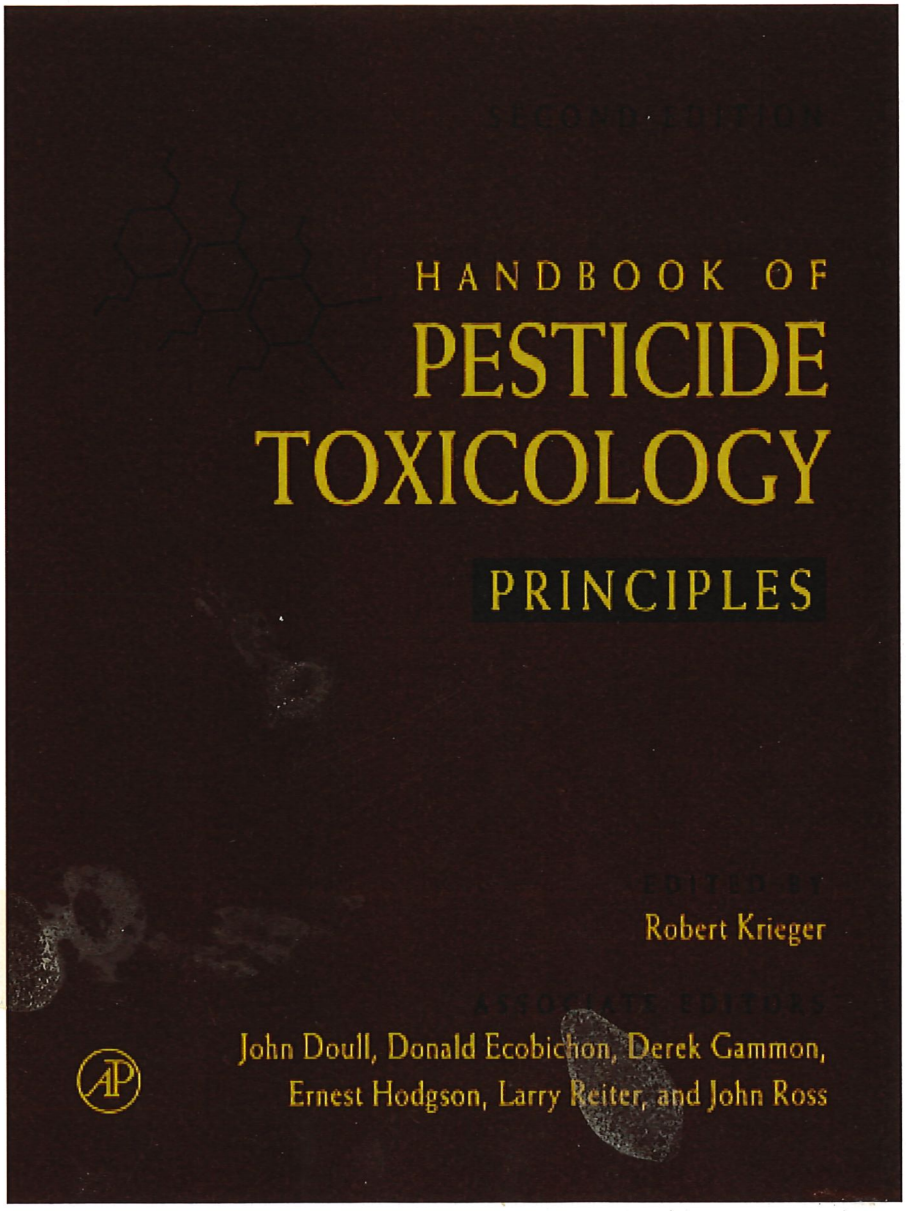
SECOND EDITION
HANDBOOK OF
PESTICIDE
TOXICOLOGY
PRINCIPLES
EDITED BY
Robert Krieger
ASSOCIATE EDITORS
John Doull, Donald Ecobichon, Derek Gammon,
Ernest Hodgson, Larry Reiter, and John Ross

pounds including crimidine (BSI, ISO) that apparently have not yet produced poisoning in humans and certainly have not been used as drugs or studied experimentally in human subjects.

## 83.2 FLUOROACETIC ACID AND ITS DERIVATIVES

Sodium fluoroacetate came to prominence in the United States as a result of a search for rodenticides that would not be subject to shortages imposed by World War II (Ward, 1945). This and related compounds had been considered earlier as systemic insecticides. At about the same time, it became known that fluoroacetate is the toxic material in the South African plant "gifblaar" (*Dichapetalum cymosum*). Later it was shown that the same compound is present intermittently in *Acacia georgiana*. The main toxicant in *D. toxicarium* is fluorooleic acid, but fluoropalmitic acid is present also. The ground seeds of *D. toxicarium* have been used by natives as a rat poison. It gave problems with secondary poisoning and human toxicity similar to that later associated with synthetic sodium fluoroacetate.

Under these circumstances, there were practical as well as academic reasons to study the mode of action of organic monofluoro compounds. It appears that the toxicity of all of the compounds depends on the same mechanism. Highly toxic compounds either have two carbon atoms or are metabolized to this form (Chenoweth, 1949; Peters, 1963a; Raasch, 1958; Saunders, 1947).

### 83.2.1 SODIUM FLUOROACETATE

#### 83.2.1.1 Identity, Properties, and Uses

**Chemical Name** Sodium monofluoroacetate is the chemical name.

**Structure** See Fig. 83.1.

**Synonyms** Sodium monofluoroacetate is also known as Compound-1080 or ten-eighty. The CAS registry number is 62-74-8.

**Physical and Chemical Properties** The empirical formula for sodium monofluoroacetate is $C_2H_2FNaO_2$ and the molecular weight is 100.3. Its forms an odorless, white, nonvolatile powder that decomposes at about 200°C. Although the compound is often said to be tasteless, dilute solutions actually tasted like weak vinegar. Sodium fluoroacetate is very water soluble and hygroscopic but is of low solubility in ethanol, acetone, and petroleum oils.

**Formulations and Uses** Sodium fluoroacetate is formulated as an aqueous solution containing a warning color. Sodium monofluoroacetate is used to kill rats, mice, other rodents, and predators. It is an intense mammalian poison, and it is used in many countries but only by trained personnel.

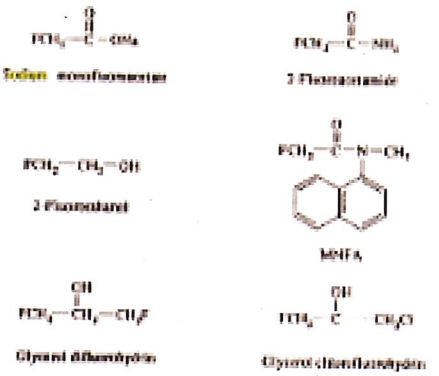

Figure 83.1 Some organic fluorine rodenticides and other organic fluorine pesticides.

#### 83.2.1.2 Toxicity to Laboratory Animals

**Basic Findings** The first paper on sodium monofluoroacetate as a rodenticide (Kalmbach, 1945) drew attention to its very high acute toxicity. LD 50 values for ordinary laboratory rats and for wild animals of the same species were reported as 2.5 and 5.0 mg/kg, respectively. The wild black rat (*Rattus rattus*), another commensal species, was much more susceptible (LD 50:0.1 mg/kg). A LD 50 of 0.22 mg/kg has been reported for *Rattus norvegicus* (Dieke and Richter, 1946). The likelihood of danger to people, domestic animals, pets, and nontarget wildlife was pointed out. The acute toxicity of the compound to an extremely wide range of wildlife was reported by Ward and Spencer (1947). See Table 83.1.

Fluoroacetate acts mainly on the central nervous system and the heart. It seems that there are species in which fluoroacetate affects chiefly the heart, such as the rabbit, the goat, and the horse, and others in which only the central nervous system is affected, such as the dog, the guinea pig, and the frog. In the cat, the rhesus monkey, the domestic pig, and birds, both systems are involved. The above results were obtained by Chenoweth and Gilman (1946) using methyl fluoroacetate instead of sodium fluoroacetate. However, since both compounds yield the fluorocitrate ion in the body, where it is converted to fluoroacetate, which is responsible for the induction of pharmacologic and toxic signs (see below), it seems that this experiment is nevertheless interesting in showing a large degree of species variability in the site of action. In all species, there was a delay of 0.5–2 hr or more between administration, either oral or intravenous, and the onset of the symptoms, and the route of administration did not significantly affect the toxicity of fluoroacetate.

Laboratory rats acquire a tolerance to sodium fluoroacetate by ingesting sublethal doses over a period of 5–14 days. However, this tolerance is lost if intake of the compound is interrupted for as little as 7 days (Kalmbach, 1945).

Tolerance of some but not all species was confirmed by several investigators, including Kandel and Chenoweth (1952). These authors found that, whereas small doses of fluoroacetate increased tolerance to challenge doses of fluoroacetate or

Consistent with the theory that fluorocitrate is the active toxicant, it was found to be at least 100 times more toxic than fluoroacetate when injected directly into the brain under various experimental conditions. An intracerebral dose of 0.115 μg failed to kill rats weighing about 250 gm, and it did not cause convulsions; doses of 0.287 μg (about 0.001 mg/kg) or greater caused convulsions and killed almost all rats (Morselli *et al.*, 1968). On the other hand, a dosage of 40–60 mg/kg is necessary to kill by the intraperitoneal route, and an oral dosage of 40 mg/kg constitutes only an LD 50. The great difference was attributed to failure of fluorocitrate to reach aconitase within critical cells of the brain and heart (Peters and Shorthouse, 1971). Species differ in the degree to which the concentration of citrate increases in different organs and also in the timing of these increases (Kirzon *et al.*, 1973). These biochemical differences presumably underlie the clinical differences between species, especially the relative importance in neurological and cardiac effects.

Accumulation of citrate was evident in mice within 2 hr after intraperitoneal injection of sodium fluoroacetate at a rate of 30 mg/kg, which is about 1.7 times the LD 50 in that species. The concentration of citrate increased from 48 ppm in controls to 74, 101, and 166 ppm within 2, 5, and 24 hr, respectively, after injection. The mice were dead at 24 hr (Matsumura and O'Brien, 1963).

Whereas Williamson *et al.* (1964) agreed that the initial effect of fluoroacetate is to produce fluorocitrate, they considered that the secondary inhibition of phosphofructokinase by the accumulated citrate was actually lethal because it deprived the cell of pyruvate, which would eventually overcome the inhibition of aconitase.

**Effects on Organs and Tissues** Loracher and Lux (1974) concluded on the basis of studies of neuromembrane depolarization that diminished inhibitory conductance is apparently important as a causative factor in convulsions induced by sodium fluoroacetate. The decreased level of ionized calcium in blood induced by the chelating effect of citrate certainly plays a role in the depolarization of the neuromembrane, as it does on the cardiac cell membranes. The effect of sodium fluoroacetate on the heart rhythm is due, as demonstrated by Noguchi *et al.* (1966), primarily to action on the cells themselves and not on the vagus nerve. Irregularity of rhythm and a condition analogous to fibrillation were produced in cultures of heart cells that had grown until cell-to-cell contact was prevalent and beating was synchronized. The average times necessary to produce irregularity and fibrillation were 9 and 48 hr, respectively, at a concentration of 10 ppm in the medium, but only 2 and 9 hr, respectively, at a concentration of 100 ppm. At a concentration of 1000 ppm, fibrillation was immediate and cytoplasmic vacuoles appeared rapidly.

**Effects on Reproduction** A dosage of sodium fluoroacetate just below the maternal LD 50 reduced oxygen consumption of the embryos as well as the mother but was not teratogenic (Spielmann *et al.*, 1973).

**Treatment of Poisoning in Animals** Hutchens *et al.* (1949) demonstrated a significant reduction of mortality in mice, guinea pigs, and rabbits (but not dogs) treated with ethanol at a rate of 800 mg/kg administered subcutaneously as a 10% solution in normal saline. The response occurred when the alcohol was given before signs of poisoning appeared and was best when given within 10 min of poisoning. In mice, sodium acetate and ethanol acted synergistically to antagonize poisoning (Tourtellotte and Coon, 1951). The beneficial effect of ethanol in rodents was confirmed by Chenoweth *et al.* (1951), but these authors found ethanol less effective in the dog and utterly useless in the monkey. In a study of a wide range of chemical substances in mice, rats, rabbits, dogs, and rhesus monkeys, they concluded that commercially available monacetin containing about 60% glycerol monoacetate was superior to any other substance tested as an antidote for poisoning by fluoroacetate. Not only did it reduce mortality, but it was able to normalize heart and brain rhythms as indicated by ECG and electroencephalogram (EEG) tracings.

Light pentobarbital anesthesia for 18–24 hr significantly reduced mortality among dogs poisoned by sodium monofluoroacetate at a rate of 0.10 mg/kg (Hutchens *et al.*, 1949; Tourtellotte and Coon, 1951).

### 83.2.1.3 Toxicity to Humans

**Accidental and Intentional Poisoning** Sodium fluoroacetate was introduced in 1946 in the United States for use by pest control operators, including persons hired for the purpose by government agencies. The poison was mixed with a dye. Solutions were supposed to be placed in shallow paper cups made in such a way that they would not tip over. These water baits were supposed to be used only in places that would be unoccupied and locked during exposure of the poison, and all cups and dead rodents were supposed to be collected and incinerated by authorized persons at the end of the exposure period. However, the regulations were not always followed. By the end of the year, at least one child who found an "empty" paper cup had died, and her 3-year-old brother had been severely poisoned. By the end of 1949, there had been at least 12 deaths and 6 cases of nonfatal poisoning. In addition, there had been 4 deaths, all in children, that probably were caused by sodium monofluoroacetate, but other sources of poisoning could not be ruled out. Of the 12 deaths clearly caused by sodium monofluoroacetate, 5 involved small children who had found and often chewed on a poison cup, 3 involved juveniles who had found the poison in a soft drink bottle, and 4 were suicides of adults. Except one, each of the survivors was a child who had found a poison cup. These accidents made such an impression on the few people who had legal access to sodium fluoroacetate that they became far stricter in carrying out the recommended precautions and in selecting situations in which the compound was used at all. As a result, the safety record of the compound in the United States improved greatly.

A typical fatal case involved a 40-year-old man who was found unconscious in his bedroom. He had an 8-year history

of severe depression, and his family had been warned of the possibility of suicide. When admitted to hospital, he had slight muscular spasms and nystagmus of both eyes; the heart rate was 92 beats per minute and rhythm was irregular. Following gastric lavage and a soft soap enema, the nystagmus became worse, and the patient had an epileptiform convulsion. The blood pressure fell to 90/40 mm Hg. Treatment consisted of plasma, oxygen, and procaine hydrochloride in the hope of desensitizing the heart. The blood pressure improved to 118/75 mg Hg, but there was no decisive change until the heart and later the respiration stopped about 17 hr after admission (Harrisson *et al.*, 1952a). Another fatal case was remarkable for its combination of prolonged survival following the ingestion of an almost certainly very large dose. Briefly, about 113,000 mg of sodium fluoroacetate was missing from a professional rat exterminator's supplies after his 17-year-old son made a solution and drank it. The boy vomited promptly and then within an hour walked into an hospital emergency room. He gradually became comatose during gastric lavage, and consciousness was never regained. Within less than 3 hr of ingestion, he had a grand mal convulsion associated with fecal incontinence. The clinical course, which lasted slightly over 5 days, was characterized by cardiac irregularity, which responded to a considerable degree to procainamide hydrochloride; dilation and failure of the heart with acute pulmonary edema, which responded surprisingly well to digitalis (lanatoside C); bouts of severe hypotension, which responded only questionably to levarterenol (norepinephrine) but somewhat better to mephentermine; cortical irritability, which responded to barbiturates and later responded more effectively to ethanol; frequent severe carpopedal spasm, controlled somewhat by calcium gluconate; and finally growing evidence of infection including a temperature reaching 42.3°C in spite of efforts to reduce it. The diagnosis based on autopsy was poisoning, bronchopneumonia with septicemia, focal infarction of the right kidney, and mediastinal emphysema (Brockmann *et al.*, 1955).

Serious illness followed by full recovery occurred in a 2-year-old boy who was found licking crystals from the screw cap of a bottle of sodium fluoroacetate solution. The parents did not know whether he drank any of the solution. Almost immediately after he was found, the boy began to vomit. He was brought to hospital about 6 hr later because he began to have generalized convulsive movements and became stuporous. On admission, the boy was comatose and exhibiting carpopedal spasms, tetanic convulsive movements, irregular respiration, and great cardiac irregularity. While a solution of calcium gluconate was being injected, there were a few seconds of cardiac asystole. Thereafter, the irregular cardiac rhythm resumed but at a much slower rate. Tetanic convulsions stopped immediately, and the child became completely flaccid. A few hours after admission, the child became responsive. Very soon the boy suffered a generalized tonic clonic convulsion lasting several minutes and followed by deep coma. Briefly, the boy remained unresponsive for 4 days. Cardiac rhythm continued to change frequently during the first 3 days. Tonic convulsions lasting several minutes occurred many times every hour, sometimes about every 10 min for many successive hours. During spasm, the pupils dilated and remained inactive to light, between seizures the pupils were miotic but responsive to light. On two occasions respiration stopped and artificial respiration was required briefly.

On the evening of the fourth day, 100 hr after ingestion, the boy began to open his eyes and look about. He tried to talk but was unable to articulate. He could neither sit up nor reach for objects but appeared alert. On the fifth day and sixth days, he rapidly regained all his motor ability, slowly lost his drowsiness, and became articulate. On the evening of the sixth day he was clinically well. He was discharged on the eleventh day. Reexamination 1 year later showed that the boy had had no further neurological trouble, and his mental and physical development has proceeded normally (Gajdusek and Luther, 1950).

In another case in which the initial dosage undoubtedly was smaller, there were no important clinical changes until 20 hr after ingestion, when the 8-month-old girl had a generalized seizure lasting about 1 min. In spite of treatment with phenobarbital, three additional seizures occurred during the next 12 hr. There was no further illness, and the patient was discharged 4 days later. Follow-ups revealed no change in behavior, intellect, or motor performance (Reigart *et al.*, 1975).

Any serious but reversible interference with respiration or general circulation is liable to produce some cases in which the patient survives but with severe brain damage. The cardiac arrhythmias characteristic of poisoning by sodium fluoroacetate are likely to produce such interference. An example involved an 8-year-old boy who was in status epilepticus when he entered hospital. The convulsions were controlled to some degree. There was no striking change until 14 hr after admission, when ventricular asystole occurred. Heart action was renewed but only after sufficient delay that the child suffered brain damage and was clearly mentally defective after a very long and stormy hospital course (McTaggart, 1970).

During the decade 1971–1981, 111 cases of accidental or unintentional poisoning with sodium fluoroacetate were collected by the National Poison Center of Israel. These cases included three cases of death and one case of mass accidental poisoning affecting 30 children, although the great majority of them only consumed a very small number of wheat grain baits impregnated with the compound. These latter cases did not result in clinical symptoms of poisoning (Roy *et al.*, 1982). These authors also described the clinical features of two cases of acute poisoning in which gastrointestinal disorders were rapidly followed by central nervous system manifestations (disorders of consciousness, convulsions, coma) and cardiac disorders, the most frequent cause of death. Ventricular ectopic beats preceded the ventricular arrhythmia, which was then followed by ventricular tachycardia and fibrillation. The electrocardiogram was characterized by a prolonged QT interval. A metabolic acidosis was commonly observed. Chung (1984) reported on five cases collected between 1975 and 1981 in Taiwan. The amount ingested ranged from 8 to 40 ml of a 1% formulation of sodium monofluoroacetate. All five patients survived. All cases had signs of transient cardiac dysfunction, but in addition acute re-

that the child would not have progressed equally well without treatment.

Although monacetin apparently has not been administered to a human patient, the work of Chenoweth *et al.* (1951) in various animals, especially monkeys, offered good reason to think it would be valuable for treating human poisoning. They recommended that it be injected intramuscularly at least every hour for several hours at the rate of 0.1–0.5 ml/kg per injection. There is no clinical evidence for or against the use of acetate in humans. On the contrary, acetamide has been administered to patients, and it seemed to be the reason for their survival. It is available at Accident and Emergency Departments throughout New Zealand. Acetamide is administered intravenously as a 10% solution in 5% glucose. In severe cases, 500 ml is given in 30 min every 4 hr; in milder cases, 200 ml is given on the same schedule. There can be no doubt that removal of the poison and supportive care are indicated. A number of patients have shown clear-cut poisoning but survived without sequelae following such treatment. Supportive care should include continuous cardiac monitoring. There is strong clinical evidence that the danger of cardiac arrhythmia can be reduced significantly by judicious and continuing use of procainamide hydrochloride. Even so, equipment for defibrillation should be ready. There is reason to hope it would be successful if required because at least one patient was revived with only external massage of the heart. There is also clinical evidence that cortical irritability can be lessened by barbiturates. There is no basis for speculating on the value of diazepam in this connection. Contrary to the evidence in monkeys, clinical evidence in humans has indicated that ethanol is beneficial and perhaps superior to barbiturates. Whereas the effect seemed to involve needed sedation, the possibility of a more fundamental effect in the biochemical lesion was not excluded.

On the basis of laboratory studies, Chenoweth *et al.* (1951) recommended against administration of calcium, potassium, sodium chloride, bicarbonate, or acetate. They considered that any necessary replacement of fluid should be done cautiously with plasma, and they considered digitalization as definitely contraindicated. However, clinical experience argues strongly against two of this prohibitions, and there is no clinical evidence to support some of the others. Calcium gluconate has proved useful in controlling carpopedal spasm, including such spasm in a patient who survived whithout sequelae. Digitalis (lanatoside C) not only improved the function of a poisoned heart that had failed to the point of acute pulmonary edema but also produced no detectable side effects.

Finally, there is clinical evidence that mephentermine is more effective than levarterenol in raising blood pressure if that becomes necessary in the course of poisoning by sodium fluoroacetate.

## 83.2.2 FLUOROACETAMIDE

### 83.2.2.1 Identity, Properties, and Uses

**Chemical Name** 2-Fluoroacetamide is the chemical name.

**Structure** See Fig. 83.1.

**Synonyms** Fluoroacetamide is also known as Compound 1081. Trade names for fluoroacetamide include Fluorakil®, Fussol®, Megarox®, and Yancock®. The CAS registry number is 640-19-7.

**Physical and Chemical Properties** Fluoroacetamide has the empirical formula $C_2H_4FNO$ and a molecular weight of 77.06. It is a crystalline solid that sublimes on heating but melts at 107–109°C. It is very soluble in water, moderately soluble in acetone, and sparingly soluble in aliphatic and aromatic hydrocarbons.

**History, Formulations, and Uses** At one times fluoroacetamide was used as a systemic insecticide for scale insects, aphids, and mites on fruits; however, it has been considered too toxic to mammals for commercial use as an insecticide. Its use as a rodenticide was suggested by Chapman and Phillips in 1995. It is used as a bait (20 gm active ingredient/kg) in areas to which the public have no access, such as sewers and locked warehouses. It is formulated as dyed cereal-based bait which is mixed with water for use.

### 83.2.2.2 Toxicity in Laboratory Animals

**Basic Findings** Fluoroacetamide is a compound of moderate to high acute toxicity depending on the species (see Table 83.2). In the WHO Recommended Classification of Pesticides by Hazards (World Health Organization, 1986), the technical material is listed in class IB, "Highly hazardous."

The compound is absorbed by the skin (Phillips and Worden, 1957). Animals acutely poisoned by this compound show listlessness, irritability, chronic convulsions, abasia, piloerection, and irregular respiration (Araki, 1972). One characteristic usually observed in animals dying from acute poisoning with fluoroacetamide as well as with sodium fluoroacetate is postmortem rigidity (Bentley and Greaves, 1960). Death generally

**Table 83.2**
Single-Dose LD 50 for Fluoroacetamide

| Species | Route | LD 50 (mg/kg) | Reference |
|---|---|---|---|
| Rat | oral | 15 | Phillips and Worden (1957) |
| Rat | oral | 13 | Bentley and Greaves (1960) |
| Rat | dermal | 20[a] | Phillips and Worden (1957) |
| Mouse | oral | 30.62 | Araki (1972) |
| Mouse | subcutaneous | 34.20 | Araki (1972) |
| Mouse | intraperitoneal | 85 | Matsumura and O'Brien (1963) |
| Rabbit | oral | 1.5–2.0 | Phillips and Worden (1957) |
| Rabbit | intravenous | 0.25 | Buckle *et al.* (1949) |
| Chicken | oral | 4.25 | Egyed and Shlosberg (1977) |

[a]Lowest lethal dose.