and cancer, despite the lack of firm evidence that 2,4,5-T alone had contributed to teratogenesis or carcinogenesis in humans.[1]

Exposure. Inhalation

Toxicology. 2,4,5-T is of low-order acute toxicity; at high doses, it is teratogenic in experimental animals.

Eleven men in two separate experiments experienced no clinical effects after ingestion of 5 mg/kg 2,4,5-T. Most did report a metallic taste lasting 1–2 hours after ingestion.[1]

Most, if not all, occupational illnesses associated with 2,4,5-T (such as chloracne) have been found to be the result of product contamination with TCDD.[2] TCDD is extremely toxic to animals, and exposure has also been associated with liver function impairment, peripheral neuropathy, personality changes, porphyria cutanea, hypertrichosis, and hyperpigmentation in humans.[3] TCDD is a chlorinated dioxin, one of a large number of related compounds referred to as "dioxins"; it has no functional use and is not intentionally produced. It has been identified as the responsible toxic agent in several industrial disasters, such as accidental releases at Nitro, WV in 1949, and at Seveso, Italy in 1976.[3,4] The role of dioxin contaminants must also be considered in the discussion of 2,4,5-T toxicology.

A study of 204 workers exposed for from 1 month to 20 years to 2,4,5-T and its contaminants (concentrations unspecified) showed no evidence of increased risk for cardiovascular disease, hepatic disease, renal damage, central or peripheral nervous system effects, reproductive problems, or birth defects.[3] Clinical evidence of chloracne persisted in 55.7%, and an association between exposure and history of upper gastrointestinal tract ulcer was found.

The oral LD_{50} for dogs was in the range of 100 mg/kg; effects were limited to a slight or moderate stiffness in the hind legs with development of ataxia.[5] Dogs survived 10 mg/kg/day for 90 days without illness. In rats fed diets containing 2000 ppm 2,4,5-T (<0.05% TCDD), the minimal cumulative fatal dose was approximately 900 mg/kg.[6]

Concern about the toxicology of 2,4,5-T has centered on its teratogenic action in experimental animals.[2] Although the first studies were carried out with 2,4,5-T contaminated by 30 ppm TCDD, subsequent experiments using analytical-grade 2,4,5-T (<0.05% TCDD) showed that 100 mg/kg/day administered subcutaneously to mice on days 6 through 15 of gestation caused an increased incidence of cleft palates.[7] Administered by gavage on gestational days 6 through 14 to various stocks and strains of mice, 2,4,5-T caused developmental toxicity at doses below those producing discernible maternal toxicity.[8] The most significant prenatal effects were cleft palate, embryolethality, and intrauterine growth retardation. The number of viable fetuses per litter and mean fetal weight decreased with increasing dose and embryolethality increased.[8] 2,4,5-T containing no detectable TCDD was feticidal and teratogenic to hamsters when administered orally on days 6–10 of gestation at a dosage of 100 mg/kg/day.[9] At 80 mg/kg/day, there was a reduction in the number of pups per litter, in fetal weight, and in survival.[9] Rats, rabbits, and monkeys have appeared relatively resistant to teratogenic effects in a number of studies.[1,2]

An epidemiological investigation of New Zealand chemical applicators using 2,4,5-T found no significant differences in the rate of congenital defects, stillbirths, or miscarriages compared with controls.[10]

Several epidemiological studies in Sweden suggested an association between exposure to phenoxyherbicides (and/or their contaminants) and soft tissue sarcomas.[11] There has also been widespread concern among Vietnam veterans that exposure to the defoliant Agent Orange, which contains equal quantities of 2,4-D and 2,4,5-T (with its contaminant TCDD), might increase their risk of adverse health effects, particularly various forms of cancer.[2] Animal studies do not support the notion that 2,4,5-T itself is carcinogenic.[12] Chronic feeding studies in rats did not produce an increased tumor incidence, even at doses of 30 mg/kg/day, which produced toxic effects.[12] The IARC has determined that there is inadequate evidence for carcinogenicity of 2,4,5-T in animals and that chlorophenoxy herbicides are possibly carcinogenic to humans.[13]

2,4,5-T was not mutagenic in bacterial assays, and it did not induce aneuploidy or somatic mutation in vitro. In vivo it did not cause micronuclei in mice or dominant lethal mutations in mice or rats.[13]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 2,4,5-trichlorophenoxyacetic acid is 10 mg/m^3.

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1,2,3-TRICHLOROPROPANE

CAS: 96-18-4

$C_3H_5Cl_3$

Synonyms: Glycerol trichlorohydrin; allyl trichloride; trichlorohydrine

Physical Form. Colorless liquid

Uses. Intermediate in the manufacture of pesticides and polysulfide rubbers; formerly used as a solvent and extractive agent

Exposure. Inhalation; skin absorption

Toxicology. 1,2,3-Trichloropropane is an irritant of the eyes and mucous membranes; in experimental animals it has caused hepatic, renal, hematologic, and central nervous system effects; it is carcinogenic to rodents exposed orally.

Human subjects exposed to 100 ppm for 15 minutes noted eye and throat irritation and objected to the unpleasant odor.[1] Ingestion of 3 g caused drowsiness, headache, unsteady gait, and lumbar pain.[2]

In rats, 1000 ppm caused death in five of six animals after 4 hours of exposure.[3] Eight of 15 mice did not survive exposure to 5000 ppm for 20 minutes; liver damage accounted for four additional deaths after 7–10 days.[2] Daily 10-minute exposures to 2500 ppm for 10 days resulted in the death of 7 of 10 mice tested.[2]

Oral LD_{50} values ranging from 150 to 450 mg/kg have been determined in rats.[4] Before death, signs suggestive of central nervous system damage have included piloerection, salivation, ataxia, and coma; hemorrhagic damage to the liver and kidneys was also observed. Repeated gavage administration of 250 mg/kg caused hepatic and renal necrosis severe enough to cause death within 2 weeks in both mice and rats.[5] Increased liver weights and altered enzyme levels were found in rats at doses as low as 16 mg/kg/day for 17 weeks, whereas 32 mg/kg/day for the same period caused increased kidney weights and slight inflammation. In another report, subacute gavage exposure of rats with 0.80 mmol/kg/day for 10 days caused myocardial degeneration and necrosis in addition to mild hepatotoxicity.[6]

Oral exposures in the near-lethal range also produced pathologic changes in the nasal turbinates of both mice and rats.[5] Effects included inflammation and necrotic alterations in the dorsal posterior of the nasal passages. Other effects in rats after repeated gavage administration were hyperkeratosis and/or acanthosis of the esophagus and stomach (doses greater than 63 mg/kg/day) and nonregenerative anemia as indicated by decreased hematocrit, hemoglobin, and erythrocyte counts (doses of 16 mg/kg day).

1,2,3-Trichloropropane was carcinogenic in Fischer-344 rats and B6C3F1 mice when administered for 2 years by gavage.[5] Rats given 3 mg/kg/day or more and mice given 6 mg/kg/day or more had increased incidences of squamous cell papillomas and/or carcinomas in the oral mucosa and/or the forestomach. Increased incidences of other tumors included pancreatic acinar adenoma, renal tubule adenoma, and adenoma and carcinoma of the preputial gland in male rats; clitoral gland adenoma and carcinoma and mammary gland adenocarcinoma in female rats; hepatocellular adenoma and carcinoma and Harderian gland adenoma in male and female mice; and uterine neoplasms in female mice.

The carcinogenicity of 1,2,3-trichloropropane is consistent with positive genotoxic findings that have included mutagenicity in *Salmonella typhimurium* and induction of sister chromatid exchanges in cultured hamster cells.[5] It forms DNA adducts *in vivo* in mice and rats.[6]

Intraperitoneal doses causing maternal toxicity in rats were not fetotoxic or teratogenic.[8] Male rats administered 80 mg/kg/day by gavage for 5 days and then mated with an untreated female did not have any meaningful changes in indices such as numbers of implants and number of live embryos compared with controls.[9] Oral administration for up to 4 months at near-lethal levels caused decreased testes and epididymis weights in rats and mice but no effects on testicular histology, sperm counts, or sperm morphology.[4]

The liquid was irritating to the skin of rabbits with prolonged or repeated exposure and was also extremely irritating when instilled in rabbit eyes.[4] The dermal absorption LD_{50} was 2.5 g/kg.[3]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 1,2,3-trichloropropane is 10 ppm (60 mg/m^3) with a notation for skin absorption.

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1,1,2-TRICHLORO-1,2,2-TRIFLUOROETHANE

CAS: 76-13-1

CCl_3CF_3

Synonyms: Refrigerant 113; fluorocarbon 113; freon 113; FC113; TCTFE

Physical Form. Colorless gas; volatile liquid

Uses. Solvent for cleaning electronic equipment and degreasing of machinery; refrigerant; dry cleaning agent

Exposure. Inhalation

Toxicology. 1,1,2-Trichloro-1,2,2-trifluoroethane (TCTFE) is a central nervous system depressant, a cardiac sensitizer, and a mild mucous membrane irritant.

Although TCTFE is not considered to be extremely toxic, several deaths have occurred when the chemical was used as a cleaning agent in small, closed, unventilated areas.[1] The vapor acts by displacing oxygen in the victim's immediate breathing zone, resulting in asphyxia followed by pulmonary edema and death. Symptoms such as headache, light-headedness, dizziness, or drowsiness may or may not precede collapse.

In experimental human studies, exposure to 4500 ppm for 30–100 minutes resulted in significant impairment in tests of manual dex-

terity and vigilance. Subjects reported loss of concentration and a tendency to somnolence, which disappeared 15 minutes after the exposure ended. At 1500 ppm, no effects were observed.[2] More prolonged human exposures of 6 hours daily, 5 days/week for 2 weeks at concentrations of approximately 500 and 1000 ppm caused mild throat irritation on the first day; there was no decrement in performance of complex mental tasks.[3] No signs or symptoms of adverse effects were found among 50 workers exposed to levels ranging from 46 to 4700 ppm for an average duration of 2.8 years.[4]

The liquid dissolves the natural oils of the skin, and dermatitis may occur as a result of repeated contact; one worker experienced drying of the skin attributed to contact with TCTFE.[4,5]

Pharmacokinetic studies have not determined whether TCTFE is metabolized by humans or eliminated unchanged.[6]

Animal studies have indicated low acute toxicity from inhaled TCTFE. The LC_{50} for 2-hour exposures ranged from 50,000 to 120,000 ppm for a number of species.[7] Dogs exposed at 11,000–13,000 ppm for 6 hours showed lethargy, nervousness, vomiting, and tremors—all reversible within 15 minutes after exposure. Chronic exposure of rats and rabbits to 12,000 ppm for up to 2 years caused no adverse effects. Rats exposed by whole body inhalation to 2000, 10,000 or 20,000 ppm 6 hours/day, 5 days/week for 24 months showed no microscopic evidence of compound-related toxicity or carcinogenicity.[8] Observations of appearance, behavior, mortality, and clinical laboratory measurements were unremarkable, except for a 5–10% decrease in body weight gains at the 10,000 and 20,000 ppm exposure levels.

In dogs, cardiac sensitization to intravenously administered epinephrine occurred at concentrations of 5,000–10,000 ppm.[9] Concentrations greater than 25,000 ppm were necessary to produce arrhythmias in animals under anesthesia.[10]

Occluded contact with rabbit skin of 5 gm/kg/day for 5 days caused local necrosis of skin and enlargement of liver cells; no effects were observed after 20 weeks of applications to uncovered skin.[7] The liquid produced no significant irritation in a rabbit eye test.[7]

TCTFE is odorless, tasteless, and colorless and provides no warning of overexposure.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 1,1,2-trichloro-1,2,2-trifluoroethane is 1000 ppm (7670 mg/m^3) with a TLV-STEL (short term excursion limit) of 1250 ppm (9590 mg/m^3).

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TRIETHANOLAMINE
CAS: 102-71-6

$N(CH_2CH_2OH)_3$

Synonyms: 2,2′,2″-nitrilotriethanol; tri(hydroxyethyl)amine

Physical Form. Clear, colorless, viscous liquid with ammonia odor

Uses. Manufacture of emulsifiers and dispersing agents; in cosmetic formulations; in household and commercial cleaners and detergents

Exposure. Inhalation; skin absorption

Toxicology. Triethanolamine is a moderate irritant to the eyes and skin.

In humans, triethanolamine is reported to be a skin sensitizer.[1]

When triethanolamine was applied to the skin of rabbits for 72 hours, there was moderate hyperemia, edema, and necrosis.[2] In a guinea pig sensitization test, there was no evidence of sensitization.[3] In the eyes of rabbits, one drop caused moderate, transient injury at 24 hours.[4]

The acute toxicity of triethanolamine is low, as reflected in the high values for the oral LD_{50} in rats of 4.2–11.3 g/kg.[5,6] In rats fed 0.73 g/kg daily for 90 days, the only major effect was fatty degeneration of the liver.[5,7] There were no effects at 0.08 g/kg.

Triethanolamine in the diet of ICR mice at levels of 0.03% or 0.3% caused a significant increase in the occurrence of thymic and nonthymic tumors in lymphoid tissues of females.[8] It has recently been suggested that this increase in lymphomas in female ICR mice may be attributable to an unusually low incidence of lymphomas reported in the control animals (i.e., the lymphoma incidence reported in the treated groups is similar to that usually found in controls).[9] In a follow-up study, B6C3F1 mice administered 1% or 2% triethanolamine in drinking water for 82 weeks showed no dose-related increase in the incidence of any tumor.[9] Administered continuously to rats as 1% or 2% of the drinking water for up to 2 years, triethanolamine was not carcinogenic, but it was toxic to the kidneys, especially in female animals.[10] Equivocal evidence of carcinogenicity, based on a marginal increase in the total incidences of renal tubule cell adenoma, was seen in male rats dermally dosed at 32, 63, or 125 mg/kg 5 days/week for 2 years.[11] At the site of application animals had varying degrees of acanthosis, inflammation, and ulceration. Triethanolamine had no carcinogenic or cocarcinogenic activity when dermally applied to mice for 18 months.[12]

The IARC has determined that there is inadequate evidence for the carcinogenicity of triethanolamine in both humans and experimental animals.[1]

Triethanolamine was not genotoxic in a variety of assays.[11] It was not mutagenic in *Salmonella typhimurium* and did not induce sister chromatid exchanges or chromosomal aberrations *in vitro*. *In vivo* there was no increase in the frequency of micronucleated erythrocytes in treated rodents.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for triethanolamine is 5 mg/m^3.

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TRIETHYLAMINE

CAS: 121-44-8

$(C_2H_5)_3N$

Synonyms: TEA; *N*,*N*-diethylethanamine

Physical Form. Colorless liquid

Uses. In the manufacture of waterproofing agents; as a corrosion inhibitor; as a propellant

Exposure. Inhalation

Toxicology. Triethylamine (TEA) causes ocular effects in humans; in animals it is a skin and mucous membrane irritant.

Two volunteers exposed to approximately 4.5 ppm for 8 hours experienced slight subjective visual disturbances.[1] At 12 ppm for 1 hour, subjects experienced heavy hazing of the visual field, an inability to distinguish outlines of objects 100 m or more away, and bluish halos around lights. There was pronounced increase in corneal thickness. The investigators suggest that the decrease in visual acuity at the end of work may be severe enough to cause accidents in the workplace or in traffic. Effects are reversible, and it appears that even repeated bouts of edema do not cause permanent damage to the cornea. In another report TEA a concentration of 3.0 mg/m^3 for 4 hours caused no effects whereas exposure to 6.5 mg/m^3 for the same period caused blurred vision and a decrease in contrast sensitivity.[2] Only minor increases in corneal thickness were noted, but there was marked edema in the corneal epithelium.

Among 19 workers repeatedly exposed to time-weighted average (TWA) levels of 3 ppm with brief excursions to higher levels, 5 workers reported foggy vision, blue haze, and halo phenomena on 47 occasions over an 11-week period.[3] In another study, these same vision symptoms (blurriness, halos around lights, and blue, hazy vision) occurred more often in currently exposed workers than those previously or never exposed to TEA.[4] There was no corneal edema, but reported symptoms were more common among those with the highest exposures (10–20.3 mg/m^3).

Exposure of six rats to 1000 ppm for 4 hours was lethal to one.[5] Rabbits survived exposures to 100 ppm daily for 6 weeks but showed pulmonary irritation, myocardial degeneration, and cellular necrosis of liver and kidneys; at 50 ppm, the effects on lung, liver, and kidneys were less severe, but there was also damage to the cornea.[6] Rats appeared to be less sensitive to the effects of TEA than rabbits.[7] Exposure to 25 or 247 ppm 6 hours/day, 5 days/week for up to 28 weeks caused no statistically significant treatment-related effects on body weight gain, organ weights, hematology, clinical chemistry, or electrocardiographic indices.[7] No gross pathologic or histopathologic lesions attributable to exposure were noted at autopsy.

In rabbits, skin application produced adverse effects ranging from irritation to corrosion, depending on the amount and duration applied.[8]

TEA was not mutagenic in bacterial assays, but it did cause aneuploidy and chromosome aberrations in rats.[8]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for triethylamine is 1 ppm (4.1 mg/m^3) with a short-term excursion limit (STEL)/ceiling of 5 ppm (20.7 mg/m^3) and a notation for skin absorption.

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TRIETHYLENE TETRAMINE

CAS: 112-24-3

$C_6H_{18}N_4$

Synonyms: TETA; Araldite hardener HY 951; DEH 24; TECZA; 1,3,7,10-tetraazadecane; Trien

Physical Form. Slightly viscous yellow liquid; commercially available form is 95–98% pure, and impurities include linear, branched, and cyclic isomers.

Uses. Hardener/cross-linker for epoxy resins; metal chelator; constituent of wet-strength paper resins; copolymer with fatty acids in metal spray coatings; constituent of synthetic elastomer formulations

Exposure. Inhalation

Toxicology. Triethylene tetramine (TETA) is a strong irritant of the eyes, mucous membranes, and skin and is a sensitizer of the respiratory tract and skin.

Exposure to the vapor causes irritation of the eyes, nose, throat, and respiratory tract.[1] Exposure to hot vapor causes itching of the face with erythema and edema.[2]

Sensitization of the respiratory tract has followed chronic exposure to fumes or dust of TETA, manifested by bronchial asthma.[3–5] One worker developed asthma after working with an epoxy resin-TETA formulation for 6 months in a job laminating aircraft windows.[5] In an environmental chamber, the worker developed flulike symptoms and asthmatic breathing after simulating the job conditions for 2 hours with the resin-TETA mixture. Similar exposure to the resin alone did not produce the symptoms.

TETA on the skin causes irritation and dermatitis, and continued exposure can induce allergic contact dermatitis.[3] Cross-sensitization to other amines has occurred.

TETA was teratogenic when fed to rats at 1.67% in the diet.[6] The dihydrochloride salt administered to mice at 3000, 6000, or 12,000 mg/l of drinking water caused a dose-related increased frequency of gross brain abnormalities such as hemorrhages, delayed ossification of the cranium, hydrocephaly, exencephaly, and microcephaly.[7] Microscopically, disorganization of neuronal cell layers, spongiform changes in white matter, and reduced myelin development were noted in the cerebrum of treated animals.

The teratogenic effects of TETA appear to be due to the chelating properties of the chem-

ical and the resulting copper deficiency.[8] Copper supplementation reduces this effect in rats. In contrast to the rat, TETA is not teratogenic in the rabbit, nor is there a reduction in the copper content of the serum and urine.

TETA was mutagenic in bacterial assays and was positive in sister chromatid exchanges and unscheduled DNA synthesis tests *in vitro*.[8] It was not clastogenic in the mouse micronucleus test *in vivo* after oral or intraperitoneal administration.

The ACGIH has not established a threshold limit value (TLV) for triethylene tetramine.

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TRIFLUOROBROMOMETHANE

CAS: 75-63-8

CF_3Br

Synonyms: Bromotrifluoromethane; trifluoromonobromomethane; freon 13B1; Halon 1301

Physical Form. Colorless gas

Uses. Fire extinguishing agent; refrigerant

Exposure. Inhalation

Toxicology. Trifluorobromomethane in animals causes sensitization of the myocardium to epinephrine and central nervous system effects.

Human exposure to 70,000 ppm for 3 minutes caused no adverse effects.[1] Lightheadedness, paresthesia, and diminished performance were reported during exposures up to 100,000 ppm; at 150,000 ppm, a feeling of impending unconsciousness developed.[2] Exposure to 10,000 ppm (1%) for 24 hours produced minor disturbances of central nervous system function as assessed by cognitive tasks.[3]

In dogs and rats repeatedly exposed to 23,000 ppm, there were no toxic signs or pathologic changes.[2] Monkeys exposed to concentrations of 200,000 ppm were lethargic and suffered spontaneous cardiac arrhythmias within 5–40 seconds of exposure.[3] Dogs exposed to 200,000 ppm or greater became agitated within 1–2 minutes, and tremor occurred within 3 minutes.[4] Epileptiform convulsions characterized by generalized rigidity, apnea, and cyanosis of the tongue were observed in about half of the dogs exposed to 500,000–800,000 ppm. Intravenous injection of a pressor dose of epinephrine produced arrhythmias in all animals exposed to 400,000 ppm; larger doses of epinephrine (5–10 µg/kg) caused ventricular fibrillation with cardiac arrest in dogs and spontaneous defibrillation in monkeys.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for trifluorobromomethane is 1000 ppm (6090 mg/m^3).

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TRIMELLITIC ANHYDRIDE

CAS: 552-30-7

$C_9H_4O_5$

Synonyms: Anhydrotrimellitic acid; 1,2,4-benzenetricarboxylic acid anhydride; 1,3-dihydro-1,3-dioxo-5-isobenzofurancarboxylic acid; TMA; TMAN (preferred)

Physical Form. White crystalline solid

Uses. As a curing agent for epoxy and other resins and as a vinyl plasticizer; also found in anticorrosive surface coatings, polymers, paints, dyes, and pharmaceuticals

Exposure. Inhalation

Toxicology. Trimellitic anhydride (TMAN) causes both respiratory irritation and immunologic respiratory disease.

In humans, four clinical syndromes (three of which are associated with immunologic reactions) are induced by inhalation of TMAN dust and fume.[1–3] The first is a direct irritant syndrome characterized by cough and upper airway irritation related to the irritant properties of the anhydride at high-dose exposures.

The second syndrome, characterized by rhinitis, asthma, or both, is an immediate-type airway response mediated by IgE antibodies directed against trimellityl-human protein conjugates. A latent period, ranging from weeks to years, is required between the sensitizing exposure and the onset of symptoms, but once sensitization has occurred, symptoms occur almost immediately on reexposure.

The third condition, late respiratory systemic syndrome, is characterized by cough, mucus production, occasional wheezing, and systemic symptoms of malaise, chills, fever, and aching muscles and joints, occurring 4–12 hours after exposure. This syndrome also has been termed TMA flu and clinically resembles hypersensitivity pneumonitis with visible chest X-ray infiltrates. High levels of IgG serum antibody and total serum antibody directed against trimellityl-human protein conjugates accompany the syndrome, and a latent period of exposure before the onset of symptoms is typical.

The fourth condition, termed pulmonary disease-anemia syndrome, is characterized by dyspnea, hemoptysis, pulmonary infiltrates, restrictive lung disease, and anemia. It occurs with high-dose exposure to fumes when heated metal surfaces are sprayed with TMAN-containing materials. High titers of antibody to trimellityl-human proteins and -erythrocytes have been found in affected workers.

It is thought that low-molecular-weight compounds such as TMAN cannot directly elicit immunologic sensitization; however, they can act as haptens.[4] Thus TMAN combines with human serum albumin or with human erythrocytes to form antigens against which numerous types of antibodies can be found. During TMAN conjugation, the anhydride group is lost, and trimellityl-protein complexes, such as TMAN-human serum albumin (TMAN-HSA), are formed.

The TMAN levels associated with various respiratory effects have not been clearly defined.[5] However, workers who may have been exposed to up to 7.5 mg/m^3 of TMAN during the manufacture of epoxy paint complained of irritation of the eyes, nose, and throat, shortness of breath, cough, nausea,

headache, and skin irritation. Symptoms of chest pain and respiratory tract irritation have been reported in workers exposed to levels in the range of 0.1–10 mg/m^3. In one study, intermittent exposure to levels ranging up to 2.1 mg/m^3 caused late respiratory systemic syndrome and allergic rhinitis in a portion of the exposed workers.[5] Reduction of the work levels to 0.03 mg/m^3 coincided with symptomatic improvement in the three workers with late respiratory systemic syndrome and a fall in total antibody binding to trimellityl-human serum albumin. However, the continued low-level exposure was sufficient to elicit and maintain a specific IgE immune response in a worker who eventually developed lacrimation and rhinorrhea. Further study of this same population showed that workers exposed only after the low levels were in place developed no immunologic syndromes and had insignificant antibody responses.[6]

A follow-up study of 29 workers with TMAN-induced immunologic lung disease who had been moved to low-exposure jobs for more than 1 year revealed that workers with late asthma or late respiratory systemic syndrome had improved symptoms, improved pulmonary functions, and lower total antibody against TMAN-HSA.[7] In contrast, 7 of 12 workers with asthma rhinitis continued to have moderate to severe symptoms, abnormal pulmonary functions, and elevated IgE against TMAN-HSA. Elevated IgE against TMAN-HSA appears to be a marker for the subpopulation of workers with asthma rhinitis that does not improve.

In animal studies, TMAN had a low acute toxicity when administered by the oral or the percutaneous route.[8] Rats given 10,000 ppm in the diet for 90 days showed an increase in the number of white blood cells. Inhalation of 0.2 mg/m^3 and above for 14 days was associated with hemorrhagic foci in the lungs.

There are no reports of carcinogenicity associated with TMAN exposure. It was not mutagenic in bacterial assays with or without metabolic activation.[9] No teratogenic effects or developmental toxicity was seen in rats or guinea pigs exposed to 500 mg/m^3 for 6 hours/day during their period of major organogenesis.[10]

The 2003 ACGIH threshold limit value-ceiling (TLV-CEILING) for trimellitic anhydride is 0.04 mg/m^3.

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TRIMETHYLAMINE
CAS: 75-50-3

$(CH_3)_3N$

Synonyms: *N*,*N*-dimethylmethanamine; TMA

Physical Form. Colorless gas

Uses. As an insect attractant, as a warning agent for natural gas, and in organic synthesis

Exposure. Inhalation

Toxicology. Trimethylamine is a skin, eye, and respiratory irritant.

In an accidental exposure, a blast of vapor that struck the eye of a student caused the epithelium to be lost from the cornea. There was no edema of the corneal stroma, and the eye was completely normal within 4 or 5 days; the exposure was thought to be minimal.

Tests of single drops of aqueous solutions applied to the eyes of animals have shown that 1% solution causes severe irritation, 5% causes hemorrhagic conjunctivitis, and 16% causes severe reaction with conjunctival hemorrhages, corneal edema, and opacities, followed by some clearing but much vascularization.[1]

In rats, 3500 ppm for 4 hours was considered an approximate lethal concentration. Rats exposed 6 hours/day for 10 days to 0, 75, 250, or 750 ppm had dose-dependent degenerative changes in the olfactory and respiratory epithelium.[2] Degeneration of the tracheal mucosa was also observed at the two higher doses.

Administered to mouse embryo cultures *in vitro*, trimethylamine was teratogenic, causing neural tube defects and inhibiting embryonic growth.[3] Trimethylamine may exert these effects by reducing macromolecular synthesis. Repeated intraperitoneal injections of trimethylamine hydrochloride in pregnant mice caused fetotoxicity only at maternally toxic doses.[4]

Trimethylamine was not mutagenic in bacterial assays.[4]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for trimethylamine is 5 ppm (12 mg/m^3) with a short-term excursion limit (STEL) of 15 ppm (36 mg/m^3).

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TRIMETHYL BENZENE
CAS: 25551-13-7

Mesitylene *108-67-8*
Pseudocumene *95-63-6*
Hemimellitene *526-73-8*

$(CH_3)_3C_6H_3$

Synonyms: The three isomers of trimethyl benzene are mesitylene (1,3,5-trimethylbenzene, sym-trimethylbenzene, 1,3,5-TMB), pseudocumene (1,2,4-trimethylbenzene, pseudocumol, 1,2,4-TMB), and hemimellitene (1,2,3-trimethylbenzene, 1,2,3-TMB).

Physical Form. Colorless liquid

Uses. As a raw material in chemical syntheses; as ultraviolet stabilizers in plastics; found in solvents and as a constituent of gasoline

Exposure. Inhalation

Toxicology. Trimethyl benzene is an eye, nose, and respiratory irritant; at high concen-

trations it causes central nervous system depression.

In one of the few reports of human exposure, 27 workers exposed for a number of years to a paint thinner containing primarily 1,2,4-TMB (50%) and 1,3,5-TMB (30%), plus other alkylbenzenes in unspecified amounts, had signs and symptoms of impairment of the respiratory, nervous, and hematopoietic systems.[1] Approximately 70% of the workers complained of headaches and drowsiness, with 51% suffering from anemia, 30% displaying signs of asthmalike bronchitis, and 30% showing a tendency to hemorrhage. The presence of other hydrocarbons and unidentified additives that accounted for 20% of the thinner suggested that the blood disturbances were probably due to a contaminant.

Mice exposed at 5100–7140 ppm 1,3,5-TMB for 2 hours suffered from a loss of righting reflex, and at 7140–9180 ppm for 2 hours mice showed depression of the central nervous system.[1,2] Similar exposures to 1,2,4-TMB produced similar results, with 8130 ppm for 2 hours causing a loss of righting reflex and 8130–9140 ppm causing a loss of reflexes and depression of the central nervous system.

In rats, exposure to 2400 ppm 1,3,5-TMB for 24 hours caused death due to respiratory failure and depression of the central nervous system in 4 of 10 animals; at 612 ppm for 24 hours there were no adverse effects.[1] Rats exposed at 600 ppm 6 hours/day, 6 days/week for 5 weeks showed no hematologic or biochemical changes. Experiments with 1,2,4-TMB showed nose and eye irritation, respiratory difficulty, lethargy, tremors, and reduced weight gain with 12 exposures to 2000 ppm for 16 hr each; at 1000 ppm there was only slight eye and nose irritation.[3] Inhalation of mixed trimethylbenzene by rats 4 hours/day for 6 months at 200 ppm caused inhibition of phagocytic activity of the leukocytes.

Rats administered 1,2,4-TMB by gavage for 2 years exhibited increased total malignant tumors and head cancers.[4] 1,2,3-TMB (but not 1,2,4-TMB or 1,3,5-TMB) was mutagenic in bacterial assays; *in vivo* none of the isomers increased the frequency of micronuclei in bone marrow; however, all three increased the frequency of sister chromatid exchanges in these cells.[5]

It is expected that repeated skin exposure to the liquid will cause drying and cracking of the skin.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for trimethyl benzene is 25 ppm (123 mg/m^3).

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TRIMETHYL PHOSPHITE
CAS: 121-45-9

$C_3H_9O_3P$

Synonyms: Methyl phosphite; phosphorus acid trimethyl ester; TMP; trimethoxyphosphine

Physical Form. Colorless liquid

Uses. Used primarily in the synthesis of organophosphate insecticides; also used in the

production of flame-retardant polymers and textiles.

Exposures. Inhalation; skin absorption

Toxicology. Trimethyl phosphite is a skin irritant, and high levels may cause ocular damage.

The adverse effects of trimethyl phosphite on humans are largely unknown. At one plant with average exposures between 0.3 and 4 ppm, and excursions as high as 15 ppm, examination of 179 workers showed no adverse effects associated with occupational exposure.[1]

Odors approaching 20 ppm are considered to be objectionable.

In rats the oral LD_{50} was 2.5 g/kg.[2] A 4-hour LC_{50} of greater than 10,000 ppm was also found in rats, with the animals indicating respiratory distress, irritation, and discomfort. Applied to the skin of rabbits trimethyl phosphite caused moderately severe irritation, and the dermal LD_{50} was 2.6 g/kg.

Rats were exposed at 600, 300, or 100 ppm 6 hours/day 5 days/week for 4 weeks.[1] At the highest dose, severe cataracts developed and 70% of the animals died; there was histologic evidence of lung inflammation. The middle dose was lethal to 10% of the exposed group and caused mild cataracts. At the low dose there were mild, reversible striate opacities. In further studies, no effects were observed in animals exposed at 10 ppm.

Trimethyl phosphite was administered by gavage to pregnant rats at rates of 16, 49, or 164 mg/kg/day, on gestation days 6 through 15.[3] Teratological evaluation revealed gross fetal abnormalities, skeletal defects, soft tissue defects, and an increased frequency of fetal resorption rates at 164 mg/kg/day. No changes were observed at the lower dose levels. The teratogenic effect of trimethyl phosphite may be associated with inhibition of cholinesterase activity.

Trimethyl phosphite was genotoxic in mouse lymphoma assays but was not mutagenic in various bacterial assays.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for trimethyl phosphite is 2 ppm (10 mg/m^3).

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2,4,6-TRINITROTOLUENE

CAS: 118-96-7

$C_7H_5N_3O_6$

Synonyms: TNT; Tritol; sym-trinitrotoluene; 1-methyl-2,4,6-trinitrobenzene

Physical Form. Colorless, monoclinic prisms, crystals; commercial crystals are yellow

Uses. Explosives

Exposure. Inhalation; skin absorption

Toxicology. 2,4,6-Trinitrotoluene (TNT) causes liver damage and aplastic anemia.

Deaths from aplastic anemia and toxic hepatitis were reported in TNT workers before the 1950s; with improved industrial practices, there have been few reports of fatalities or serious health problems related to its use.[1]

Exposures exceeding 0.5 mg/m^3 cause destruction of red blood cells.[2] Hemolysis is partially compensated for by enhanced regeneration of red blood cells in the bone marrow, which is manifest as an increased percentage of reticulocytes in peripheral blood.[2] Among some groups of workers, there is a reduction in average hemoglobin and hematocrit values.[2] Workers deficient in glucose-6-phosphate dehydrogenase may be particularly at risk of acute hemolytic disease.[3] Three such cases

occurred after a latent period of 2–4 days and were characterized by weakness, vertigo, headache, nausea, paleness, enlarged liver and spleen, dark urine, decreased hemoglobin levels, and reticulocytosis.[3] Although no simultaneous measurements of atmospheric levels were available, measurement on other occasions showed levels up to 3.0 mg/m^3.[3]

Above 1.0 mg/m^3, the liver is unable to handle the increased amounts of red blood cell breakdown products and indirect bilirubin levels rise.[2] Elevations of liver function enzymes may occur, particularly in new employees or those recently exposed to higher levels. There are suggestions of marked individual susceptibility to liver damage, with most not showing effects unless exposures considerably exceed 1.0 mg/m^3.[2]

A characteristic TNT cataract is reportedly produced with exposures regularly exceeding 1.0 mg/m^3 for more than 5 years.[2] In one study, 6 of 12 workers had bilateral peripheral cataracts, visible only with maximum dilation.[4] The opacities did not interfere with visual acuity or visual fields. The induced cataracts may not regress once exposure ceases, although progression is arrested.

The vapor or dust can cause irritation of mucous membranes, resulting in sneezing, cough, and sore throat.[5] Although intense or prolonged exposure to TNT may cause some cyanosis, it is not regarded as a strong producer of methemoglobin.[6] Other occasional effects include leukocytosis or leukopenia, peripheral neuritis, muscular pains, cardiac irregularities, and renal irritation.[2] The skin, hair, and nails of exposed workers may be stained yellow.[5]

TNT is absorbed through skin fairly rapidly, and reference to airborne levels of vapor or dust may underestimate total systemic exposure if skin exposure also occurs.[2] Apparent differences in dose-response relationships based only on airborne levels may be explained by differences in dermal absorption.[2] TNT causes sensitization dermatitis; the hands, wrist, and forearms are most commonly affected, but skin at friction points such as the collar line, belt line, and ankles is also often involved. Erythema, papules, and an itchy eczema can be severe.[7]

A study at two explosive manufacturing facilities in China found an increased incidence of malformed spermatozoa in TNT-exposed workers.[8]

Rats administered 50 mg/kg/day in their diets had anemia, splenic lesions, and liver and kidney damage.[9] Testicular atrophy and atrophic seminiferous tubules have been reported in rats after 13 weeks of treatment at high doses.[10] Hyperplasia and carcinoma of the urinary bladder were also observed in females exposed for 24 months. A statistically significant incidence of leukemia and/or malignant lymphoma of the spleen was present in female mice receiving 70 mg/kg/day for 24 months.[10] The IARC has determined that there is inadequate evidence in experimental animals and humans for the carcinogenicity of TNT.[11]

In bacterial and mammalian *in vitro* cell systems TNT is a direct-acting mutagen.[10] However, inclusion of exogenous metabolic activation appears to abolish the genotoxicity. In vivo assays of TNT have not shown it to be genotoxic, suggesting that TNT may be reduced to nonmutagenic metabolic products in the whole animal.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 2,4,6-trinitrotoluene is 5 mg/m^3 with a notation for skin absorption.

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TRIORTHOCRESYL PHOSPHATE

CAS: 78-30-8

$(CH_3C_6H_4)_3PO_4$

Synonyms: TOCP; tri-*o*-tolyl phosphate; phosphoric acid, tri-*o*-tolyl ester

Physical Form. Colorless or pale yellow liquid

Uses. Plasticizer in vinyl plastics, lacquers, and varnishes; flame retardant

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Triorthocresyl phosphate (TOCP) causes peripheral neuropathy with flaccid paralysis of the distal muscles of the upper and lower extremities, followed in some cases by spastic paralysis.

Thousands of people have been poisoned by the accidental ingestion of TOCP in contaminated foods and beverages.[1] The most notable example was the consumption of an adulterated Jamaica ginger extract ("Jake").[2] However, reports of intoxication from occupational exposure are rare.[1] Shortly after ingestion, there may be nausea, vomiting, diarrhea, and abdominal pain.[1] After a symptom-free interval of 3–28 days, most patients complain of sharp, cramplike pains in the calf muscles; some patients complained of numbness and tingling in the feet and sometimes the hands.[1,3] Within a few hours, there is increasing weakness of the legs and feet, progressing to bilateral footdrop.[3] After an interval of another 10 days, weakness of the fingers and wristdrop develop, but the paralysis is not usually as severe as that in the feet and legs. This process does not extend above the elbows; the thigh muscles are infrequently involved. Sensory changes, if they occur, are minor.[4,5]

With severe intoxication, lesions of the anterior horn cells and the pyramidal tracts may also occur.[5,6] Muscular weakness may increase over a period of several weeks or months; recovery may take months or years and in 25–30% of cases, permanent residual effects remain, usually confined to the lower limbs.[3,5] Gait impairment, characterized by high steps and footdrop and permanent in some, was called "Jake Walk."[2]

Fatalities are rare and occur principally in those who have taken large quantities in a short period of time; autopsy of six human cases revealed involvement of anterior horn cells and demyelination of nerve cells.[4] The lethal dose for humans by ingestion is about 1.0 g/kg; severe paralysis has been produced by ingestion of 6–7 mg/kg.[4]

In workers engaged in the manufacture of aryl phosphates (including up to 20% TOCP) and exposed to concentrations of aryl phosphates at 0.2–3.4 mg/m^3, there was some inhibition of plasma cholinesterase but no correlation of this effect with degree of exposure or with minor gastrointestinal or neuromuscular symptoms.[7,8] No effects on the eyes or skin have been reported; TOCP is readily absorbed through the skin without local irritant effects.

In affected cats and hens, extensive damage is observed in the spinal cord and sciatic nerves; damage to the myelin sheath and Schwann cells

is secondary to the destructive lesion in the axon, which starts at the distal end of the longer axons.[9]

No evidence of teratogenic effects was observed in the offspring of rats orally dosed with 90, 175, or 350 mg/kg/day on gestation days 6 through 18.[10] TOCP is, however, a reproductive toxin in male rats, causing testicular toxicity and decreased fertility.[11] With the administration of 150 mg TOCP/kg/day by gavage there was an increase in the number of necrotic spermatids, and by day 14, 90% of the seminiferous tubules were devoid of sperm.[12] Atrophy of the seminiferous tubules also occurred in male rats fed 6600 or 13,000 ppm of a mixed isomer of tricresyl phosphate for 13 weeks.[13]

In chronic 2-year feeding studies of the mixed isomer, there was no evidence of carcinogenicity in rats given up to 300 ppm or mice given up to 250 ppm in the diet.[13] Tricresyl phosphate was not mutagenic in *Salmonella typhimurium*, nor did it induce chromosomal aberrations or sister chromatid exchange in Chinese hamster ovary cells.[13]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for triorthocresyl phosphate is 0.1 mg/m^3 with a notation for skin absorption.

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TRIPHENYL AMINE
CAS: 603-34-9

$(C_6H_5)_3N$

Synonyms: N,N-diphenylaniline; *N,N*-diphenylbenzenamine; triphenylamine

Physical Form. Colorless crystalline solid

Uses. It is coated on photographic film, where it acts as photoconductor.

Exposure. Inhalation

Toxicology. Triphenyl amine is considered to have low systemic toxicity, but it may act as a slight skin irritant.

Adverse effects have not been reported in humans.[1]

In rats the oral LD_{50} was between 3200 and 6400 mg/kg. Clinical signs were unremarkable, with death delayed up to 11 days. In mice the LD_{50} ranged between 1600 and 3200 mg/kg, with deaths delayed up to 2 days.

Applied to the skin of guinea pigs for 24 hours, a 10% solution caused only slight erythema at 10–20 ml/kg whereas 5 ml/kg caused no effect. There was no evidence of systemic toxicity after topical application. Triphenyl amine was not a skin sensitizer, as determined by repeated application of a 0.1 M solution to guinea pigs.

Triphenyl amine was not mutagenic in bacterial assays with or without metabolic activation.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for triphenyl amine is 5 mg/m^3.

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TRIPHENYL PHOSPHATE

CAS: 115-86-6

$(C_6H_5O)_3PO_4$

Synonyms: TPP; Celluflex TP; Phosflex TPP

Physical Form. Colorless crystalline powder

Uses. Noncombustible substitute for camphor in celluloid; impregnating roofing paper; plasticizer in lacquers and varnishes.

Exposure. Inhalation

Toxicology. Triphenyl phosphate is of low toxicity in humans.

A group of 16 workers exposed to vapor, mist, or dust at an average concentration of 3.5 mg/m^3, and occasionally as high as 40 mg/m^3, for 8–10 years exhibited no signs of illness; the only positive finding was a slight but statistically significant reduction in erythrocyte cholinesterase activity.[1] In workers engaged in the manufacture of aryl phosphates (including triphenyl phosphates and up to 20% tri-*o*-cresyl phosphate) and exposed to concentrations of aryl phosphates of 0.2–3.4 mg/m^3, there was some inhibition of plasma cholinesterase but no correlation of this effect with degree of exposure or with minor gastrointestinal or neuromuscular symptoms.[2,3]

Anecdotal cases of contact dermatitis from triphenyl phosphate have been reported.[4] A positive patch test to 5% triphenyl phosphate occurred in a hobby worker who worked with a plastic glue and had symptoms of psoriasiform dermatitis of both palms.

Two of six cats given a single intraperitoneal injection of triphenyl phosphate at 0.1–0.5 g/kg developed paralysis after 16–18 days.[1] The effects of triphenyl phosphate on the eye have not been reported; application in ethanol to the skin of mice produced no more irritation than was expected from the solvent.[1]

Triphenyl phosphate was not teratogenic or maternally toxic when fed to rats from 4 weeks after weaning for 91 days, through mating and gestation, at levels of up to 1% of the diet.[5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for triphenyl phosphate is 3 mg/m^3.

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TRIPHENYL PHOSPHITE

CAS: 101-02-0

$P(O\text{-}C_6H_5)_3$

Synonyms: Phenyl phosphite; triphenoxyphosphine; TPP

Physical Form. Water-white to pale yellow, solid (below 22°C) or oily liquid

Uses. Stabilizer/antioxidant for vinyl plastics and polyethylene, polypropylene, styrene copolymers, and rubber

Exposure. Inhalation

Toxicology. Triphenyl phosphite (TPP) is a skin irritant and sensitizer in humans and is neurotoxic in laboratory animals.

Systemic effects have not been reported in humans.

In an early study in rats, subcutaneous injections of triphenyl phosphite caused two distinct stages of neurotoxic action.[1] The early, rapidly developing stage was characterized by fine or coarse tremor, usually involving the large muscle groups. The tremor disappeared in surviving animals within a few hours. The later stage occurred several days after treatment and was characterized by hyperexcitability, some spasticity, and incoordination, followed by partial flaccid paralysis of the extremities. The posterior extremities were usually more affected.

In the same study, cats received a one-time subcutaneous injection of 0.1, 0.2, 0.3, or 0.5 mg/kg. At the lower doses, the compound produced ataxia and paresis of the extremities after several days. The intermediate dose (0.3 ml/kg) was eventually lethal in two animals and produced rapidly progressing ataxia on day 6 followed in 1–2 days by extensor rigidity. The highest dose (0.5 ml/kg) produced death within 30 hours.

In a later report, rats were injected with two 1.0 ml/kg (1184 mg/kg) subcutaneous injections spaced 1 week apart and were euthanized after the second injection.[2] Dysfunctional changes, including tail rigidity, circling, and hind limb paralysis were noted. However, the pattern of triphenyl phosphite-induced spinal cord damage in conjunction with marginal neurotoxic esterase inhibition suggested that this toxic neuropathy differed from those previously described for organophosphorus-induced delayed neuropathy (OPIDN). Follow-up studies of the central nervous system of rats found widespread axonal and terminal degeneration involving not only spinal cord and brain stem, as is the case with other organophosphorus compounds, but also the midbrain, thalamus, and cerebral cortex.[3] Subcutaneous injection of triphenyl phosphite in the hen also produced patterns of severe and widespread central nervous system neuropathology including damage to the spinal cord, brain stem, and other higher-order centers responsible for sensorimotor, visual, and auditory information.[4]

Interperitoneal injection of rats at doses insufficient to produce clinical signs of neurotoxicity did cause reduction in T-maze spatial alternation scores. The authors concluded that acute TPP administration has a persistent effect on the neural systems required for spatial alternation learning in rats.[5]

Applied to human skin in patch tests, triphenyl phosphite diluted 1:3 with cold cream

produced slight irritation in two-thirds of volunteers tested after a 48-hour contact time. A challenge with the compound 14 days later produced a moderate sensitization reaction.[6] When applied to the skin of laboratory animals, the undiluted chemical was severely irritating and produced moderate sensitization. Instillation of 0.1 ml of triphenyl phosphite into the eyes of rabbits did not produce primary eye irritation.[7] However, another report lists triphenyl phosphite as an eye irritant.[8]

The ACGIH has not established a threshold limit value (TLV) for triphenyl phosphite.

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TUNGSTEN (and Compounds)
CAS: 7440-33-7

W

Synonyms: Wolfram

Compounds. Tungsten carbide, tungsten sulfide, tungsten carbonyl, tungsten chloride, tungsten fluoride, tungsten oxychloride, tungsten silicide, tungsten oxide, tungstic acid, various tungstates

Physical Form. Gray hard, brittle metal

Uses. Ferrous and nonferrous alloys, filaments in incandescent lamps, heating elements, welding electrodes, manufacture of abrasives and tools, manufacture of textiles and ceramics

Exposure. Inhalation

Toxicology. The soluble compounds of tungsten are distinctly more toxic than the insoluble forms.

Tungsten and tungsten carbide are considered inert dusts. Tungsten metal and tungsten carbide have not appeared to exert a significant effect on the respiratory system. Studies in a number of factories producing tungsten carbide products have found increased incidence of pulmonary fibrosis. This "hard-metal disease," however, is thought to be related to cobalt exposure, with which tungsten carbide is fused. It has been suggested that tungsten carbide might enhance the solubility of cobalt in protein-containing fluid.[1] A study by Russian investigators reportedly indicated an incidence of pulmonary fibrosis of 9–11% among employees exposed to tungsten and not cobalt, but no details are available.[2]

More recently, tungsten oxide fibers have been detected in a hard metal production plant.[3] Subsequent *in vitro* experiments showed that the tungsten oxide fibers were cytotoxic to human lung cells. The role of tungsten in the development of hard metal dust pulmonary fibrosis remains unclear.

No allergic reactions to tungstate were observed in patch testing of 853 individuals who were working or had worked with tungsten carbide in hard metal manufacture. Irritant pustular reactions appeared in 2% of the patch tests.[4]

No acute effects were produced in rats after intratracheal injection with 5% suspensions of metallic tungsten powder and of tungsten carbide. After intratracheal installation of tungsten carbide, no cellular reaction (other than that expected from an inert dust) was observed in rats during an 18-week follow-up period.[1] Focal interstitial pneumonitis and bronchiolitis was observed in guinea pigs after intratracheal injection of tungsten metal in three 50-mg doses. Near-complete recovery was observed after 1 year. Only negligible reactions were observed after the same treatment with tungsten carbide dust.[1] Inserted into rabbit eyes for 1 year, tungsten caused no reaction and was classified as completely inert.[5]

There are no reports of occupational exposure to soluble compounds of tungsten, but they show considerable systemic toxicity in animal experiments.[2] The LD_{50} of sodium tungstate by subcutaneous injection in rats is 140–160 mg/kg as tungsten. Both sodium tungstate and tungsten oxide were lethal to rats fed a diet containing 0.5% as tungsten. Guinea pigs treated orally or intravenously with tungsten or sodium tungstate experienced anorexia, colic, weight loss, incoordination, trembling, and dyspnea, before a delayed death.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for tungsten is 1 mg/m^3, as W for soluble compounds, with a short-term excursion limit (STEL) of 3 mg/m^3, and 5 mg/m^3 as W for insoluble compounds with a STEL of 10 mg/m^3.

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TURPENTINE
CAS: 8006-64-2

$C_{10}H_{16}$

Synonyms: Spirit of turpentine; oil of turpentine; wood turpentine

Physical Form. Volatile liquid, colorless or yellow, which is a mixture of natural substances obtained from resinous exudates or resinous wood from living or dead coniferous trees, especially pine trees. The chemical composition can vary with the source and method of derivation, but a typical analysis of turpentine is α-pinene, 82.5%; camphene, 8.7%; β-pinene, 2.1%; unidentified natural turpenes, 6.8%.

Use. Solvent

Exposure. Inhalation; skin absorption; ingestion

Toxicology. Turpentine is a skin and mucous membrane irritant and a central nervous system depressant.

Several human subjects had nose and throat irritation at exposures of 75 ppm for 3–5 minutes; 175 ppm was intolerable to the major-

ity.[1] Although often reported in the older literature, toxic nephrosis characterized by albuminuria, dysuria, hematuria, and glycosuria is seldom seen today with turpentine overexposure.[2] The apparent rarity of renal lesions in current poisonings may be related to the change in composition of domestic turpentine; turpentine is now more "pure" because of the removal of a hydroperoxide of delta 3-carene.[2]

By ingestion, the mean lethal dose for humans probably lies between 120 and 180 ml.[2] Symptoms include burning pain in the mouth and throat, abdominal pain, nausea, vomiting, and occasionally diarrhea.[2] Central nervous system effects are excitement, ataxia, confusion, and stupor. Convulsions may occur several hours after ingestion. Fever and tachycardia are common, and death is usually attributed to respiratory failure.[2]

The liquid may cause conjunctivitis and corneal burns.[3]

Turpentine from any source is a skin irritant if allowed to remain in contact for a sufficient length of time; hypersensitivity occurs in some persons.[3] A study of nearly 85,000 patients between 1979 and 1988 from five different countries found that fewer than 1.8% had positive patch tests to 10% turpentine in oil.[4] The liquid can be absorbed by the skin and mucous membranes, and intoxication by this route has been reported.[2]

There are no specific reports on turpentine carcinogenicity or mutagenicity.[5] However, in one case control study, paternal exposure to turpentine was one of several substances associated with an increased risk of neuroblastoma in offspring.[6]

The LC_{50} for rats was 3590 ppm for 1 hour and 2150 ppm for 6 hours; hyperpnea, ataxia, tremor, and convulsions were noted.[7] Mucous membrane irritation, particularly of the eyes, and mild convulsions were observed in cats exposed to 540–720 ppm for a few hours.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for turpentine is 100 ppm (556 mg/m^3).

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URANIUM
CAS: 7440-61-1

U

Synonyms: Soluble: Uranyl nitrate, uranyl fluoride, uranium hexafluoride; insoluble: uranium dioxide, uranium tetrafluoride

Physical Form. Solids

Uses. Nuclear fuel and in weapons systems; used in photography; as a catalyst

Exposure. Inhalation

Toxicology. Uranium is a weakly radioactive alpha-emitting heavy metal that exists in several isotopic forms. Insoluble compounds

of uranium are respiratory irritants, whereas soluble compounds are also toxic to the kidneys.

Soluble Compounds: Animals repeatedly exposed to dusts of soluble uranium compounds in concentrations from 3 to 20 mg/m^3 died of pulmonary and renal damage; both feeding and percutaneous toxicity studies on animals indicated that the more soluble compounds are the most toxic.[1] In animals, effects on the liver are a consequence of the acidosis and azotemia induced by renal dysfunction.[1]

Animal studies indicate that the primary toxic effect of uranium exposure is on the kidney, with particular damage to the proximal tubules. Functionally, this may result in increased excretion of glucose and amino acids. Structurally the necrosis of tubular epithelium leads to formation of cellular casts in the urine. If exposure is insufficient to cause death from renal failure, the tubular lesion is reversible with epithelial regeneration. Although bone is the other major site of deposition, there is no evidence of toxic or radiocarcinogenic effects to bone or bone marrow from experimental studies.[2]

Insoluble Compounds: These compounds are generally considered to be less toxic than the soluble compounds.[3] Repeated exposures of three animal species to uranium dioxide dust at a concentration of 5 mg uranium/m^3 for periods up to 5 years resulted in no kidney injury. More than 90% of the uranium found in the body was in the lungs and tracheobronchial lymph nodes (TLN).[2] Fibrotic changes suggestive of radiation injury was seen occasionally in the TLN of dogs and monkeys and in the lungs of monkeys after exposure periods longer than 3 years; the estimated alpha dose to tissues was greater than 500 rads for lungs and 7000 rads for TLN.[4]

Uranium: A number of studies document no lung cancers solely from inhaled uranium-bearing dust. It is generally accepted that lung cancers developed subsequent to inhalation of uranium-containing dusts were due to radon daughters and long-term cigarette smoking, and not due to uranium metallotoxicity or uranium radioactive emissions.[3,5] In some mining cohorts part of the lung cancer excess has also been attributed to arsenic exposure that occurred in men who worked in both uranium and gold mines.[6]

In a group of uranium mill workers, there was an excess of deaths from malignant disease of lymphatic and hematopoietic tissue; data from animal experiments suggested that this excess may have resulted from irradiation of lymph nodes by thorium-230, a disintegration product of uranium.[5] Some absorbed uranium is deposited in bone. A potential risk of radiation effects on bone marrow has been postulated, but extensive clinical studies on exposed workers have disclosed no hematologic abnormalities.[7,8]

Accidental exposure of workers to a mixture of uranium hexafluoride, uranyl fluoride, hydrofluoric acid, and live steam caused lacrimation, conjunctivitis, shortness of breath, paroxysmal cough, rales in the chest, nausea, vomiting, skin burns, transitory albuminuria, and elevation of blood urea nitrogen.[7] Two deaths occurred among the most heavily exposed workers shortly after exposure. The persons having the greatest exposure showed the highest urinary uranium levels. In addition, their urinary abnormalities were the most severe, including albuminuria plus red blood cells and casts in the urinary sediment, and blood urea nitrogen remained elevated for several weeks. The injurious effects observed on the skin, eyes, and respiratory tract were apparently caused by the irritant action of the hydrofluoric acid, whereas the uranium was believed to be responsible for the transient renal changes.

No evidence of chronic toxicity, either chemical or radiation, was observed for any uranium compound during the first 6 years of the atomic energy program; all exposed workers were under very close medical surveillance.[1]

Several uranium compounds tested on the eyes of animals caused severe eye damage as well as systemic poisoning. The anion and its hydrolysis products determine the degree of injury.[9,10] A hot nitric acid solution of uranyl nitrate spilled on the skin caused skin burns, nephritis, and heavy metal encephalopathy.[9] Prolonged skin contact with uranium com-

pounds should be avoided because of potential radiation damage to basal cells. Dermatitis has occurred as a result of handling uranium hexafluoride.[9]

In genotoxic assays, significant increases in frequencies of chromosomal aberrations in peripheral lymphocytes have been reported in uranium miners.[3] This effect has been attributed to radon daughter products and more recently to mutagenic mycotoxins produced by molds present in the uranium mines.[11]

Oral administration of 3 mg uranium/kg/day as uranyl acetate dihydrate to pregnant mice on gestation days 6–15 caused an increase in fetotoxicity (stunted fetuses, external and skeletal malformations, and developmental variations) and maternal toxicity.[12] In reproductive studies, no adverse effects were observed in testicular function or spermatogenesis in male mice treated with up to 80 mg/kg/day uranyl acetate dihydrate for 64 days.[13]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for uranium (soluble and insoluble compounds, as U) is 0.2 mg/m^3 with a short-term excursion limit (STEL) of 0.6 mg/m^3.

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USED MINERAL-BASED CRANKCASE OIL

Synonyms: Used motor oil; used engine oil

Physical Form. brown to black oily liquid; new mineral-based crankcase oil contains petrochemicals (straight-chain hydrocarbons, aromatic hydrocarbons, and polyaromatic hydrocarbons or PAH) plus stabilizers and detergents including zinc dithiophosphate, zinc diaryl or dialkyl dithiophosphates (ZTDP), calcium alkyl phenates, magnesium, sodium, and calcium sulfonates, tricresyl phosphates, molybdenum disulfide, heavy metal soaps, cadmium, and zinc.[1]

In a crankcase-lubricated engine, the oil compartment acts as a sink for heavy molecular incomplete combustion products such as PAH, which can be present at up to 1000 times original concentrations.[2] The lubricating oil is altered by nitration, cracking of polymers,

oxidation, and decomposition of organometallic compounds. It contains metals such as aluminum, cadmium, chromium, copper, iron, lead, manganese, nickel, silicon, tin, and zinc that come from engine parts that wear down. It also contains small amounts of water, gasoline, antifreeze, and chemicals that come from gasoline as it burns inside the engine.

Uses. Used mineral-based crankcase oil is mixed with other oils to produce cutting oils or other lubricating oils. It is incinerated for energy in oil burners in homes, industrial steam boilers, municipal incinerators, and rotary cement kilns. It is also used in asphalt production.

Exposure. Skin contact and absorption; inhalation

Toxicology. Used mineral-based crankcase oil poses a primary risk of skin cancer from frequent and prolonged contact and is minimally irritating to the respiratory tract.

Several studies have examined the dermal carcinogenicity of used mineral-based crankcase oil in mice.[3–7] These studies have shown that the incidence of dermal papillomas and carcinomas in male (C3H/HEJ) and female (CFLP) mice is increased after chronic dermal exposure to used mineral-based crankcase oil from gasoline-powered automobiles. The greatest tumor incidence was observed in mice exposed to oil from cars driven the longest distance, and the tumor incidence correlated to the PAH content.[7] No tumors were observed in mice exposed to unused motor oil.[3,7] Fractionation of the oil showed tumor induction only with the fraction containing PAH with more than three rings.[4–6] In contrast to used mineral-based crankcase oil from gasoline-powered automobiles, oil from diesel-powered automobiles showed no increase in tumors, even when the automobiles were driven extremely long distances before removal of the crankcase oil.[7]

Increased cancer mortality has been associated with exposure to the PAH present in used metal-work cutting oils and mineral oils.[8–11] The carcinogenic potential of these complex mixtures was related to their PAH content, primarily, but not totally, to benzo[*a*]pyrene content.

Inhalation studies in humans suggest that used mineral-based crankcase oil is minimally irritating to the tissues of the respiratory tract, but exposure levels were not well described.[12]

The ACGIH has not established a threshold limit value for used mineral-based crankcase oil.

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n-VALERALDEHYDE

CAS: 110-62-3

$C_5H_{10}O$

Synonyms: Amyl aldehyde; butyl formal; pentanal; valeric aldehyde

Physical Form. Colorless liquid

Uses. In food flavorings and in the acceleration of rubber vulcanization

Exposure. Inhalation; ingestion

Toxicology. *n*-Valeraldehyde has low systemic toxicity but is considered an eye and skin irritant.

No effects from exposure have been reported in humans.

The oral LD_{50} for rats was 4.6 g/kg, and the rabbit dermal LD_{50} was 4.9 g/kg.[1] Three of six rats succumbed to 4 hours of exposure at 4000 ppm. Ten-hour exposure at 670 ppm caused some deaths in mice and guinea pigs but not in rabbits.[2] Mice exposed in a head-only exposure chamber at 1100 ppm for 10 minutes had a 50% decrease in respiratory rate.[3]

Applied to the rabbit eye or guinea pig skin the liquid was severely irritating.

n-Valeraldehyde caused chromosomal and DNA effects in mammalian cells in culture but was not mutagenic in an Ames bacterial test.[4]

An odor threshold of 0.028 ppm has been reported.[5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for *n*-valeraldehyde is 50 ppm (176 mg/m^3).

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VANADIUM PENTOXIDE

CAS: 1314-62-1

V_2O_5

Synonyms: Vanadic anhydride; divanadium pentoxide; vanadium oxide; vanadic acid

Physical Form. Yellow-red or green crystals

Uses. In the production of high-strength steel alloys; catalyst in oxidation reactions; in pesticides; in dyes and inks

Exposure. Inhalation

Toxicology. Vanadium pentoxide primarily affects the respiratory system.

The fume is recognized as being generally more toxic than dust because of the smaller

particle size of fume, which allows more complete penetration to the small airways of the lungs.

Sixteen workers exposed to concentrations of dust (and possibly some fume) in excess of 0.5 mg/m^3 with particle sizes ranging from 0.1 µ to 10 µ developed conjunctivitis, nasopharyngitis, hacking cough, fine rales, and wheezing. In three workers exposed to the highest concentrations, the onset of symptoms occurred at the end of the first workday.[1] The bronchospastic element in the more seriously ill persisted for 48 hours after removal from exposure; rales lasted for 3–7 days, and, in several cases, cough lasted for up to 14 days.[1] Among those with acute intoxication, there was dramatically increased severity of symptoms from repeated exposures of lesser time and intensity.

Absorbed vanadium is primarily excreted in the urine, and it was detectable in 12 of the workers for periods of up to 2 weeks. Urinary vanadium concentrations were elevated in workers exposed to mean air concentrations of 0.1–0.28 mg/m^3, but there was no correlation between the air and urinary concentrations. Although most absorbed vanadium was excreted within 1 day after cessation of exposure, increased excretion relative to unexposed controls continued for more than 2 weeks among chronically exposed workers.[2]

Workers exposed to a mixture of ammonium metavanadate and vanadium pentoxide at concentrations near 0.25 mg/m^3 developed green tongue, metallic taste, throat irritation, and cough.[3] Of 36 workers examined 8 years after their original exposure to vanadium pentoxide, there was no evidence of either pneumoconiosis or emphysema, although 6 of the workers still had bronchitis with rhonchi resembling asthma and bouts of dyspnea.[4]

Two volunteers exposed to a concentration of 1 mg/m^3 for 8 hours developed a persistent cough, which lasted for 8 days; 21 days after the original exposure, reexposure for 5 minutes to a heavy cloud of vanadium pentoxide dust occurred and, within 16 hours, marked cough developed; the following day, rales and expiratory wheezes were present throughout the entire lung field, but pulmonary function was normal.[5] Subjects exposed to a concentration of 0.2 mg/m^3 for 8 hours developed a loose cough the following morning; other subjects exposed for 8 hours to 0.1 mg/m^3 developed slight cough with increased mucus, which lasted 3–4 days.

Although some cases of emphysema have been observed among workers with exposure to vanadium pentoxide, other possible causes, such as smoking, were not excluded. Cases of asthma have occurred more frequently, suggesting that this may be an effect of chronic exposure.[3]

Animal studies in cynomolgus monkeys have not found evidence of increased pulmonary reactivity to vanadium pentoxide after repeated exposures; cytological/immunologic and skin test results also indicated the absence of allergic sensitization.[6]

Exposure to the dust can cause eye irritation, and skin rashes have been reported. Green discoloration of the tongue may occur as a result of direct deposition of vanadium.[7]

No adverse effects on fertility, reproduction, or parturition were found when male and female rats were treated with sodium metavanadate by gavage and then mated.[8]

Male and female mice exposed at concentrations up to 4 mg/m^3 6 hours/day for 104 weeks had clear evidence of carcinogenicity based on increased incidences of alveolar/bronchiolar neoplasms.[9] In rats similarly exposed at concentrations up to 2 mg/m^3 there was some evidence of carcinogenicity in male rats and equivocal evidence in females based on the occurrence of alveolar/bronchiolar neoplasms. Exposure to vanadium pentoxide also caused a spectrum of nonneoplastic lesions in the respiratory tract including alveolar and bronchiolar epithelial hyperplasia, inflammation, fibrosis, and alveolar histocytosis of the lung. Hyperplasia of the bronchial lymph node occurred in female mice, and an unusual squamous metaplasia of the lung occurred in rats.[9]

Vanadium pentoxide was not mutagenic in *Salmonella* strains and did not increase the frequency of micronucleated erythrocytes in mice.[9] In other studies vanadium compounds have produced clear evidence of aneuploidy in somatic cells after exposure by several different routes.[10]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for vanadium pentoxide is 0.05 mg/m^3 as respirable dust or fume.

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VINYL ACETATE
CAS: 108-05-4

$C_4H_6O_2$

Synonyms: 1-Acetoxyethylene; acetic acid ethenyl ester; ethanoic acid; ethenyl ethanoate; vinyl ethanoate

Physical Form. Colorless liquid that polymerizes to a transparent solid on exposure to light

Uses. Production of vinyl acetate polymers

Exposure. Inhalation

Toxicology. Vinyl acetate is an irritant of the eyes, nose, and throat; it is carcinogenic in experimental animals at high doses.

Volunteers exposed to vinyl acetate showed a wide variation in individual sensitivity to its irritant effects; one of three had throat irritation at 20 ppm for 4 hours, whereas 72 ppm for 30 minutes produced eye irritation in three of four participants.[1] All subjects agreed that they could not work at 72 ppm for 8 hours.

From a study of 21 workers exposed for an average of 15 years at concentrations between 5 and 10 ppm (with occasional excursions above 300 ppm), vinyl acetate produced no serious chronic effects.[2] Some subjects were sensitive at concentrations of about 6 ppm, and concentrations above 20 ppm produced irritation in most persons.

Prolonged dermal contact, such as that afforded by clothing wet with vinyl acetate, may result in severe irritation or blistering of the skin in some persons.[1] Direct eye contact with the liquid or vapor can cause irritation of the eyes.[3]

The LC_{50} for 4 hours in rats was 14,000 mg/m^3 (about 4667 ppm).[4] Dogs exposed 6 hours daily for several weeks starting at 91 ppm and ending after 11 weeks at 186 ppm exhibited eye irritation and lacrimation.[5] Rats exposed repeatedly to 100 ppm showed no effects.[6]

Rats administered 0, 200, 1000, or 5000 ppm in the drinking water from the time of gestation up to 104 weeks showed no evidence of systemic organ toxicity and/or carcinogenicity.[7] Decreased food consumption and concurrent body weight decrement was observed in the high-dose group. In rats and mice exposed at 0, 50, 200, or 600 ppm by inhalation for 2 years, significant histopathologic changes were noted in the nasal cavity at the two highest dose levels.[8] Epithelial atrophy, basal cell hyperplasia, and regenerative effects (squamous metaplasia and respiratory metaplasia of the olfactory epithelium) were observed in both species. In rats the total tumor incidence in the high-exposure group was 9% and included papillomas, squamous cell carcinoma, and carcinoma in situ in olfactory regions and papillomas of the respiratory region. It has been noted that the unique nature, both structurally and functionally, of the rodent nasal cavity may make it an unsuitable model for assessing human risk. More recently, vinyl acetate monomer was shown to be a multipotential carcinogen in mice administered up to 5000 ppm in the drinking water for 78 weeks; zymbal gland, lung, uterine, oral cavity, tongue, esophageal, and forestomach cancers were increased.[9]

One human study of workers in a US synthetic chemical plant failed to find any specific association between exposure to vinyl acetate and excess lung cancer.[10]

Vinyl acetate has been tested for teratogenicity in inhalation and oral assays.[3] Pregnant rats exposed to levels as high as 1000 ppm by inhalation or 5000 ppm in drinking water on gestation days 6–15 had significantly reduced weight gain during exposure. The fetuses of the rats exposed via inhalation were also significantly smaller than control fetuses and had an increased incidence of minor skeletal defects. However, investigators thought that the fetal effects were a consequence of the maternal growth retardation, and not of vinyl acetate treatment. In the drinking water study, there were no significant effects on the fetuses, and the investigators concluded that vinyl acetate did not elicit embryolethality, embryotoxicity, or teratogenicity. Rats administered up to 5000 ppm vinyl acetate in the drinking water over two generations did not show selective reproductive effects.[11]

Vinyl acetate was genotoxic in a number of mammalian system assays, inducing micronuclei, chromosomal aberrations, sister chromatid exchange, and DNA cross-links.[3] It has also been noted that the primary metabolite of vinyl acetate, acetaldehyde, is genotoxic in a wide range of assays.

The IARC has determined that there is limited evidence in experimental animals and inadequate evidence in humans for the carcinogenicity of vinyl acetate.[12]

The ACGIH threshold limit value-time-weighted average (TLV-TWA) for vinyl acetate is 10 ppm (35 mg/m^3) with a short-term excursion level (STEL) of 15 ppm (53 mg/m^3) and an A3-confirmed animal carcinogen with unknown relevance to humans designation.

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VINYL BROMIDE

CAS: 593-60-2

C_2H_3Br

Synonyms: Bromoethene; bromoethylene

Physical Form. Gas

Uses. Production of flame-resistant plastics or thermoplastic resins

Exposure. Inhalation

Toxicology. Vinyl bromide causes central nervous system depression in animals at high levels and is carcinogenic in rats.

There are no data on human exposures.

Exposure of rats to 100,000 ppm for 15 minutes resulted in deep anesthesia and death.[1] Exposure to 50,000 ppm caused anesthesia in 25 minutes and was lethal after exposure for 7 hours.

A significant decline in animal body weights was the only treatment-related effect after exposure at 10,000 ppm, 7 hours/day for 4 weeks. In a 6-month inhalation study in a number of species, serum bromide levels increased after exposure to 250 and 500 ppm.

In male and female rats exposed to 10, 50, 250, or 1250 ppm vinyl bromide in a lifetime inhalation study, there was a dose-related increase in angiosarcomas of the liver in both sexes.[2] A significant increase in hepatocellular neoplasms was also seen in male rats exposed at 250 ppm and in female rats exposed at 10, 50, and 250 ppm. The lack of increase in hepatocellular neoplasms in rats at the 1250 ppm level was probably due to their early mortality and termination at 72 weeks. In limited mice studies, no local tumors were produced by skin application or subcutaneous administration.[3]

Vinyl bromide is mutagenic in bacterial assays and *Drosophila*.[3] It is activated via a P-450-dependent pathway to its epoxide that can covalently bind to DNA.[3]

The IARC has determined that there is sufficient evidence for the carcinogenicity of vinyl bromide to experimental animals and that it is probably carcinogenic to humans.[3]

The liquid was moderately irritating to the rabbit eye but essentially nonirritating to the skin.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for vinyl bromide is 0.5 ppm (2.2 mg/m^3) with an A2-suspected human carcinogen designation.

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VINYL CHLORIDE
CAS: 75-01-4

C_2H_3Cl

Synonyms: Chlorethene; chloroethylene; ethylene monochloride

Physical Form. A colorless gas, but usually handled as a liquid under pressure

Uses. Production of polyvinyl chloride resins; organic synthesis

Exposure. Inhalation

Toxicology. Occupational exposure to vinyl chloride is associated with an increased incidence of angiosarcoma of the liver and other malignant tumors, acroosteolysis, Raynaud syndrome, scleroderma, thrombocytopenia, circulatory disturbances, and impaired liver function. Very high concentrations cause central nervous system (CNS) depression.

Vinyl chloride, at sufficiently high levels (probably above 100,000 ppm based on animal experiments), may be fatal to humans after inhalation exposure.[1] Humans exposed to 20,000 ppm for 5 minutes experienced dizziness, light-headedness, nausea, and dulling of vision and auditory cues.[2] For 5-minute exposures, 8000 ppm caused some dizziness whereas 4000 ppm was without effect. Longer exposures at 1000 ppm may cause drowsiness, faltering gait, visual disturbances, and numbness and tingling in the extremities.[3]

Chronic exposure to high levels of vinyl chloride vapor has resulted in a syndrome termed vinyl chloride disease, which includes the following symptoms: enhanced collagen deposition and thickening of the subepidermal layer of the skin; Raynaud phenomenon (arteriole constriction causing whitening of the fingers and numbness); and in some cases, acroosteolysis (resorption of the terminal phalanges).[1] Raynaud phenomenon was often the first manifestation noted by a majority of subjects with vinyl chloride disease, suggesting that the vascular lesion anteceded the bone changes in most cases.[4] Radiological findings in patients with acroosteolysis included lytic lesions in the distal phalanges of the hands, in the styloid processes of the ulna and radius, and in the sacroiliac joints.[4] Vinyl chloride disease has been associated with exposure to several hundred ppm for periods ranging from months to years; no new cases have been reported in the US since 1974, when occupational exposure levels were reduced to 1 ppm.[1] Other effects in exposed workers include thrombocytopenia, hepatic changes including hypertrophy and hyperplasia of hepatocytes and fibrosis, and increased levels of circulating immune complexes.[1]

Of 20 autoclave cleaners with exposure to vinyl chloride, 16 had thrombocytopenia, 7 had splenomegaly, 6 had hepatomegaly, 4 had fibrosis of the liver capsule, and 4 had signs of acroosteolysis.[5]

Vinyl chloride has been associated with cancer in humans in a number of epidemiological studies. In four facilities engaged in the polymerization of vinyl chloride for at least 15 years, workers exposed for at least 5 years had a significant number of excess deaths due to malignant neoplasms (35 deaths observed, 23.5 expected).[6] The excesses were found for four organ systems: CNS (3 observed, 0.9 expected), respiratory system (12 observed, 7.7 expected); hepatic system (7 observed, 0.6 expected), and lymphatic and hematopoietic systems (4 observed, 2.5 expected).

By 1975, over 30 cases of angiosarcoma of the liver had been reported among vinyl chloride polymerization workers in the US and nine other nations.[7] Because this tumor is extremely rare, the occurrence of these cases under similar occupational conditions strongly suggests a causal relationship to some phase of vinyl chloride production.[8] Clinical features of seven patients with the malignancy varied from no signs or symptoms to weakness, pleuritic pain, abdominal pain, weight loss, gastrointestinal bleeding, and hepatosplenomegaly. Liver function abnormalities were present in all subjects, but without a consistent pattern.[8] In addition to the malignant tumors, four cases of nonmalignant hepatic disease characterized by

portal fibrosis and portal hypertension have been attributed to vinyl chloride exposure.[8]

A large multicentric cohort study of European vinyl chloride workers revealed a nearly threefold increase in liver cancer based on 24 observed deaths vs. 8.4 expected. The excess was clearly related to time since first exposure, duration of employment, and estimated ranked and quantitative exposures.[9] A cohort study of 10,173 US men who had worked at least 1 year in jobs involving exposure to vinyl chloride confirmed a significant mortality excess in angiosarcoma (15 deaths), cancer of the liver and bilary tract [standardized mortality ratio (SMR) = 641], and cancer of central nervous system (SMR = 180).[10] A recent follow-up of this cohort found that excess mortality risk from cancer of the liver and biliary tract, largely due to angiosarcoma, continued; risk of mortality from brain cancer had attenuated; and excess of deaths from cancer of connective and soft tissue appeared for the first time but was based on few cancers of assorted histology.[11]

The tumorigenic potential of vinyl chloride has been confirmed in a number of animal studies. Zymbal gland carcinomas, nephroblastomas, and angiosarcomas were the prevailing tumors in treated rats. Results ranged from a 16% tumor incidence at an exposure level of 250 ppm to a 39% incidence at 10,000 ppm. In mice, liver angiosarcomas, pulmonary adenomas, and mammary carcinomas were observed after exposures ranging from 50 to 10,000 ppm.[12] The development of some tumors was more dependent on duration of exposure than on concentration of vinyl chloride.[12]

Vinyl chloride was genotoxic in a variety of *in vitro* assays.[1] It is also reportedly mutagenic and clastogenic in humans. Increased frequencies of chromosomal aberrations, micronuclei, and sister chromatid exchanges have been found in the peripheral blood lymphocytes of workers exposed to high levels of vinyl chloride.[13]

The IARC has determined that there is sufficient evidence of carcinogenicity to humans and animals.[14]

Developmental effects in animals, consisting of resorptions, delayed development, and increased incidences of soft tissue anomalies, have generally been observed at doses that produce some maternal toxicity.[1] Testicular damage and decreased male fertility have been found in rats exposed by inhalation. Vinyl chloride workers have complained of impotence and decreased libido, and decreased androgen levels have been measured.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for vinyl chloride is 1 ppm (3 mg/m^3) with an A1-confirmed human carcinogen designation.

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4-VINYLCYCLOHEXENE

CAS: 100-40-3

C_8H_{12}

Synonyms: 4-Ethenylcyclohexene; 1-vinyl-3-cyclohexene; VCH

Physical Form. Colorless liquid

Uses/Sources. As an intermediate in the production of flame retardants, flavors, fragrances, and vinyl cyclohexene dioxide (which itself is used in the manufacture of epoxy resins); found in gases discharged during the process of curing rubber in tire manufacturing.

Exposure. Inhalation; skin absorption

Toxicology. 4-Vinylcyclohexene (VCH) is a moderate skin irritant and causes ovarian toxicity in mice. It is carcinogenic in some animal species when metabolically activated.

In one isolated report, Russian rubber workers exposed to concentrations averaging 271–542 ppm with excursions to 677 ppm were reported to suffer keratitis, rhinitis, headache, leukopenia, neutrophilia, lymphocytosis, and impairment of pigment and carbohydrate metabolism.[1] It is not clear what other confounding chemical exposures may have been concurrent. It has also been noted that these exposure levels contrast significantly with those found in the discharged off-gases to which domestic rubber workers were exposed in the tire-curing process, which measured 118 ppb.[2]

In rats the oral LD_{50} was 2.6 g/kg.[3] Inhalation of 8000 ppm for 4 hours was lethal to four of six rats.[3] The liquid produced moderate irritation when applied to the skin of rabbits and caused a small necrotic area on the cornea when instilled into a rabbit eye.

All rats and most mice died in 14-day studies when administered VCH by gavage in corn oil at doses greater than or equal to 1250 mg/kg/day.[1] Before death, tremors and inactivity were observed in mice, whereas rats showed central nervous system depression, tremors, and gastrointestinal distress. No compound-related gross pathologic or histopathologic effects were observed.

Subchronic inhalation exposure for 13 weeks (6 hours/day, 5 days/week) to 1000 ppm VCH caused mortality in mice but not in rats; the most notable adverse histopathologic effect was ovarian atrophy in exposed female mice.[4]

Final body weights were reduced in 13-week studies in male rats receiving oral doses of 400 mg/kg/day or more, in female rats receiving 800 mg/kg/day, and in female mice receiving 600 mg/kg/day.[1] Compound-related histopathologic effects included hyalin droplet degeneration of the proximal convoluted tubules of the kidney in male rats and a reduction in the number of primary follicles and mature graafian follicles in the ovaries of female mice dosed at the 1200 mg/kg/day level. No compound-related gross pathologic or histopathologic effects were observed in female rats or male mice in this study.

Administration of VCH by oral intubation to rats 5 days/week for 2 years at 0, 200, or 400 mg/kg/day was associated with slightly increased incidence of epithelial hyperplasia of the forestomach and squamous cell papillomas or carcinomas of the skin in high-dose males.[1] Poor survival of the dosed animals may have compromised the study. In mice similarly dosed, the number of uncommon ovarian neo-

plasms and ovarian pathologies was significantly increased in the females and there was some suggestion of increased numbers of adrenal gland adenomas in the high-dose females. Among high-dosed male mice there were scattered instances of lymphomas and cancers of the lung, but, again, poor survival confounded results.

Toxicological studies have suggested that the species specificity for induction of ovarian tumors (produced in mice but not rats) occurs because the blood level of the ovotoxic VCH metabolite VCH-1,2-epoxide is dramatically higher in VCH-treated female mice compared with rats.[5] VCH has been shown to be metabolized by the liver of mice to the ovotoxic metabolite (VCH-1,2-epoxide), which circulates in blood and is delivered to the ovary, where it destroys small oocytes. This destruction of small oocytes is considered to be an early event in carcinogenesis. Species difference in epoxidation of VCH by hepatic microsomes correlates well with the differences observed in the blood concentration of VCH-1,2-epoxide and VCH ovarian toxicity. Further *in vitro* studies have found that the rate of VCH epoxidation in humans by human hepatic microsomes was 13- and 2-fold lower than epoxidation by mouse and rat systems respectively.[6] Therefore, if the rate of hepatic VCH epoxidation is the main factor that determines the ovotoxicity of VCH, rats may be a more appropriate animal model for humans.

In a reproductive study using the continuous breeding protocol, 500 mg/kg/day administered by gavage to mice caused slight generalized toxicity and reduced the number of oocytes by 33% in females and testicular sperm count by 17% in males but did not adversely affect the reproductive competence of F_0 and F_1 generations.[7]

VCH was not mutagenic in *Salmonella typhimurium*; however, several of its metabolites, including 4-vinylcyclohexene dioxide, are genotoxic.[1,8]

The IARC has determined that there is inadequate evidence in humans, but sufficient evidence in animals, for the carcinogenicity of VCH.[8]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for 4-vinylcyclohexene is 0.1 ppm (0.4 mg/m^3) with an A2-suspected human carcinogen designation.

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VINYL CYCLOHEXENE DIOXIDE

CAS: 106-87-6

$C_8H_{12}O_2$

Synonyms: 4-Vinylcyclohexene diepoxide; 1,2-epoxy-4-(epoxyethyl)cyclohexane; 1-epoxyethyl-3,4-epoxycyclohexane; VCD

Physical Form. Colorless or pale yellow liquid

Uses. As a chemical intermediate and as a reactive diluent for diepoxides and epoxy resins.

Exposure. Inhalation; skin absorption

Toxicology. Vinyl cyclohexene dioxide (VCD) is an irritant to the skin, eyes, and respiratory system. It is ovotoxic and carcinogenic in experimental animals.

In humans VCD is considered to be a mild to moderate skin irritant, although occasional instances of marked irritation have been reported. In one case severe vesiculation of the skin of both feet occurred when a worker wore shoes previously contaminated with VCD.[1] A single case of allergic contact dermatitis has also been reported in a worker whose gloves were permeable to VCD.[2] Systemic illness in humans has not been reported in association with exposure.[1]

In rats the inhalation LC_{50} is 800 ppm for 4 hours, and the oral LD_{50} is 2.1 g/kg.[3] Dermal application of the undiluted material to rabbits caused edema and redness equivalent to a moderate first-degree burn. The liquid can penetrate the skin and is more toxic when applied dermally than by other routes. The dermal LD_{50} in rabbits is 0.62 ml/kg body weight.

VCD is an alkylating agent and is selectively active against rapidly dividing cells, such as the blood-forming elements in the bone marrow, lymphoid tissues, and reproductive organs.[4] Immunotoxic effects were observed in mice after 5-day dermal exposures at 10 mg/day.[3] Hematologic studies indicated a significant decrease in the leukocyte count that was related to the decreased numbers of circulating lymphocytes at this same dose. A decrease in the lymphoproliferative response to phytohemagglutinin and concanavalin A and suppression of the antibody plaque-forming cell response indicated that VCD was immunosuppressive.

Repeated intramuscular injections of 400 mg/kg VCD to male rats for 7 days decreased the size of the spleen, thymus, and testis and resulted in enlarged adrenal glands.[4] The leukocyte count fell more than 60%, and the myeloid-to-erythroid ratio was increased.

In 14-day dermal studies, rats receiving 139 mg/rat or higher for males and 112 mg/rat or higher for females died before the end of the treatment period.[3] There was congestion and/or hypoplasia of the bone marrow, and most had acute nephrosis. Skin lesions included epidermal necrosis and ulceration, epidermal hyperplasia, and hyperkeratosis. Male rats receiving 68 mg/rat and females receiving 57 mg/rat had final mean body weights lower than those of control animals; skin lesions were similar to those seen at the higher dose levels but of less severity.

VCD is ovotoxic, causing follicle destruction in both rats and mice.[5] After 30 days of intraperitoneal dosing with 80 mg/kg the number of oocyte-containing primordial and primary follicles was reduced 80% in rats and 92% in mice.

All rats survived dermal doses of up to 60 mg/rat administered over 13 weeks.[3] Mean body weights were up to 14% lower than controls, and redness, scabs, and ulceration occurred at the application site. In mice, applications of up to 10 mg/mouse produced increased liver and kidney weights. Compound-related skin lesions included sebaceous gland hyperplasia and hyperplasia and hyperkeratosis of the stratified squamous epithelium at the site of application; ovarian atrophy was also considered to be compound related.

Two-year studies were conducted by administering VCD in acetone by dermal application 5 days per week for over 100 weeks to groups of rats of each sex at 0, 15, or 30 mg/animal and to groups of mice at 0, 2.5, 5, or 10 mg/animal. Acanthosis and sebaceous gland hypertrophy of skin from the scapula were observed at increased incidences in both species. Squamous cell papillomas in male rats and squamous cell carcinomas in males and females were observed in exposed rats at an increased incidence. The combined incidence of basal cell adenomas or carcinomas was also increased in both sexes. Squamous cell carcinomas were found in the exposed mice. Follicular atrophy and tubular hyperplasia of the

ovary in female mice were increased with increasing dose, and the combined incidences of luteomas, granulosa cell tumors, benign mixed tumors, or malignant granulosa cell tumors in mid- and high-dose female mice were increased. Increased incidences of lung neoplasms in females may also have been related to chemical exposure.

Under the conditions of the study, there was clear evidence of carcinogenicity in rats as shown by squamous cell and basal cell neoplasms of the skin and in mice as shown by squamous cell carcinomas of the skin and ovarian neoplasms in females. No information has been reported on the carcinogenicity of VCD in humans.

A number of early studies also demonstrated the carcinogenicity of VCD in rodents. Dermal application of 16 mg, 5 days per week, for 12 months resulted in squamous cell carcinomas or sarcomas in 9 of 20 exposed male mice.[6] One skin neoplasm and four malignant lymphomas occurred in 16 of 20 mice surviving a total dermal dose of 70 mg over 14 months.[7]

The IARC has determined that there is sufficient evidence in experimental animals and inadequate evidence in humans for the carcinogenicity of VCD.[8]

VCD has been found to be mutagenic in a number of bacterial tester strains in the presence and absence of mammalian microsomal metabolic activation. It induced direct sister chromatid exchange and chromosomal aberrations in cultured Chinese hamster ovary cells.[8]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for vinyl cyclohexene dioxide is 10 ppm (57 mg/m^3) with an A2-suspected human carcinogen designation.

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VINYLIDENE CHLORIDE
CAS: 75-35-4

$C_2H_2Cl_2$

Synonyms: 1,1-Dichloroethylene; VDC; asym-dichloroethylene; 1,1-dichloroethene; 1,1-DCE; vinylidene dichloride

Physical Form. Clear liquid that is highly flammable and reactive and in the presence of air can form complex peroxides in the absence of chemical inhibitors

Uses. Production of copolymers of high vinylidene chloride content, the other major monomer usually being vinyl chloride such as Saran and VELON for films and coatings

Exposure. Inhalation

Toxicology. Vinylidene chloride (VDC) causes central nervous system (CNS) depression at high levels, and repeated exposure to lower concentrations results in liver and kidney damage in experimental animals.

Limited information is available on the human health effects of exposure to VDC.[1] Upper airway irritation consisting of inflammation of mucous membranes has been reported after acute exposure, whereas CNS toxicity has been associated with levels of 4000 ppm.[1]

In male rats, the 4-hour LC_{50} was 6350 ppm.[2] The oral LD_{50} of VDC in corn oil was 1500 mg/kg in male rats.[3] Rats exposed 6 hours/day for 20 days to 200 ppm exhibited only slight nasal irritation.[4]

Results from animal studies indicate that the liver is a primary target for VDC-induced toxicity.[1] Hepatotoxicity following both inhalation and oral exposures has ranged from biochemical changes, including increases in serum enzyme markers of liver dysfunction and induction of hepatic enzymes, to marked histologic changes including centrilobular vacuolization, swelling, degeneration, and necrosis. The effects appear to follow a dose-response relationship and may also be influenced by duration of exposure. Mice exposed to 50 ppm for 6 hours exhibit slight centrilobular swelling, whereas hepatic degeneration was observed in mice exposed up to 200 ppm 6 hours/day, 5 days/week for 2 weeks. VDC also affects several liver enzymes: It decreases the activity of hepatic glucose-6-phosphatase and the content of glutathione and increases serum alanine α-ketoglutarate transaminase activity and liver content of triglycerides.[5]

Renal toxicity including enzyme changes, hemoglobinuria, and tubular swelling, degeneration, and necrosis have been observed in experimental animals after VDC exposure.[1] Severe histologic lesions of the kidney were observed in mice after acute exposure to 10–50 ppm of VCD, whereas exposures of up to 300 ppm were necessary to produce the same effects in rats.

Studies in mice have shown that selective covalent binding of VDC occurs in the proximal tubules, the liver lobules, and the mucosa of the upper respiratory tract and corresponds to sites of potential toxicity.[6] Additional events such as depletion of glutathione appear to be necessary for VDC-induced cell death to occur.

In rats, ingestion of drinking water containing up to 200 ppm VDC caused mild, dose-related changes in the liver but did not affect the reproductive capacity through three generations that produced six sets of litters.[7] Prenatal exposure to doses ranging from 15 to 450 ppm resulted in skeletal defects in rats, rabbits, and mice and also caused maternal toxicity in the form of decreased body weight and death.[1]

In a carcinogenicity study, Swiss mice were exposed to 10 or 25 ppm 4 hours/day, 5 days/week for 52 weeks.[8,9] After 98 weeks, 25 ppm had caused kidney adenocarcinomas in 24 of 150 males and 1 of 150 females whereas none were seen in the control group. Rats exposed to 75 ppm 6 hours/day, 5/days week for 18 months and then held until 24 months showed a reversible hepatocellular fatty change but no increase in tumor incidence that could be attributed to VDC exposure.[10] Several other studies in other strains of mice, rats, and hamsters did not produce carcinogenic effects.[5]

In one epidemiological study of 138 exposed workers, no excess of cancer cases was found, but follow-up was incomplete; nearly 40% of the workers had less than 15 years latency since first exposure, and only 5 deaths were observed.[11] The IARC has determined that there is inadequate evidence for carcinogenicity to humans and limited evidence for carcinogenicity to animals.[5]

VDC was genotoxic in a number of test systems; it induced chromosome aberrations and sister chromatid exchanges in cultured mammalian cells and DNA damage in mice in vivo; gene mutations were observed in vitro for bacteria, yeast, and plant cells after metabolic activation.[1]

The liquid is moderately irritating to the eyes and irritating to the skin of rabbits.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for vinylidene chloride is 5 ppm (20 mg/m^3) with a short-term excursion level (STEL) of 20 ppm (79 mg/m^3).

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VINYLTOLUENE

CAS: 25013-15-4

C_9H_{10}

Synonyms: Ethenylmethylbenzene; methylstyrene; tolyethylene; methylvinylbenzene

Physical Form. Colorless liquid

Uses. As a reactive monomer in the production of polymers and coatings

Exposure. Inhalation

Toxicology. Vinyltoluene is an irritant of the eyes and mucous membranes; at high concentrations it causes narcosis in animals, and it is expected that severe exposure will produce the same effect in humans.

Commercial vinyltoluene is a mixture of *meta* and *para* isomers with small amounts of *ortho* isomer.[1]

Human subjects exposed to 200 ppm detected a strong odor, but excessive discomfort was not experienced; at 400 ppm, there was strong eye and nasal irritation.[2] Central nervous system effects, such as depression, poor memory, and slow visuomotor performance, have been associated with heavy exposures.[1]

Exposure of rats and guinea pigs to 1350 ppm 7 hours/day for 100 days caused the death of some of the rats and slight liver damage in guinea pigs; there were no effects in female monkeys at this concentration.[2]

Rats tolerated exposure to 300 ppm for 60 hours without clinical symptoms, although they appeared relatively inactive.[3] At this concentration, vinyltoluene was found to accumulate in perirenal fat and was more effective than styrene, xylene, or toluene in producing neurochemical effects as determined by enzyme assays.

Mice administered 0, 10, 50, or 250 mg/kg and rats given 0, 10, 50, 250, or 500 mg/kg by gastric intubation once a day for 83 and 107 weeks, respectively, showed no treatment-related increases in malignant or benign tumors.[4] Chronic inhalation experiments in B6C3F1 mice (10 or 25 ppm) and Fischer 344/N rats (100 or 300 ppm) produced hyperplasia of the respiratory epithelium of the nasal passages in both species, but there was no evidence of treatment-related increases in the incidences of any tumor.[5]

The IARC has determined that there is evidence suggesting the lack of carcinogenicity

of vinyltoluene in experimental animals and inadequate evidence in humans.[1]

Vinyltoluene induces sister chromatid exchange and chromosomal aberrations in cultured human lymphocytes and micronuclei in mouse bone marrow cells *in vivo*.

The liquid dropped in the eyes of rabbits caused slight conjunctival irritation.[2] Applied to rabbit skin, vinyltoluene produced erythema with the development of edema and superficial necrosis.[2]

Vinyltoluene has a disagreeable odor detectable at 50 ppm.[2]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for vinyltoluene is 50 ppm (242 mg/m^3) with a short-term excursion limit (STEL) of 100 ppm (483 mg/m^3).

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VM&P NAPHTHA
CAS: 8030-30-6

Synonyms: Varnish makers' and printers' naptha; light naphtha, dry-cleaners' naphtha; spotting naphtha

Physical Form. Clear colorless to yellow liquid; petroleum distillate containing C5 to C11 hydrocarbons; a typical composition is paraffins 55.4%, naphthenes 30.3%, alkyl benzene 11.7%, dichloroparaffins 2.4%, and benzene less than 0.1%.

Uses. Diluent for paints, coatings, resins, printing inks, rubbers, and cements; solvent

Exposure. Inhalation

Toxicology. VM&P naphtha vapor is a central nervous system (CNS) depressant and a mild irritant of the eyes and upper respiratory tract.

In human tests, exposure to 880 ppm (4100 mg/m^3) for 15 minutes resulted in eye and throat irritation with olfactory fatigue.[1] The chief effect of exposure to high levels of the vapor is reported to be CNS depression.[2,3] However, in an accidental brief exposure of 19 workers from an overheated solvent tank, the chief effect was dyspnea, which lasted for several minutes after the exposure.[2] Two of the workers were cyanotic with tremor and nausea, but these were of brief duration. The absence of CNS depression was noteworthy.

The LC_{50} in rats was 3400 ppm for 4 hours; incoordination was observed.[4] In rats and beagle dogs exposed to 500 ppm for 30 hours weekly for 13 weeks, there was no evidence of latent or chronic effects.

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for VM&P naphtha is 300 ppm (1370 mg/m^3).

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WARFARIN

CAS: 81-81-2

$C_{19}H_{16}O_4$

Synonyms: 3-(a-Acetonylbenzyl)-4,hydroxycoumarin; coumadin; compound 42

Physical Form. Colorless crystals

Uses. Rodenticide; used clinically as an anticoagulant

Exposure. Ingestion; skin absorption

Toxicology. Warfarin causes hypoprothrombinemia and vascular injury, which results in hemorrhage; the main risks are potentially fatal gastrointestinal or intracerebral bleeding.

Warfarin acts as a vitamin K antagonist and suppresses the hepatic formation of prothrombin and of factors VII, IX, and X, causing a markedly reduced prothrombin activity of the blood.[1,2] Warfarin also causes dilatation and engorgement of blood vessels and an increase in capillary fragility.[1] The two effects can combine to produce hematomas, severe blood loss, and death from shock or hemorrhage.[2] The inhibition of prothrombin formation does not become apparent until the prothrombin reserves are depleted, which usually requires exposure for a number of days.[1] Accidental ingestion of approximately 2 mg/kg/day for 15 days by 14 family members caused massive bruising and hematomas on the buttocks and at the knee and elbow joints after 7–10 days; gum and nasal bleeding subsequently appeared, and blood was noted in the urine and feces.[2] Two individuals succumbed to the poisoning, whereas the other 12 recovered after treatment. Fatalities are attributable to internal bleeding from multiple organs, resulting in shock and death.

A farmer whose hands were intermittently wetted with an 0.5% solution of warfarin over a period of 24 days developed gross hematuria 2 days after the last contact with the solution; the following day, spontaneous hematomas appeared on the arms and legs.[3] Within 4 days, other effects included epistaxis, punctate hemorrhages of the palate and mouth, and bleeding from the lower lip. Four days later, after treatment for 2 days with phytonadione, hematologic indices had returned to the normal range. Other effects of warfarin intoxication have included back pain, abdominal pain, vomiting, and petechiae of the skin.[1,4]

Teratogenic effects have been observed in humans after maternal warfarin exposure.[2] The effects are primarily seen in the nasal region of the fetus and include nasal hypoplasia, bone stippling, and mental retardation. Central nervous system abnormalities due to localized hemorrhaging and scarring have occurred after second- or third-trimester exposures, whereas exposure during early pregnancy may result in dysmorphism.[5,6]

Treatment for warfarin poisoning includes vitamin K administration and, in severe cases, transfusions of whole blood.[2]

No data suggest that warfarin is either mutagenic or carcinogenic.[7]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for warfarin is 0.1 mg/m^3.

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WOOD DUST

Physical Form. Wood is a complex biological and chemical material consisting primarily of cellulose, hemicellulose, and lignin. The two general classes are hardwood and softwood, each with its own structure and composition. Woods also may contain a variety of organic compounds, including glycosides, quinones, tannins, stilbenes, terpenes, aldehydes, and coumarins.[1] Not only is the composition of wood extremely variable from species to species, but different parts of the same tree may have different compositions. Various solvents, adhesives, fungicides, insecticides, and microorganisms also may be associated with wood. As a result of this variability, wood dust cannot be treated as a single agent.[2]

Exposure. Inhalation; skin contact

Toxicology. Wood dust exposure may cause eye and skin irritation, respiratory effects, and hardwood nasal cancer. Irritation of the skin and eyes resulting from contact with wood dust is relatively common and may result from mechanical action (e.g., irritation caused by bristles and splinters), chemical irritation, sensitization, or a combination of these factors.[1]

Primary irritant dermatitis caused by wood contact consists of erythema and blistering, which may be accompanied by erosions and secondary infections. Irritant chemicals typically are found in the bark or the sap of the outer part of the tree. Therefore, loggers and persons involved in initial wood processing are most affected. In most reports of contact dermatitis, hardwoods of tropical origin have been implicated, although other woods, including pine, spruce, western red cedar, elm, and alder, have been cited.

Allergic dermatitis arising from exposure to wood substances is characterized by redness, scaling, and itching, which may progress to vesicular dermatitis after repeated exposures. The hands, forearms, eyelids, face, neck, and genitals generally are first affected. Allergic dermatitis may appear after several years' contact but typically ensues after a few days or a few weeks of contact. Chemicals causing sensitization generally are found in the heartwood; therefore, workers involved in secondary wood processing (carpenters, sawyers, furniture makers) are more often affected than persons involved in initial processing. Numerous sensitizing agents in wood have been identified, including lapachol (teak), usnic acid (western red cedar), quinones (rosewood), and anthothecol (African mahogany).[3]

Another type of wood-related dermatitis is woodcutters' eczema, which is not caused by contact with wood or wood dust, but rather by contact with epiphytes, lichens, and liverworts growing on bark or shrubs.

Respiratory ailments associated with wood dust exposure include irritation, bronchitis, nasal mucociliary stasis, impairment of ventilatory function, and asthma.

A correlation between the incidence of sinusitis, sneezing, watery nasal discharge, nasal mucosal irritation, and cough and wood

dust concentration was found in German furniture workers. Fourteen persons were exposed to a dust concentration below 5 mg/m^3, 15 to 5–9 mg/m^3, 26 to 10–19 mg/m^3, and 36 to 20 mg/m^3 or more.[3]

Middle ear symptoms occurred significantly more frequently among Danish furniture workers exposed to dust levels above 5 mg/m^3.[4] Other illnesses, such as sinus inflammation, long-lasting colds, asthma, nosebleed, and sneezing, also occurred more frequently in the higher-exposure group.

Impairment of mucociliary clearance, the rate at which mucus is transported from the nose to the pharynx, was found in a study of 68 Danish hardwood furniture workers.[5] Mucostasis (defined as a nasal transit time of 40 or more minutes) increased in direct proportion to the dust concentration; at 25.5 mg/m^3, 63% had mucostasis vs. 11% at 2.2 mg/m^3.

Obstructive lung disease, as measured by pulmonary function tests, has been associated with wood dust exposure. Vermont woodworkers with hardwood or pine dust exposures greater than 10 mg-years/m^3 generally had lower pulmonary function, as determined by FEV_1/FVC, than those with exposure indices of 0–2 mg-years/m^3.[6] Higher exposures also significantly lowered values of the maximal midexpiratory flow rate (MMEFR), compared with theoretical values.

Although no dose-response relationship was established, a study of employees from five plants with dust levels ranging from 0.46 to 8.3 mg/m^3 found decreases in FEV_1 and FVC of up to 0.19 l during the work shift for workers employed at the dustier furniture plant.[7]

A hypersensitivity reaction leading to asthma (defined as reversible airway obstruction) has been reported from exposure to a number of wood dusts, including oak, mahogany, and redwood, as well as more exotic woods, such as iroko cocobolo, zebrawood, and abiruana.[1,2] Connecting asthma to wood dust exposure has been difficult because, frequently, the subject has worked with wood for years with no reaction.[2] Sensitization typically begins as eye and nose irritation, followed by nonproductive cough and difficulty in breathing. In a sensitized individual, exposure may produce an immediate onset of symptoms and rapid reversibility or a delayed onset of 5–8 hours with a more gradual reversibility.

Immunologic findings in individuals with wood dust-induced asthma also vary.[1] In some cases, a Type 1 allergic reaction is confirmed by the presence of IgE antibodies. Positive skin reactions and the presence of precipitating antibodies to wood dust or extracts may or may not occur.

Extensive studies have been done on a clearly defined asthma syndrome produced by exposure to western red cedar.[8–10] Plicatic acid has been identified as the etiologic agent. The western red cedar asthma syndrome includes rhinitis, conjunctivitis, wheezing, cough, and nocturnal attacks of breathlessness characterized by a precipitous decline in FEV_1. There is no apparent relation between skin sensitivity and respiratory changes. No precipitating IgG antibodies are found in the serum of sensitized individuals, and circulating IgE antibodies are present in about one-third of affected individuals.

It has been estimated that approximately 5% of exposed workers are affected.[1] The asthmatic reaction is species specific; subjects who exhibit asthma with one type of wood dust show no reaction when challenged with another type.[2]

Other syndromes are associated with exposure to fungi present on wood.[11] Organic dust toxic syndrome is characterized by generalized feelings of feverishness, often accompanied by dry cough, fatigue, and shaking chills; it appears to be caused by high-dose exposures to fungal spores in moldy materials. Extrinsic allergic alveolitis has been associated with fungi found in bark and wood flour. Findings include abnormal X ray, reduced lung volume and serum precipitating antibodies to fungal antigens. Lung biopsy studies have reported interstitial infiltration with granuloma formation.

The association between nasal cancer and occupations involving exposure to wood dust has been established from case reports and epidemiological studies.[12] This relationship first was noted in the late 1960s in Great Britain,

where the incidence of nasal adenocarcinoma, a rare type of nasal cancer, among woodworkers in the furniture industry was found to be 10–20 times greater than among other woodworkers and 100 times greater than in the general population.[1] In a 19-year follow-up study of 8141 Swedish furniture workers, nasal adenocarcinoma was 62 times higher than expected, whereas sinonasal adenocarcinoma and sinonasal carcinoma were 44 and 7 times higher than expected, respectively.[13]

A study of deaths in furniture-making counties of North Carolina found that 8 of 37 (21.6%) people dead from nasal cancer had been employed in the furniture industry, whereas only 5 of the 73 (6.8%) controls had been so employed.[14] Of 215 patients with nasal cancer in Connecticut, 2.8% probably had been occupationally exposed to wood dust vs. only 0.8% of 741 persons dying of other cancers with similar exposures.[15]

A pooled reanalysis of 12 case control studies confirmed as increasing risk of sino-/nasal adenocarcinoma with increasing estimated levels of exposure to wood dust, but the evidence in regard to squamous cell carcinomas was ambiguous.[16] Although estimates of the relative risk of nasal adenocarcinoma vary considerably because of differences in exposure levels, types of wood dust, latency periods, selection of controls, and other confounding factors, the IARC has concluded that wood dust is carcinogenic to humans.[12] The carcinogenic agent(s) in wood dust have not been identified, nor has the importance of particle size and shape been investigated.[17]

It has been postulated that wood dust carcinoma results from a multistep process: Exposure causes loss of cilia and hyperplasia of the goblet cells and initiation of cuboidal cell metaplasia, followed (after a quiescent period) by squamous cell metaplasia.[8] Decades later, cellular aplasia leads to nasal adenocarcinoma. The time between first occupational exposure to wood dust and the development of nasal cavity adenocarcinoma averages 40 years.[17]

Other cancers, including lung cancer, Hodgkin disease, multiple myeloma, stomach cancer, and colorectal cancer and lymphosarcoma, have been mentioned in relation to wood dust exposure. Data are insufficient, inconclusive, and lacking in consistency regarding the relationship between occupational exposure to wood dust and cancers other than nasal adenocarcinoma.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) is 1 mg/m^3 for hardwoods with an A1 confirmed human carcinogen designation and 5 mg/m^3 for softwoods with a short-term excursion limit (STEL) of 10 mg/m^3.

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XYLENE
CAS: 1330-20-7

o-Xylene: 95-47-6
m-Xylene: 108-38-3
p-Xylene: 106-42-3

$C_6H_4(CH_3)_2$

Synonyms: Xylol; dimethylbenzene

Physical Form. Colorless liquid

Uses. Solvent; manufacture of certain organic compounds; cleaning agent; component of fuels

Exposure. Inhalation; skin absorption

Toxicology. Xylene vapor is an irritant of the eyes, mucous membranes, and skin; at high concentrations it causes narcosis.

Three painters working in the confined space of a fuel tank were overcome by xylene vapor estimated to be 10,000 ppm; they were not found until 18.5 hours after entering the tank, and one died from pulmonary edema shortly thereafter. The other two workers recovered completely in 2 days; both had temporary hepatic impairment (inferred from elevated serum transaminase levels), and one had evidence of temporary renal impairment (increased blood urea and reduced creatinine clearance).[1]

Giddiness, anorexia, and vomiting occurred in a worker exposed to a solvent containing 75% xylene at levels of 60–350 ppm, with possible higher excursions.[2] In another report, eight painters exposed to a solvent consisting of 80% xylene and 20% methylglycolacetate experienced headache, vertigo, gastric discomfort, dryness of the throat, and signs of slight drunkenness.[3]

Volunteers exposed to 460 ppm for 15 minutes had slight tearing and light-headedness.[4] A level of 230 ppm was not considered to be objectionable to most of these subjects. However, in an earlier study, the majority of subjects found 200 ppm irritating to the eyes, nose and throat, and judged 100 ppm to be the highest concentration subjectively satisfactory for an 8-hour exposure.[5]

Before 1940, most reports on the possible chronic toxicity of xylene also involved exposure to solvents that also contained high percentages of benzene or toluene as well as other compounds. Consequently, the effects attributed to xylene in these reports are questionable.[6] Blood dyscrasias, such as those reportedly caused by benzene exposure, have not been associated with the xylenes.[6]

Both human and animal data suggest that mixed xylene, *m*-xylene, *o*-xylene, and *p*-xylene all produce similar effects, although the potency with regard to a given effect may vary with individual isomers.[7] In mice the 6-hour LC_{50} values for *m*-, *o*-, and *p*-xylene were determined to be 5267, 4595, and 3907 ppm, respectively.[7] The 4-hour LC_{50} value for mixed xylene in rats ranged from 6350–6700 pm.

Exposure of rats to 1600 ppm for 2 or 4 days produced mucous membrane irritation, incoordination, narcosis, weight loss, increased

erythrocyte count, and death. Exposure to 980 ppm for 7 days caused leukopenia, kidney congestion, and hyperplasia of the bone and spleen.[5]

Repeated exposure of rabbits to 1150 ppm of a mixture of isomers of xylene for 40–55 days caused a reversible decrease in red and white blood cell counts and an increase in thrombocytes; exposure to 690 ppm for the same time period caused only a slight decrease in the white blood cell count.[8]

Fetotoxic effects have been reported after inhalation exposure to xylenes and include altered enzyme activities in rat pups.[9] Oral treatment has resulted in prenatal mortality, growth inhibition, and malformations, primarily cleft palate, but only at maternally toxic doses. No reproductive effects were found in rats after inhalation of 500 ppm of xylene before mating and during gestation and lactation.[7] However, prenatal exposure at this level impaired development of neuromotor ability and learning and memory in rats, with the effects more pronounced in females.[10] After intermediate and chronic exposures, there was no histologic evidence of reproductive organ damage in mice administered 1000 mg/kg/day or rats given 800 mg/kg/day.[11]

In 2-year gavage studies, there was no evidence of carcinogenicity of mixed xylenes for male or female rats given 250 or 500 mg/kg/day, or for male or female mice given 500 or 1000 mg/kg/day.[11] Limited epidemiological studies have not established an association between xylene exposure and cancer due to multiple-exposure circumstances and weak consistency of the findings.[12]

Mixed xylene and the individual xylene isomers have tested negative in a wide variety of genotoxic assays; they are considered to be nonmutagenic.[7]

The IARC has determined that there is inadequate evidence in humans and experimental animals for the carcinogenicity of xylenes.[12]

Repeated application of 95% xylene to rabbit skin caused erythema and slight necrosis. Instilled in rabbit eyes, it produced conjunctival irritation and temporary corneal injury. Exposure to the vapors produced reversible vacuoles in the corneas of cats.

The odor threshold has been reported as 1 ppm.[6]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for xylene (*o*-, *m*-, *p*-isomers) is 100 ppm (434 mg/m^3) with a short-term excursion limit (STEL) of 150 ppm (651 mg/m^3).

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XYLIDINE (Mixed Isomers)
CAS: 1300-73-8

$C_8H_{11}N$

Synonyms: Aminodimethylbenzene; dimethylaniline

Physical Form. Liquid, except *o*-4-xylidine is a solid

Uses. Chemical intermediate in the manufacture of pesticides, dyes, antioxidants, pharmaceuticals, synthetic resins, and fragrances

Exposure. Inhalation

Toxicology. Xylidine causes liver damage in experimental animals and is a mild methemoglobin former; it caused tumors of the nasal cavity in rats.

There are six isomeric forms of xylidenes with the commercial product consisting primarily of the 2,4- and 2,6-isomers.[1]

The oral LD_{50} in rats ranged from 470 mg/kg for 2,4-xylidine to 1300 mg/kg for 2,5-xylidine.[2] Although cyanosis has been observed in severely intoxicated animals, methemoglobin-induced hypoxia did not appear to be severe enough to be the cause of death.

The extent of methemoglobin formation from xylidines appears to be species dependent, with cats more susceptible than humans and dogs less susceptible.[3] Administered intravenously to cats, 0.28 mM/kg produced 10% methemoglobin in cats, whereas similar exposure in dogs did not produce methemoglobin.[3]

Oral doses of 2,4-, 2,5-, and 2,6-xylidine administered to dogs for 4 weeks caused hepatotoxicity at doses of 2, 20, and 50 mg/kg/day, respectively; all three isomers induced fatty degeneration of the liver, with the 2,6-isomer being the most toxic.[4] In rats, doses up to 700 mg/kg for 4 weeks caused hepatomegaly, but liver histology was normal.

Chronic 2-year studies showed a significant increase in the incidences of adenomas and carcinomas of the nasal cavity in high-dose rats fed diets containing 3000 ppm of 2,6-xylidine.[1] The carcinomas were highly invasive and frequently destroyed the nasal turbinates and nasal septum. Rhabdomyosarcomas, a rare tumor of the nasal cavity were also observed in the high-dose male and females. The nonneoplastic lesions observed in the nasal cavity included acute inflammation, epithelial hyperplasia, and squamous metaplasia. In addition, subcutaneous fibromas and fibrosarcomas occurred in both males and females and there was an increased incidence of neoplastic nodules in the livers of female rats.

The IARC has determined that there is sufficient evidence for the carcinogenicity of 2,6-xylidine in experimental animals and inadequate evidence in humans.[5] Overall, 2,6-xylidine is considered possibly carcinogenic to humans.

In genotoxic assays, 2,6-xylidine induced sister chromatid exchanges and chromosomal aberrations in cultured mammalian cells but did not induce micronuclei in the bone marrow of mice treated in vivo; conflicting results have been reported in the *Salmonella typhimurium* assay.[5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for xylidine (mixed isomers) is 0.5 ppm (2.5 mg/m^3) with an A2-suspected human carcinogen classification.

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YTTRIUM

CAS: 7440-65-5

Y

Compounds: Yttrium chloride; yttrium nitrate; yttrium oxide; yttrium phosphate

Physical Form. White powder

Uses. Yttrium is mixed with rare earths as phosphors for color television receivers; oxide for mantles in gas and acetylene lights; in ceramics; in superconductors

Exposure. Inhalation

Toxicology. Yttrium compounds cause pulmonary irritation in animals.

No effects in humans have been reported.

Intratracheal administration of 50 mg of yttrium oxide in rats caused granulomatous nodules to develop in the lungs by 8 months.[1] Nodules in the peribronchial tissue compressed and deformed several bronchi; the surrounding lung areas were emphysematous, the interalveolar walls were thin and sclerotic, and the alveolar cavities dilated. Intraperitoneal injection of yttrium chloride in animals caused peritonitis with serous or hemorrhagic ascites.[2] It was speculated that the development of ascites may have been related to the acidity of the administered solution rather than to the yttrium.[2] In a more recent report, the toxicity of intratracheally administered yttrium chloride, as determined by lactate dehydrogenase activity in bronchoalveolar lavage fluid, was judged to be higher than zinc oxide but lower than cadmium compounds.[3]

Intravenous administration of 1 mg of yttrium chloride to rats caused formation of colloidal material in blood plasma, which accumulated primarily in the liver and spleen causing injury to these organs.[4]

Application of a 0.1 M solution of yttrium chloride to the eyes of rabbits caused no injury; similar exposure of eyes from which the corneal epithelium had been removed resulted in immediate slight haziness of the cornea, which subsequently became opaque and vascularized.[5]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for yttrium and compounds is 1 mg/m^3 as Y.

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ZINC CHLORIDE FUME
CAS: 7646-85-7

$ZnCl_2$

Synonym: Zinc dichloride fume

Physical Form. White fume

Uses. Smoke generators; flux in soldering

Exposure. Inhalation

Toxicology. Zinc chloride fume is an irritant of the eyes, mucous membranes, and skin, and at very high concentrations, causes pulmonary edema.

Ten deaths and 25 cases of nonfatal injury occurred among 70 persons exposed to a high concentration of zinc chloride released from smoke generators.[1] Presenting symptoms were conjunctivitis (two cases with burns of the corneas), irritation of nose and throat, cough with copious sputum, dyspnea, constrictive sensation in the chest, stridor, retrosternal pain, nausea, epigastric pain, and cyanosis. Of the 10 fatalities, a few died immediately or within a few hours with pulmonary edema, whereas those who survived longer developed bronchopneumonia. Between the second and fourth days after exposure, almost all cases developed moist adventitious sounds in the lungs and the majority continued to present a pale, cyanotic color. A prominent feature was the disparity between the severe symptoms and the paucity of physical signs in the lungs. Recovery in survivors occurred within 1–6 weeks after the incident.

In a firefighter who was fatally exposed to a high but undetermined concentration of zinc chloride fume from a smoke generator, presenting symptoms were nausea, sore throat, and chest tightness aggravated by deep inspiration.[2] The patient improved initially but developed tachypnea, substernal soreness, fever, cyanosis, and coma. The lung fields were clear on auscultation despite diffuse pulmonary infiltrations seen on the chest roentgenogram. Death occurred 18 days after exposure, and autopsy revealed active fibroblastic proliferation of lung tissue and cor pulmonale.

An outdoor exposure to zinc chloride aerosol after the detonation of a smoke bomb in an airport disaster drill resulted in upper respiratory tract irritative symptoms in the victims, correlating with the presumed intensity and duration of exposure.[3] Questionnaire responses by 81 exposed individuals most commonly reported cough, hoarseness, and sore throat, with onset primarily at the time of exposure. Other symptoms among individuals with self-reported moderate and heavy exposures included listlessness, metallic taste, light-headedness, chest tightness, and soreness in the chest. Wheezing was relatively uncommon, and, by spirometry 1–2 days after exposure, the mean results for FEV_1 and FVC as a percentage of predicted were normal. The predominance of upper respiratory symptoms was attributed to the solubility and hygroscopic tendency of zinc chloride, resulting in upper respiratory tract deposition. On dissolution of zinc chloride, both hydrochloric acid and zinc oxychloride are formed, contributing to the corrosive action. Most of the exposed victims became asymptomatic within 48 hours, but symptoms persisted in a few patients for up to several weeks.[3]

Accidental installation in a human eye of one drop of a 50% zinc chloride solution caused immediate and severe pain, which persisted despite immediate irrigation with water. The corneal epithelium was burned, and corneal vascularization followed. After many weeks, areas of opacification and vascularization remained in the cornea.[4] Zinc chloride has caused ulceration of the fingers, hands, and forearms of workers who used it as flux in soldering.[5]

In guinea pigs 120 mg zinc/m^3 as zinc chloride 1 hour/day, 5 days/week for up to 3 weeks was lethal; focal alveolitis, consolidation, emphysema, infiltration with macrophages, and fibrosis were observed at necropsy. Mice and rats exposed to 122 mg zinc/m^3 as zinc chloride for 1 hour/day, 5 days/week, survived 20 weeks of exposure but showed increased macrophages in lungs when euthanized 13 months after exposure.[6]

In mice, zinc chloride, administered by gavage at doses as low as 0.78 mg/kg, adversely

affected some reproductive parameters, resulting in decreased implantation efficiency, reduced litter size, and abnormal nursing and nesting behaviors.[7]

Injection of zinc chloride solution into the testes of 49 Syrian hamsters resulted in areas of necrosis occupying about 25% of each testis; two embryonal carcinomas of the testis were found 10 weeks later at necropsy.[8] There is no evidence that zinc compounds are carcinogenic after administration by any other route.[9]

In general exposure to zinc chloride does not increase mutation frequencies in bacterial or mammalian test systems.[10]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for zinc chloride fume is 1 mg/m^3 with a short-term excursion level (STEL) of 2 mg/m^3.

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ZINC DITHIOCARBAMATES—RUBBER COMPONENTS

CAS: Zinc diethyldithiocarbamate: 14324-55-1
Zinc dibutyldithiocarbamate: 136-23-2
Zinc dimethyldithiocarbamate:137-30-4

Synonyms: Zinc diethyldithiocarbamate (ZDEC; Ethyl Ziram; zinc bis-diethyldithiocarbamate; diethyldithiocarbamic acid, zinc salt); zinc dibutyldithiocarbamate (ZDBC; zinc bis-dibutyldithiocarbamate; dibutyldithiocarbamaic acid, zinc salt); zinc dimethyldithiocarbamate (ZDMC; Ziram; zinc bis-dimethyldithiocarbamate; dimethyldithiocarbamic acid, zinc salt)

Uses. Rapid vulcanization accelerators in the rubber industry; as preservatives in paints, oils, metal-working fluids

Exposure. Dermal

Toxicology. Zinc dithiocarbamates (ZDC) are contact allergens and are one of the chemical groups in rubber that cause the type IV delayed-type hypersensitivity skin reaction (DTH).[1,2]

ZDC was implicated as a cause of a DTH skin reaction in an early case report. In 1981 a 19-year-old woman began work as a kitchen employee and wore rubber latex gloves to protect her hands when washing dishes. Eight months later, she developed urticaria on the wrists every time she washed dishes at work, where she wore cotton and Formi-rubber latex domestic gloves. Wheals began on wrists a few minutes after she began wearing the gloves, and occasionally she had edema of the eyelids.

Symptoms lasted 30 minutes after glove removal. Itching was intense, with resultant scratching causing excoriations on arms. There was no history of skin disease or atopy. Immediate reactions were not observed in patch tests. In scratch chamber tests, a small piece of rubber gloves and ZDC produced a wheal greater than histamine control at 15 minutes. No urticaria appeared after switching to different gloves.

A study of the mutagenicity of ZDC used a battery of in vitro mutagenicity studies. ZDMC and ZDEC were positive in both the Ames *Salmonella typhimurium* assay and the human lymphocyte cell mutation assay but not in the mouse lymphoma cell mutation assay.[3] In contrast, ZDBC was not positive in the assays.

The ACGIH has not established a threshold limit value for ZDC.

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ZINC OXIDE

CAS: 1314-13-2

ZnO

Synonyms: Calamine; zincite

Physical Form. White to yellowish powder that may exist as a fume or dust

Uses. Metallic zinc in galvanizing, electroplating, dry cells, alloying; zinc oxide in pigments

Exposure. Inhalation

Toxicology. Inhalation of zinc oxide fume causes an influenza-like illness termed metal fume fever.

During human exposure to zinc oxide fume, effects are dryness and irritation of the throat, a sweet or metallic taste, substernal tightness and constriction in the chest, and a dry cough.[1–5] Several hours after exposure, the subject develops chills, lassitude, malaise, fatigue, frontal headache, low back pain, muscle cramps, and occasionally blurred vision, nausea, and vomiting. Physical signs include fever, perspiration, dyspnea, rales through the chest, and tachycardia; in some instances, there has been a reversible reduction in pulmonary vital capacity. There is usually leukocytosis, which may reach 12,000–16,000/cmm.[2] The pathogenesis of the syndrome is not clear, but an allergic response has been suggested, with zinc entering the blood circulation and forming a sensitizing complex with plasma proteins.[5]

An attack usually subsides after 6–12 hours but may last for up to 24 hours; recovery is usually complete.[3] Most workers develop an immunity to these attacks, but it is quickly lost; attacks tend to be more severe on the first day of the workweek.[3] Despite the severity of the acute subjective symptoms there appear to be no consistent functional or pathological respiratory effects attributable to chronic exposure.[1]

The critical factor in the development of the syndrome is the size of the ultrafine zinc oxide particles produced when zinc is heated to temperatures approaching its boiling point in an oxidizing atmosphere.[4] The particles must be small enough (<1 μm) to reach the alveoli when inhaled. The syndrome is not produced when normal zinc oxide powder is either inhaled or taken orally.[2] Only freshly formed fume causes the illness, presumably because flocculation occurs in the air with formation of larger particles that are deposited in the upper respiratory tract and do not penetrate deeply into the lungs.[6]

Data on exposure concentrations and durations associated with metal fume fever are insufficient.[7] Early studies found moderate symptoms after 12 minutes at 600 mg/m^3; other investigators found no signs of chronic toxicity with occupational exposures of 3–15 mg/m^3 for periods up to 35 years. In another report, each of four volunteers reported one or more of the symptoms of metal fume fever (sore throat, chest tightness, and/or headache) approximately 6–10 hours after a 2-hour exposure at 5 mg/m^3 (particle size 0.06 µm).[8] The symptoms were not accompanied by changes in pulmonary function. Other investigators have found that exposure to 23–171 mg/m^3 for up to 30 minutes results in the increase of several pulmonary lavage parameters including neutrophils, macrophages, and activated T lymphocytes.[9]

A short-term study of guinea pigs exposed to zinc oxide fume 3 hours/day for 6 days at the threshold limit value (TLV) of 5 mg/m^3 revealed pulmonary function changes and morphologic evidence of small airway inflammation and edema. Pulmonary flow resistance increased, compliance decreased, and lung volumes and carbon monoxide diffusing capacity decreased. Some of these changes persisted for the 72-hour duration of postexposure follow-up.[10]

Zinc oxide is not considered to be a skin irritant.[4] Early reports of development pustules on the axilla and inner thighs in workers whose skin was frequently covered with zinc oxide were thought to be due to clogging of sebaceous glands by sweat, bacteria, and dust and subsequent infection.

In general, genotoxic studies have not found evidence for mutagenicity of zinc.[4]

The larger particle sized dusts of zinc oxide are considered nuisance dusts that have little adverse effect on the lung and do not produce significant organic disease when exposures are kept under reasonable control.[1]

The 2003 ACGIH threshold limit value-time-weighted average (TLV-TWA) for zinc oxide fume is 5 mg/m^3 with a short-term exposure limit (STEL) of 10 mg/m^3; the dust has a TLV-TWA of 10 mg/m^3.

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ZIRCONIUM COMPOUNDS
CAS: 7440-67-7

Zr

Synonyms: Zirconium dioxide; zirconium silicate; zirconium tetrachloride

Physical Form. Solids

Uses. Structural material for atomic reactors; ingredient of priming and explosive mixtures; reducing agents; pigment; textile water repellent

Exposure. Inhalation

Toxicology. Zirconium compounds are of low toxicity, although granulomas have been produced by repeated topical applications of zirconium salts to human skin.

A study of 22 workers exposed to fume from a zirconium reduction process for 1–5 years revealed no abnormalities related to the exposure.[1] There are no well-documented cases of toxic effects from industrial exposure. In the most recent follow-up of 178 zirconium-exposed workers, 12 of 175 men had calcified nodules; no pulmonary granulomas were identified.[2] No associations were seen between the presence of nodules and duration of zirconium exposure, and no significant effect of cumulative zirconium exposure on lung function was recognized.[2] Two persons given zirconium malate in 50-mg intravenous injections developed vertigo.[3] Granulomas of the human axillary skin have occurred from use of deodorants or poison ivy remedies containing zirconium.[4]

In rats, the oral LD_{50} of several zirconium compounds ranged from 1.7 to 10 g/kg.[5] Animals acutely poisoned by zirconium compounds show progressive depression and decrease in activity until death.[3] Repeated inhalation of zirconium tetrachloride mist by dogs for 2 months at 6 mg zirconium/m^3 caused slight decreases in hemoglobin and in erythrocyte counts, with some increased mortality over that of controls. These effects may have been due to the liberation of hydrogen chloride.[5] Animals exposed to zirconium dioxide dust for 1 month at 75 mg zirconium/m^3 showed no detectable effects. Rats exposed to high concentrations of zirconium silicate dust for 7 months developed radiographic shadows in the lungs; these were attributed solely to the deposition of the radiopaque particles, because histologic examination showed no cellular reaction. The addition of 5 ppm of zirconium as the sulfate to the drinking water of mice for their lifetime did not increase the incidence of tumors.[6]

The 2003 threshold limit value-time-weighted average (TLV-TWA) for zirconium is 5 mg/m^3 with a short-term excursion level (STEL) of 10 mg/m^3.

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