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Neurotoxicity of Chemicals Commonly Used in Agriculture

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A multitude of chemical agents used in agriculture are known to have significant toxicity, many of them specifically developed to be toxic to animals. This chapter concentrates on the neurological consequences of occupational exposure to these and other common agents, including insecticides, pesticides, heavy metals, and volatile organic and plant toxins.

A physician in rural practice should be acquainted with the strategies for providing emergency care, especially after acute exposure to potent toxins. Acute exposure is suggested by a set of symptoms that include rapidly developing fatigue, dizziness, nystagmus, disorientation, confusion, hallucination, as well as other neurological presentations (e.g., symptoms of intracranial hypertension such as headache, nausea, or vomiting), muscle fasciculations, seizures, or coma (1).

A possibility of occupational exposure must be considered in all agricultural workers and their families; however, those who work in a confined space with little or no means of personal protection, who lack the necessary training or sufficient knowledge of the native language, or lack access to industrial hygiene data should be considered likely candidates for a detailed evaluation.

Often patients provide the best clues by attributing their medical condition to a specific agent or to the possibility of exposure. Patients may complain that their symptoms were preceded by the presence of a chemical smell or a spill of a chemical. They may also note that their symptoms get worse at the end of the shift, workweek, or season. This "undulating" presentation when symptoms are less acute during the weekend or time-off periods may be of special significance as it may allow gauging of personal susceptibility to a specific agent (2,3).

Occupational exposure may be suspected if the patient presents with reversible, static, or progressive neurological symptoms after removal from exposure, symptoms that occur slowly, especially if these symptoms are attributable to central nervous system (CNS) changes such as headache,

confusion, disorientation, and behavior or memory changes. Slow onset of peripheral neuropathy, often presenting with numbness in the feet and hands, pain, weakness, or difficulty walking is also highly suggestive of occupation-related toxicity. In the majority of cases, severity of symptoms may be directly related to the length of employment in the field or in processes that expose workers to toxic agents (4,5).

Both clinical and subclinical dysfunction is often noted by abnormal neurophysiological, neuropsychological, or neuroimaging testing results. Detailed evaluation of patients whose occupational or environmental history is deemed significant is warranted as it provides a snapshot of the patient's condition against which future changes can be judged.

In all cases strive to achieve unhindered communication with both the patient and the employer. Assistance of qualified interpreters may be needed and chemical names may differ significantly among languages (e.g., nitrogen is "azote" in several European languages). When evaluating the patient, consider both common and rare agents, keeping in mind that what may be rare in an urban/suburban setting may be common in the rural and agricultural setting.

Algorithm to Assess for Neurotoxic Illness

Step One: Background History

Assess for:

1. Significant medical and family histories, noting issues such as education, fluency in language, instruction about and adherence to use of personal protection equipment (see Chapter 6)
2. Residence history of the patient and cohabitants, and health problems in relatives and cohabitants
3. Current and historical medication, recreational drug use, and use of dietary supplements

Step Two: Potential Toxic Agents

Obtain:

1. A personal narrative through spontaneous communications and guided by open-ended questions about the patient's perception of occupational hazards and toxic chemicals he or she might have been exposed to
2. Material Safety Data Sheets (MSDS) for all chemicals of concern from the employer
3. Identification and comparison of chemical agents that may contribute to a patient's presentation, both past and present
4. Additional reference information as necessary

Step Three: General Medical Examination

Proceed with systemic examination, including a detailed assessment of skin and its derivatives (hair, nails), the lymph system, and dental health. Obtain past medical records as necessary.

Step Four: Neurological Examination and Confirmatory Testing

Check for mental status changes, seizure-like presentations, brainstem signs (e.g., nystagmus), motor and sensory neuropathies, and changes in reflexes. If appropriate, identify soft neurological signs for the purposes of later monitoring. Separately address cerebellar signs (ataxia, dystaxia, or dysmetria), as they may shed light on the identity of certain toxic agents. Exclude common diagnoses and differentiate between possible contributing factors such as peripheral neuropathy in patients with both chemical exposure and diabetes or alcoholism.

Neurophysiological testing provides irreplaceable data useful for assessment of the current condition and for neurological monitoring. Additional information should be obtained from imaging and neuropsychological tests, as appropriate. Industrial hygiene tests may be necessary, especially if legal issues are anticipated.

Step Five: Determine the Diagnosis and Extent of Injury

Determine if:

1. The dose and duration of exposure are consistent with the described dysfunction
2. The proposed mechanism for the exposure-induced dysfunctions

Step Six: Reevaluation Strategy

1. Decide on the need for reevaluation, its frequency and possible markers or end points
2. Discuss the reevaluation schedule and educate the patient about symptoms and manifestations that are consistent with both improvement and worsening of the condition
3. Alert the patient to possible situations, symptoms, and manifestations that warrant emergency care

Neurotoxicity of Wild Plants

Many plants cause nonspecific gastrointestinal upset. Among significantly toxic plants are philodendron, holly, dumbcane, poison ivy, pothos (devil's

ivy), English ivy, yew, rhododendron (azalea), and eucalyptus. Poison hemlock ingestion is suggested when gastrointestinal upset is accompanied by the early onset of increased secretions followed by syndromes such as respiratory difficulty, altered mental status, and seizures. Plant ingestion alone is unlikely to cause isolated altered mental status except in cases of exposure to water hemlock and chinaberry plants (6).

Water Hemlock (Cicuta maculata)

Water hemlock *(Cicuta maculate)* and most other species of *Cicuta* are similar in appearance and grow to heights of 6 feet. These plants are found in wetlands throughout the United States. Cicutoxin is distributed throughout the plant, with the highest concentration in the tuberous roots. One mouthful of root is sufficient to kill an adult (as documented by, among others, Plato). Toxicity has also been documented after dermal contact (7).

Cicutoxin ingestion produces symptoms in 15 to 60 minutes. Muscarinic actions manifest as abdominal pain, vomiting, diarrhea, trismus, and hypersalivation. More central effects manifest as CNS depression, respiratory distress, and possibly tonic-clonic seizures. Death is usually secondary to respiratory arrest. Treatment is mostly supportive, as anticholinergics have not been shown effective in animal models (7).

Chinaberry (Melia azedarach)

Chinaberry *(Melia azedarach)* is a tree with serrated leaves, long leaflets, and scented, purple flowers arranged in clusters. The toxic agent is concentrated in the berries that are yellow, contain smooth black seeds, and persist after the leaves are shed. Chinaberry trees grow in the South from Florida to Hawaii. Ingestion of as few as six to eight berries has been reported to cause fatalities (8).

In patients who ingest the berries, a prolonged latency period is followed by development of mental confusion, ataxia, dizziness, and stupor. Some patients may develop intense vomiting and bloody diarrhea, which results in hypovolemic shock. Respiratory depression, seizures, and paralysis also have been reported (8).

The treatment is primarily symptomatic in nature. Gastric decontamination may benefit by reducing the absorbed dose. Benzodiazepines remain the mainstay of management of seizures induced by plant alkaloids.

Neurotoxicity of Rodenticides

Rodenticides are a heterogeneous group of compounds that exhibit markedly different toxicities to humans and rodents. Table 23.1 lists the effects and neurological presentations for different examples. According to the Toxic

TABLE 23.1. Effects of specific rodenticides.

Chemical (brand name)	Effects	Possible neurological presentation
Sodium monofluoroacetate	Poisons the Krebs cycle	Dizziness, weakness, nausea
N-3-pyridylmethyl-Np-nitrophenyl urea [PNU] (Vacor)	Destroys the pancreatic beta cell	Dizziness, weakness, nausea
Strychnine	Antagonist of glycine at the postsynaptic spinal cord motor neuron	Seizure-like, extensor posturing with risus sardonicus
Barium compounds	Causes potassium redistribution (intracellular influx), may lead to hypotonia	Headache, weakness, nausea, shortness of breath, brain anoxia
Yellow phosphorus	Causes chemical burns, hemolysis	Agitation, weakness
Arsenic compounds	React with sulfhydryl groups of multiple enzymes	Nausea, vomiting, weakness
Zinc phosphide	Causes hemolysis	Nausea, vomiting, weakness
Bromethalin	Identified as a mitochondrion poison (uncouples oxidation)	Nausea, vomiting, weakness
Norbormide	Causes ischemia (via vasoconstriction)	Dizziness, seizure-like presentation possible
Warfarin-like anticoagulants and brodifacoum	Cause hemorrhages	Multiple dose- and organ-dependent complaints

Source: Data from Feldman (1), Carod Artal (6), and Van Sittert and Tuinman (9).

Exposure Surveillance System (TESS) of the American Association of Poison Control Centers (AAPCC), 20,300 human exposures to rodenticides were reported in 1 year (1998) (9,10).

Management of toxicity induced by rodenticides is toxin-specific and usually involves emergency care for acute exposure. Strychnine may be of special interest to a physician, due to its unique and well-studied mechanism of toxicity. This plant alkaloid is no longer widely used in the United States but is more widely used in the developing countries. Consider strychnine toxicity if an individual presents with generalized seizure-like appearance, with or without loss of consciousness. Of note is the fact that strychnine may be used as an adulterant in street drugs, especially those sold as lysergic acid diethylamide (LSD) (9).

Neurotoxicity of Heavy Metals

Nearly all organ systems are affected in heavy metal toxicity, most commonly the nervous, gastrointestinal, hematopoietic, renal, and cardiovascular systems. To a lesser extent, lead toxicity involves the musculoskeletal and reproductive

systems. The organ systems affected and the severity of the toxicity vary with the particular heavy metal involved, the age of the individual, and the level of exposure (11).

Heavy metals bind to sulfhydryl groups in proteins, resulting in alterations of enzymatic activity; however, specific metals also have unique mechanisms of toxicity that may explain the variety of presentations (11).

Encephalopathy is one of the leading causes of mortality in patients with heavy metal poisoning and is especially common in cases of lead poisoning. Neuropathies are also common, often presenting a challenge to diagnose and necessitating extended diagnostic studies (12).

Lead Toxicity

Lead disrupts the normal physiological effects of calcium, causing inappropriate release of neurotransmitters, and interferes with excitatory neurotransmission by glutamate, especially the *N*-methyl-D-aspartate (NMDA) receptor, which is blocked selectively by lead. Disruption of NDMA-mediated long-term potentiation is believed to be responsible for the cognitive manifestations of lead toxicity, especially in children. At higher blood levels, lead disrupts the function of endothelial cells in the blood–brain barrier, causing subsequent hemorrhagic encephalopathy, seizures, and coma (see Chapter 9 for biological monitoring) (13,14).

Mental status examination may detect changes in more severe cases of lead toxicity, while detailed neuropsychological testing is often needed to diagnose the less obvious cases. In both children and adults, impaired fine-motor coordination or subtle visual-spatial impairment may be seen, while chronic distal motor neuropathy with decreased reflexes and weakness of extensor muscles and relatively spared sensory function is more common in adults (15).

In addition to common environmental sources of lead (paint and leaded gasoline), identification of some of the sources of lead may present a challenge, since cosmetics ("surma" or kohl in the Middle East), folk remedies (often applied to the umbilical stumps of infants), and even alternative medical remedies may contain lead. A puzzling use of lead acetate is as an aphrodisiac, which has been reported historically and in some areas of Latin America (15).

Laboratory Tests and Studies

Blood lead levels higher than 10 μg/dL are considered toxic, but no level of lead, no matter how minute, is considered safe. A complete blood count (CBC) with peripheral smear may demonstrate basophilic stippling of the red blood cells (RBCs), a finding also observed in arsenic toxicity, sideroblastic anemia, thalassemia, and normocytic or microcytic anemia (11,12,15).

Cerebral edema and microhemorrhages may be seen on magnetic resonance imaging (MRI) in patients presenting with encephalopathy. Patchy calcifications, although not specific, are seen on MRIs of patients with chronic lead exposure. In adults, neurophysiological testing may be helpful if symptoms of lead-induced neuropathy are seen (15).

Management

The key to treating lead toxicity is removal of the offending agent and reducing the total body load. Chelation agents [calcium disodium ethylenediaminetetraacetic acid ($CaNa_2$ EDTA), dimercaprol, 2,3-dimercaptosuccinic acid (DMSA)] are used to reduce the body stores of lead. Treatment for acutely ill patients includes whole-bowel irrigation with polyethylene glycol electrolyte solution if radiographic evidence of lead toxicity is present (15).

A water-soluble, oral chelating agent, DMSA (succimer, Chemet®), is appropriate for use with blood lead levels ranging from 40 to 70 µg/dL. It is contraindicated in children with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency or those allergic to sulfa drugs. D-penicillamine (Cuprimine) is a second-line oral chelating agent, although it is not approved by the U.S. Food and Drug Administration (FDA) for use in lead poisoning (15).

Calcium disodium ethylenediaminetetraacetic acid ($CaNa_2$ EDTA) is a parenteral chelating agent that is administered intravenously to patients with blood lead levels in the range of 40 to 70 µg/dL who do not respond to succimer or cannot take it. In addition, it is used immediately before oral succimer in patients with blood lead levels higher than 70 µg/dL (15).

Dimercaprol [British antilewisite (BAL)] is another parenteral chelating agent recommended by some authors as an agent of first choice. With high blood lead levels (> 100 µg/dL), it is used in conjunction with $CaNa_2$ EDTA (16).

Mercury Toxicity

The clinician needs to distinguish between toxicity of the inorganic compounds (elemental mercury and the ions: mercuric and mercurial) and the toxicity of organic compounds (alkyls of mercury: methylmercury). Organic methylmercury toxicity causes prominent neuronal loss and gliosis in the calcarine and parietal cortices and cerebellar folia, as seen in cases of Minamata disease. Inorganic mercury causes cerebral infarctions as well as systemic features, such as pneumonia, renal cortical necrosis, and disseminated intravascular coagulopathy. Inorganic mercury impairs adenosine diphosphate (ADP)-dependent protein genesis in animal models, while organic mercury compounds may induce excitotoxicity and dysregulation of the nitric oxide system with subsequent cerebellar damage in rodents (17–19).

Patients presenting with gait ataxia, tremulousness, hearing loss, visual field constriction, dysarthria, and distal limb sensory loss, coupled with

cognitive and emotional dysfunction should be evaluated for mercury toxicity, although none of these symptoms is specific (18).

Organic mercury toxicity, seen in Minamata disease and in patients consuming grains contaminated with mercury-based fungicides, often leads to hearing loss and visual field impairments. Distal sensory loss, uncoordinated limb movements, resting tremors, gait ataxia, and a positive Romberg sign are associated with both inorganic and organic types of toxicity. Impairments in the frontal lobe domains (emotional and cognitive) observed with neuropsychological testing are somewhat more characteristic of acute inorganic mercury toxicity, although this presentation (the "Mad-Hatter" syndrome) is possible in all cases (19–23).

Laboratory Tests and Studies

A 24-hour urine specimen should be obtained for measurement of inorganic mercury levels, while whole blood mercury levels should be measured for alkyls of mercury (organic mercury). Blood and urine levels of mercury should not exceed 10 ng/mL (see Chapter 9). Hair levels are more useful in cases of organic mercury poisoning and should not exceed 2 ng/mL (24).

Electrophysiological studies are necessary and often demonstrate a sensorimotor neuropathy, typically axonal. Visual-evoked potential studies may also present with abnormalities. The utility of MRI appears to be primarily for ruling out other causes of symptomatic presentations, while sural nerve biopsies in patients with Minamata disease caused by organic mercury toxicity indicated preferential loss of large myelinated nerve fibers (19,20,25).

Management

Administration of chelating agents that contain thiol groups is the accepted standard of care. For acute, inorganic toxicity, dimercaprol (BAL) has been recommended traditionally, but oral agents are gaining prominence. Chelation with DMSA (Succimer) has been shown to result in increased mercury excretion compared to *N*-acetyl-D,L-penicillamine in adults with acute mercury vapor exposure. DMSA is generally well tolerated in adults and children (16).

Chelation removes only a small portion of the toxin, especially in cases of organic mercury poisoning. The placebo response has been observed in patients concerned with the occupational exposure in dentistry, and there is a general paucity of studies showing neurological improvement following any kind of chelation therapy (25,26).

Arsenic Toxicity

Arsenic toxicity may be mistaken for Guillain-Barré syndrome, as it presents with paresthesias and numbness in a symmetric stocking-glove distribution and muscle weakness. Arsenic-induced neuropathy may persist after exposure

stops, but long-term exposure may present with a sensory neuropathy that resembles alcoholic neuropathy. Burning paresthesias in glove and stocking distribution, early loss of stretch reflexes, and later weakness are also seen. In severe cases, flaccid paralysis may appear in the lower extremities and then the upper extremities, again resembling Guillain-Barré syndrome (27–29).

Laboratory Tests and Studies

A 24-hour urine specimen should be obtained for measurement of arsenic levels, as well as a CBC with peripheral smear. Analysis of hair and fingernail clippings is less useful as there is a significant risk of environmental contamination (27-29).

Management

Chelation therapy with BAL, DMSA, or d-penicillamine is the primary treatment of arsenic toxicity. Removal of the offending agent and aggressive gastric decontamination aids in reducing ongoing absorption of arsenic. Hemodialysis may be beneficial in patients with acute renal failure (16,27–29).

Thallium Toxicity

Thallium poisoning induces a painful sensory neuropathy, particularly at the soles and palms, which may be followed by lower extremity weakness, ataxia, confusion, hallucinations, convulsions, and coma. Neuro-ophthalmic symptoms such as diplopia, abnormal color vision, and impairment of visual acuity may develop early, while dermatologic manifestations such as alopecia, rashes, palmar erythremia, and Mees lines in the nails and gums may be delayed by several weeks. Electrodiagnostic findings include an axonal sensorimotor neuropathy with nerves innervating the feet most significantly involved (30).

Management

Gastrointestinal decontamination, activated charcoal, and Prussian blue (potassium ferric hexacyanoferrate) are recommended in thallium ingestions. Activated charcoal and Prussian blue bind thallium decrease the enterohepatic recycling, and enhance fecal elimination of the metal. Prussian blue binds more thallium than charcoal on a gram-bound per gram-agent basis and should be used instead of charcoal if possible. Prussian blue is available only as a laboratory reagent in the United States and Canada, and is not approved by the FDA as a pharmaceutical agent. Prolonged neurological exposure to thallium, especially in cases of acute poisoning when proper diagnosis is not established and detoxification is delayed almost universally leads to long-term and/or irreversible neurological sequelae (30,31).

Neurotoxicity of Volatile Organic Compounds

Volatile organic compounds (VOCs), such as solvents, esters, hydrocarbons, aromatic compounds, and other organic chemicals, are characterized by low boiling temperature and higher volatility (Table 23.2). They are ubiquitous in agriculture, providing power for vehicles and used in every technological process. Volatile organic compound toxicity is divided into clinical syndromes based on the organ system: the lungs are affected most commonly, but instances of neurological, cardiac, gastrointestinal, renal, hematological, and skin pathology are also well documented. Three factors affect the selectivity and severity of toxic effects: the identity of the VOC, the dose, and the route of exposure (Table 23.2) (32–34).

Almost all VOCs are strongly lipophilic and attracted to neural tissue. Demyelinating peripheral polyneuropathy is associated with exposure to 6-carbon aliphatic hydrocarbons (n-hexane, methyl-n-butyl-ketone) that are metabolized into a compound that interferes with axonal transport. Long-term workplace exposure or inhalant abuse (solvent sniffing) may result in chronic headaches, cerebellar ataxia, and encephalopathic findings of cognitive and psychopathic impairment (34).

Butane, benzene, toluene, and xylene are CNS depressants, have a disinhibiting euphoric effect, and are used as agents of abuse. Patients present with symptoms of CNS disinhibition, such as dizziness, slurred speech, ataxia, and obtundation. Ventilatory drive may be compromised. The initial

TABLE 23.2. Chemicals found in specific products.

Product	Solvents
Balsa wood cement	Ethyl acetate
Contact adhesives	Toluene, hexane, esters
Tire adhesive	Toluene, xylenes
PVC cement	Trichloroethylene
Air freshener, deodorants, fly spray, hair lacquer, spray paints, aerosol packages	Halons (chloro-fluoro-organic compounds), butane, dimethyl ether, methylbutyl ketone
Anesthetics/analgesics	Nitrous oxide, ether, chloroform
Commercial dry cleaning, domestic spot remover	1,1,1-Trichloroethane, tetrachloroethylene, trichloroethylene
Fire extinguishers	Bromochlorodifluoromethane, halons 11 and 12
Cigarette lighters	n-Butane, isobutane, propane
Nail/varnish remover	Acetone and esters
Paints/paint thinners	Butanone, esters, hexane, toluene, xylene
Paint stripper	Dichloromethane, toluene
Surgical plaster/chewing gum removers	Trichloroethylene
Paint thinners	1,1,1-Trichloroethane, toluene, hexane, methyl n-butyl ketone

PVC, polyvinyl chloride.
Source: Data from Feldman (1), Ford (3), and LaDou (4).

TABLE 23.3. Toxic effects of various volatile organic compounds.

Specific compound	Signs and symptoms
Aliphatic hydrocarbons	Dizziness, syncope, giddiness, hypotension, cerebral ischemia, headache, tachycardia
n-Butyl, isobutyl, and amyl nitrite	Increased intraocular pressure, confusion, sudden death, convulsion, coma
Naphtha, kerosene	Irritation of mucous membranes, nausea, ataxia, dizziness, hallucinations
Gasoline	Respiratory arrest, syncope, death, myoclonia, chorea, encephalopathy, tremor, pulmonary hemorrhage and edema, pneumonitis, plumbism, anemia, lead encephalopathy, confusion, dementia, cerebral edema, peripheral and cranial neuropathies, paresthesias, proteinuria, hematuria
n-Hexane	Eye and nasopharynx irritation, dizziness, giddiness, nausea, headache, CNS depression, peripheral neuropathy, anemia, basophilic stippling, bone marrow depression, fatal overdose
Benzene	Irritation of conjunctivae and visual blurring; irritation of mucous membranes; dizziness; headache; unconsciousness; convulsions; tremors; ataxia; delirium; tightness in chest; irreversible brain damage with cerebral atrophy; fatigue; vertigo; dyspnea; respiratory arrest; cardiac failure and ventricular arrhythmias; leukopenia; anemia; thrombocytopenia; petechiae; blood dyscrasia; leukemia; bone marrow aplasia; fatty degeneration and necrosis of liver, heart, adrenal glands; fatal overdose
Naphthalene	Irritation and injury of conjunctivae and corneas, perspiration, nausea, vomiting, headache, cataracts, hemolytic anemia (greater in G-6-PD deficiency), hepatic necrosis, hematuria, jaundice, proteinuria, oliguria, anemia, excitement, confusion, convulsions, coma, dermatitis, fatal overdose
Styrene	Irritation of mucous membranes, CNS depression and narcosis, fatal overdose
Toluene	CNS depression, syncope, coma, cardiac arrhythmias and sudden death, ataxia, convulsions, rhabdomyolysis, increased creatine phosphokinase, abdominal pain, nausea, vomiting, hematemesis, peripheral neuropathy, paresthesias, encephalopathy, optic neuropathy, cerebral ataxia, distal renal tubular acidosis, hyperchloremia, hypokalemia, azotemia, hypophosphatemia, hematuria, proteinuria, pyuria, hepatosplenomegaly, lymphocytosis, macrocytosis, basophilic stippling, hypochromia, eosinophilia, EEG abnormalities, decreased cognitive function, fatal overdose

presentation may mimic alcohol intoxication. In some patients, an initial component of CNS stimulation may present as agitation, tremor, or seizure (Table 23.3) (35–37).

A physician dealing with the predominantly rural population may expect to see intermediate and long-term, low-level exposures that can lead to reversible and nonreversible neurological abnormalities. In some cases exposures that caused long-term neurotoxic effects have been estimated

TABLE 23.3. Toxic effects of various volatile organic compounds. (continued)

Specific compound	Signs and symptoms
Xylene	Irritation to eye and mucosa; CNS depression and narcoses; reversible corneal damage; death; pulmonary edema and hemorrhage; fatty degeneration of heart, liver, and/or adrenal glands; abnormal liver function tests
Esters	Irritation of eyes, skin, and mucous membranes; CNS depression; liver and kidney necrosis; fatal overdose
Glycols	Oxalosis, impaired renal and liver function, stupor, coma, convulsions, irreversible brain damage, pulmonary edema, respiratory failure, nausea, vomiting, headache, tachycardia, hypotension, hypoglycemia, hypocalcemia, intravascular hemolysis, lymphocytosis, proteinuria, hematuria, fatal overdose
Trichloroethane, trichloroethylene, methylchloroform	Decreased myocardial contractility, arrhythmias, cardiac arrest and failure, myocarditis, renal failure, paresthesias, tinnitus, ataxia, headache, narcosis, CNS damage, sudden death
Carbon tetrachloride, ethylene dichloride	Nausea; vomiting; confusion; unconsciousness; coma; respiratory slowing; color blindness; blurred vision; memory loss; paresthesias; tremors; dermatitis; CNS edema, congestion, and hemorrhage; edema and inflammation of the lungs, kidneys, spleen, and pancreas; fatty degeneration of liver; cardiac arrhythmias; sudden death
Methylene chloride	Liver and kidney abnormalities, fatal overdose
Methyl alcohol	Abdominal discomfort, dizziness, fatigue, headache, nausea, vertigo, CNS depression, coma, vomiting, acidosis, mydriasis, retinal edema and ganglion cell destruction, philophobia, mydriasis, areflexia, hemorrhagic infiltration of basal ganglia, decreased vision and blindness, fatal overdose
Isopropyl alcohol	Irritation of eyes and mucous membranes, nausea, vomiting, abdominal pain, hematemesis, narcosis, coma, areflexia, depressed respiration, oliguria, diuresis, fatal overdose
Butyl alcohol	Coma, areflexia, depressed respiration, oliguria and diuresis, fatal overdose, irritation of eyes and mucous membranes, CNS depression, kidney and liver damage, fatal overdose

CNS, central nervous system; G-6–PD, glucose-6–phosphate dehydrogenase.
Source: Data from Feldman (1), Ford (3), LaDou (4), and So (5).

to be below levels designated in regulations as acceptable for workers (Table 23.4) (37).

Imaging Studies

Electromyogram (EMG) and nerve conduction study (NCS) abnormalities have been demonstrated in individuals and groups exposed to VOCs. Evidence of a mixed sensory/motor neuropathy has been found in many of these patients, while some studies have even demonstrated dose-response data correlating exposure dose to physiological abnormalities (36).

TABLE 23.4. Levels of exposure believed to be acceptable for workers.

Compound	Measured in:	Compounds and levels believed safe
Acetone	Urine	Acetone, formic acid: 100 mg/L
Benzene	Urine	Total phenol: 50 mg/g at end of shift
Benzene	Expired air	Benzene: preshift 0.08 ppm; at end of shift 0.12 ppm
Carbon disulfide	Urine	2-TTCA (2–thiothiazolidine 4-carboxylic acid): 5 mg/g
Ethylene oxide	Urine, blood, expired air	None
N-hexane	Urine	2,5-hexanediol: 5 mg/g at end of shift
Hydrogen sulfide	Urine, blood, expired air	None
Methane	Urine, blood, expired air	None
Methyl mercaptan	Urine, blood, expired air	None
Methanol	Urine	Formic acid: 80 mg/g at start of work week; Methanol: 15 mg/g at end of shift
Methyl-*n*-butyl ketone	Urine, blood, expired air	None
Methylene chloride	Urine, blood, expired air	None
Organochlorine	Urine, blood, expired air	None
Organophosphates	Urine, blood, expired air	None
Perchlorethylene (PER)	Blood	PER: 1 mg/L
Perchlorethylene	Expired air	PER: 10 ppm before last shift of week
Styrene	Urine	End of shift: mandelic acid (MA): 800 mg/g, phenylglyoxylic acid (PGA): 240 mg/g Before shift: MA 300 mg/g, or PGA 100 mg/g
Styrene	Blood	Styrene: at start of shift 0.02 mg/L; end of shift 0.55 mg/L
Toluene	Urine, blood, expired air	Hippuric acid in urine, toluene in blood and expired air: none
1,1,1-Trichlorethane (methyl chloroform)	Urine	Trichloroacetic acid (TCA) at end of workweek: 10 mg/L Total trichloroethanol at end of shift and at end of workweek: 30 mg/L
1,1,1-Trichlorethane (methyl chloroform)	Blood	Total trichloroethanol: 1 mg/L
1,1,1-Trichlorethane (methyl chloroform)	Expired air	Methyl chloroform prior to last shift of workweek: 40 ppm
Trichloroethylene (TCE)	Urine	TCE or TCA: 100 mg/g at end of workweek TCA plus TCE: 300 mg/g at end of workweek
Trichloroethylene	Blood	TCE: 4 mg/L at end of workweek
Vinyl chloride	Urine, blood, expired air	None
Xylene	Urine	Methylhippuric acid: 1.5 g/g at end of shift

Source: Data from American Conference of Governmental Industrial Hygienists (39).

A study performed on industrial workers in Scandinavia assessed 87 patients with diagnoses of chronic solvent intoxication after occupational exposure. Sixty-two percent had abnormal EMG/NCS results on the first evaluation and 74% on the second evaluation 3 to 9 years later. Fibrillations were noted in 54% on initial examination and 61% on reexamination. The same authors found a high percentage of slow motor and sensory conduction velocities and/or prolonged motor distal latencies in car painters versus none in nonexposed controls (38).

Computed tomography (CT) scan, MRI, positron emission tomography (PET), and single photon emission computed tomography (SPECT) have been utilized to evaluate the mechanism and extent of VOC neurotoxicity in specific cases but have shown no consistent or unique pattern of pathological change. Cerebral, cerebellar, and olivopontocerebellar atrophy are commonly reported, with most frequent abnormalities noted in the temporal lobes and frontal lobes, with associated changes in the basal ganglia and the thalamus (38).

Electroencephalographic abnormalities also have been demonstrated in many populations exposed to organic solvents. In one study, acute effects of exposure to less than 400 ppm of xylene were assessed in healthy volunteers. Such exposure increased the dominant alpha frequency and percentage during the early phase of exposure and counteracted the effect of exercise. These effects were deemed minor and not deleterious. This (or any other) study did not address the more germane issue of longer-term exposure (38).

In acute intoxication cases, the most important presentations include lethargy and depressed sensorium, while coma is relatively uncommon. Other systems (gastrointestinal, skin, respiratory) are often affected and present with easy-to-interpret changes (pneumonitis, skin erythema, vomiting) (38).

Management

Management of acute cases is supportive since no specific antidotes to VOCs are available. Indicated medications for altered mental status of unclear etiology and for suspected opioid co-ingestion include dextrose, thiamine, and naloxone and for bronchospasm selective beta-2-agonists (albuterol).

In cases of chronic exposure all reasonable means of reduction or complete removal of the toxic agent are warranted, and a consultation with poison control or an industrial hygienist may be helpful. The use of personal protective equipment and training in its use are often neglected, especially in the field and by temporary workers (see Chapters 5 and 6). In severe cases, the patient should be reevaluated with thorough neurophysiological and, if applicable, neuropsychological testing on a repeated basis with average frequency of one EMG and NCS study every 9 to 12 months until sufficient progress or stabilization is noted (39).

Neurotoxicity of Organochlorine Compounds

Pesticides such as dichlorodiphenyltrichloroethane (DDT), endrin, dieldrin, aldrin, endosulfan, chlordane, heptachlor, lindane, and chlordecone have been in use since the late 1940s and are readily available, in most countries, to be used alone or in combination with other pesticides as sprays, powders, pellets, and dusts (see Chapter 13). These are lipophilic compounds and many of them have been demonstrated to form depots in tissues with high lipid content, especially the brain. This specific chemistry of organoclorines makes serum level measurements uninformative, as severe toxicity has been documented in patients with low serum levels as a result of chronic exposure and sequestration of the toxin in the organism. Most of these compounds (cyclodienes, hexachlorocyclohexanes, and toxaphene organochlorines) inhibit the γ-aminobutyric acid (GABA) receptors and prevent chloride influx in the CNS, resulting in a typical "GABA-ergic" clinical picture of agitation, confusion, and seizures (40–42).

Organochlorines are divided into highly toxic (aldrin, dieldrin, endrin [banned in the United States], and endosulfan) and moderately toxic (chlordane, DDT [banned in the United States], heptachlor, kepone, lindane, mirex, and toxaphene). There are no nontoxic organochlorine-based pesticides, and cumulative exposure to even moderately toxic agents may lead to severe disability (42).

In acute exposure, the onset of symptoms is abrupt and caused by CNS stimulation and lowering of the seizure threshold. Patients often develop nausea and vomiting, followed by confusion, tremors, coma, seizures, and respiratory depression. Fatality may occur within 4 to 8 hours and is primarily due to respiratory failure or seizures. Cerebral edema may occur and is viewed as a negative prognostic sign. Emergency treatment with cholestyramine has been associated with better prognosis and somewhat higher efficacy than the commonly used activated charcoal (these agents can be used concurrently). Induced diuresis, hemodialysis, and hemosorption with activated charcoal have not been shown to be effective in enhancing the elimination of the toxin (40,41).

Patients with long-term occupational exposure to organochlorine pesticides may develop a variety of nonspecific complaints including headaches, nausea, fatigue, muscle twitching, and visual disturbances. There is no reliable statistical data associating exposure to organochlorines with any specific type or location of cancer. Some of the less obvious signs of cumulative toxicity of these chemicals include paresthesias of the face, auditory or visual hallucinations, and perceptual disturbances, although the latter are more reliably associated with acute toxicity (41–44).

Management

Treatment is supportive, although in cases of significant exposure, seizure control may be necessary. Seizures induced by organochlorine pesticides

respond well to benzodiazepines. The prognosis is variable based on amount and type of exposure (42).

Neurotoxicity of Organophosphate and Carbamate Compounds

Organophosphate compounds such as diazinon, disulfoton, azinphos-methyl, chlorpyrifos, and fonofos are used widely in agriculture. Some have been phased out in the United States but remain in active use in other countries. Other agents with similar action include toxic nerve gases that have gained significant publicity as potential chemical warfare and terrorism agents (Sarin). Carbamate compounds also have been developed as pesticides and are associated with less toxic effects in humans. Currently, agricultural exposure is the most common epidemiological site of organophosphate poisoning, and any worker in the industry can be affected, including manufacturers, field workers, truckers who transport pesticides or produce, and crop dusters (45).

Pathophysiology

Carbamate and carbamate-based pesticides exhibit their toxic action via inhibition of acetylcholinesterase, an enzyme found in nicotinic and muscarinic receptors in nerve, muscle, gray matter of the brain, and red blood cells. Inhibition of this enzyme leads to central, parasympathetic, and sympathetic neurotoxicity (45).

Most organophosphates (especially the nerve gases) induce irreversible phosphorylation of the serine hydroxyl moiety at the binding site of the enzyme, thus reducing the esterase activity. This block may be reversed by the administration of the commonly used specific antidote pralidoxime (2-PAM), but with passage of time the natural cellular proteinases are activated and the majority of poisoned enzyme is taken inside the cell (thus rendering it inaccessible to the action of 2-PAM) and proteolytically destroyed within 24 hours. Although the rate of synthesis of acetylcholinesterase in the neuron has not been measured with satisfactory precision, the much more easily measured enzyme levels in the erythrocyte increase very slowly, by less than 1% a day (46).

Acetylcholinesterase inhibition induced by carbamate-based pesticides is reversible, and the agents themselves have poor ability to penetrate the blood–brain barrier, which limits their clinical significance as neurotoxic agents (45,46).

In addition to the well-established rapid toxicity related to the cholinergic crisis, some of the organophosphates exhibit delayed neurotoxicity, which is due to their ability to induce axonal pathology and resulting polyneuropathy. This area of research is controversial, as is the association of preventive use

of antidotes during the first Gulf War. In several well-established cases of organophosphorous ester–induced delayed neuropathy, patients have developed the condition as a result of both acute and cumulative exposure, with a significant time delay factor (more than a week) after single acute exposures and an even less certain and more expanded latent period in chronic exposure. Typically, the spinal cord tracts and distal axons of the lower extremities are involved more than the upper extremities. Primary axonopathy is accompanied by secondary demyelination in which both sensory and motor fibers are involved. The delayed toxicity is not due to acetylcholinesterase poisoning but rather a result of phosphorylation of a receptor protein. In complicated cases of neuropathy following pesticide exposure, a sural nerve biopsy may be performed and blood samples may be analyzed for the levels of the target protein (45,46).

A unique case addressed neuropathic changes observed in a middle-aged man who had one episode of exposure to sarin during the 1995 terrorist attack in a Tokyo subway. Peripheral nerve biopsy found severe sensory and motor fiber loss and a postmortem examination revealed nearly total loss of myelinated fibers in the white matter of the spinal cord with apparent sparing of the posterior columns. Brain changes were also found to be consistent with hypoxic-ischemic encephalopathy (47).

Genetic predisposition may play a role in the development of chronic exposure–induced delayed neurotoxicity. At least two research groups found the correlation between the development of Parkinson's disease as a result of exposure to organophosphate pesticides and genetic polymorphisms of glutathione transferase, an antioxidant enzyme. As dopamine is the only known major neurotransmitter that produces an active (and toxic) free radical when metabolized by monoaminooxidase, patients with decreased cellular proxidant scavenging ability may be more susceptible to development of Parkinson's disease and dementia with Lewy bodies (44,48,49).

Elbaz and colleagues (50) performed a case-control study of Parkinson's disease in a population characterized by a high prevalence of pesticide exposure. The authors also studied the joint effect of pesticide exposure and the activity of a cytochrome CYP2D6, a protein commonly implicated in the association between pesticide neurotoxicity and the development of Parkinson's disease. The authors found that pesticides have a modest effect of increasing the incidence of Parkinson's disease in subjects who are not CYP2D6 poor metabolizers and that the effect of pesticides is increased approximately twofold in poor metabolizers. This study also found that individuals who are CYP2D6 poor metabolizers are not at increased Parkinson's disease risk in the absence of pesticide exposure (51).

Another commonly implicated protein that may be a part of the pesticide exposure link to neurodegenerative disease is alpha-synuclein, a small, highly charged protein expressed predominantly in neurons. It is the major building block of pathological inclusions that characterize many neurodegenerative disorders, including Parkinson's disease, dementia with Lewy bodies (DLB),

and neurodegeneration with brain iron accumulation type 1 (NBIA-1), which collectively are termed synucleinopathies. Several ongoing studies have established preliminary links between exposure to pesticides with abnormal levels of expression of synuclein and related proteins (52).

Alpha-synuclein is a presynaptic protein characterized by the lack of rigid well-defined structure. This protein may either stay unfolded or adopt an amyloidogenic folded conformation. It also might form several morphologically different types of aggregates, including oligomers, amorphous aggregates, and/or amyloid-like fibrils. This plasticity may explain why a single protein is believed to be involved in such a varied spectrum of neurodegenerative diseases. Preliminary evidence suggests that the ultimate structural fate of this and other amyloidogenic proteins depends on the levels of free radicals in tissue. This finding may explain the presence of the cytochrome system inhibition in the clinical history of some of the patients, as the malfunctioning cytochrome system is a known source of free radicals (53,54).

While measurement of synuclein in the brain tissue remains technically difficult, the issue of inhibition and induction of CYP2D6 is much more real and practical for all physicians. Table 23.5 summarizes current knowledge of the chemicals that induce and inhibit this cytochrome. Physicians may be well served by noting the connection between CYP2D6 status and prescribing

TABLE 23.5. Chemical compounds and cytochrome 2D6.

CYP2D6 substrates	CY2D6 inducers	CYP2D6 inhibitors
Most tricyclic antidepressants: amitriptyline, nortriptyline, clomipramine, desipramine, imipramine, doxepin	Carbamazepine	Amiodarone
Many antipsychotics: clozapine, risperidone, chlorpromazine, haloperidol, fluphenazine, thioridazine	Phenobarbital	Cimetidine
Opioids and opioid-like analgesics: codeine, hydrocodone, oxycodone, morphine, methadone meperidine, tramadol	Phenytoin	Clomipramine
Some antidepressants: fluoxetine, paroxetine, venlafaxine, trazodone	Rifampin	Desipramine
Many beta-1-blockers: bisoprolol, metoprolol, propranolol, timolol	Ritonavir	Fluoxetine
Alzheimer's disease medication: donepezil		Fluphenazine
Antiarrhythmics: flecainide, mexiletine, propafenone		Haloperidol
Stimulants: methamphetamine		Mibefradil
		Paroxetine
		Propafenone
		Quinidine
		Ritonavir
		Sertraline
		Thioridazine

Source: Data from Michalets (55).

medications that are less likely to inhibit this enzyme or to compete with other substrates, such as pesticides (55).

Diagnosis

Patients with acute poisoning present with classical symptoms of cholinergic excess. Two acronyms are used as mnemonic devices to aid in memorization of symptoms:

1. DUMBELS: diarrhea, urination, miosis, bronchospasm, emesis, lacrimation, and salivation
2. SLUDGE: salivation, lacrimation, urination, diarrhea, gastrointestinal distress, and emesis

Both mnemonics emphasize the muscarinic side of the cholinergic crisis, while no acronym has been suggested for the nicotinic side, often manifesting as fasciculations, muscle weakness, hypertension, and tachycardia. Additional muscarinic effects include reduction of sinus node and atrioventricular conduction, causing bradyarrhythmias or resultant ventricular dysrhythmias (56).

Organophosphate poisoning should be suspected in any agricultural workers who present with constricted pupils, especially if they also exhibit restlessness, emotional lability, or confusion. Other warning signs include slurred speech, ataxia, tremor, muscle weakness with cramping, fasciculations, and, less commonly, seizures. In these cases a rapid and reliable measurement of red blood cell esterase activity may be both of confirmatory diagnostic and of significant prognostic value (see Chapter 9) (56).

Emergency physicians have agreed on the classification of the degree of severity of poisoning based on easily measured red blood cell cholinesterase (see Chapter 9 for a discussion of baselines):

1. Mild poisoning: loss of 20% to 50% of baseline activity
2. Moderate poisoning: observed activity of only 10% to 20% of the expected baseline (80% to 90% loss of activity)
3. Severe poisoning: patients with less than 10% of esterase activity (or more than 90% loss) (56)

Management

Atropine was used as the sole treatment until the enzyme-specific antidote pralidoxime chloride (Protopam, 2-PAM, a relatively nontoxic substance) was developed and is still used as the sole treatment in developing countries. In the United States, the standard protocol calls for the use of pralidoxime in mild cases and coadministration of pralidoxime and atropine in moderate and severe poisonings. In cases of oral ingestion, activated charcoal in suspension may be used if the patient is seen within 30 minutes of ingestion (Table 23.6) (56)

TABLE 23.6. Medications useful in management of toxicity associated with agricultural exposure.

Drug	Adult dosage	Contraindications	Interactions	Pregnancy	Complications and adverse effects
Dimercaprol (BAL suspension in peanut oil)	0.5–3 mg/kg q4h IM for 2 d, then q.i.d. for 1 d followed by b.i.d. for 10 d. Higher doses may be needed. Maximum dose is 5 mg/kg	Documented hypersensitivity; hypersensitivity to peanuts; G-6-PD deficiency; concurrent iron supplementation therapy	Selenium, uranium, iron, or cadmium may increase toxicity	Class C—Safety for use during pregnancy has not been established	Fever, tachycardia, hypertension, headache, CNS stimulation, nausea and vomiting. Sterile abscess may develop at injection site. May induce hemolysis in G-6-PD–deficient patients
Succimer (Chemet)	PO dose 10 mg/kg q8h × 5 d; 10 mg/kg q12h × 14 d	Documented hypersensitivity	Do not administer concomitantly with edetate calcium disodium or penicillamine	Class B—Usually safe but benefits must outweigh the risks	Excreted via kidneys, adequate hydration must be maintained; patients with renal insufficiency should be treated with caution. Not the 1st choice in arsenic poisoning. Watch for nausea/vomiting, thrombocytopenia, eosinophilia, and cardiac dysrhythmias.
Penicillamine (Cuprimine, Depen)	25 mg/kg PO, q6h to maximum 1 g/d	Documented hypersensitivity	Increases effects of immunosuppressants, phenylbutazone, and antimalarials; decreases digoxin effects zinc salts, antacids, and iron may decrease effects	Class B—Usually safe but benefits must outweigh the risks	Nausea, vomiting, fever, rash, neutropenia, thrombocytopenia, eosinophilia, and Stevens-Johnson reaction

continued

TABLE 23.6. Medications useful in management of toxicity associated with agricultural exposure. (continued)

Drug	Adult dosage	Contraindications	Interactions	Pregnancy	Complications and adverse effects
Atropine (Atropair)	1 mg IV (initial or diagnostic) 2–4 mg IV q15min (therapeutic). Also, 2 mg/kg/h IV drip as needed to control secretions	Documented hypersensitivity; thyrotoxicosis, narrow-angle glaucoma, and tachycardia	Coadministration with other anticholinergics have additive effects; pharmacologic effects of atenolol and digoxin may increase; antipsychotic effects of phenothiazines may decrease; antidepressants with anticholinergic activity may increase effects of atropine	Class C—Safety for use during pregnancy has not been established	Caution in patients with (1) brain damage to prevent hyperreactive response; (2) coronary heart disease, congestive heart failure, cardiac arrhythmias, and hypertension; (3) peritonitis, ulcerative colitis, hepatic disease, and reflux esophagitis; (4) prostatic hypertrophy.
Pralidoxime (2–PAM, Protopam)	1–2 g IV over 15 min initial; followed by 500 mg/h IV until improved muscle strength	Documented hypersensitivity	None reported	Class C—Safety for use during pregnancy has not been established	Relatively nontoxic compounds; not effective for poisonings caused by organophosphates without anticholinesterase activity.

Source: Data from Jeyaratnam and Maroni (56).

Aggressive and timely therapy usually leads to recovery from acute toxicity within 10 to 14 days. Delayed intervention or chronic exposure may lead to impaired recovery and possible permanent neurological sequelae. Such sequelae may lead to delayed fatalities as observed after the 1995 Tokyo terrorist attack (56).

Acute poisoning does not warrant extensive imaging or electrophysiological studies, as they may contribute little new information in a typical case. Of course, any focal deficit must be investigated as aggressively as the case warrants and local conditions would allow. Both NCS and EMG are helpful and should be repeated on a regular basis (every 9 to 12 months) in cases of pesticide-induced neuropathies and, somewhat surprisingly, also in patients who require mechanical ventilation. Singh et al. (44) examined the phrenic nerve conduction of 29 patients with organophosphate toxicity admitted to the hospital in 1997, 14 of whom required mechanical ventilation. They found that the reduction in compound muscle action potential (CMAP) correlated with the need for ventilatory assistance. By following patients with daily nerve conduction studies, the authors were able to predict successful weaning.

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