

Vertebrate Pest Conference Proceedings collection
Proceedings of the Eleventh Vertebrate Pest
Conference (1984)

University of Nebraska - Lincoln

Year 1984

TOXIC CHARACTERISTICS OF
FLUOROCITRATE, THE TOXIC
METABOLITE OF COMPOUND 1080

Peter J. Savarie
Denver Wildlife Research Center, U.S. Fish and Wildlife Service

TOXIC CHARACTERISTICS OF FLUOROCITRATE, THE TOXIC METABOLITE OF COMPOUND 1080

PETER J. SAVARIE, Denver Wildlife Research Center, U.S. Fish and Wildlife Service, Building 16, Federal Center, Denver, Colorado 80225

ABSTRACT: This paper reviews toxicological research involving fluorocitrate, the toxic metabolite of sodium monofluoroacetate (fluoroacetate), which is the active ingredient in the pesticide Compound 1080. Many toxicological studies have been done with fluoroacetate and the results obtained are actually due to the fluorocitrate because it has been definitely proved that, from a biochemical perspective, fluoroacetate is not toxic but fluorocitrate is. The classical explanation of the toxic action of fluorocitrate is that it inhibits the enzyme aconitase in the tricarboxylic acid cycle. Deactivation of aconitase results in decreased energy production by cells and ultimately death of the organism. However, the more recent explanation of fluorocitrate's mode of action is that it binds with mitochondrial protein which prevents transport of citrate and its utilization by cells for energy production. Metabolism studies indicate that only small amounts, perhaps less than 3%, of fluorocitrate is formed from fluoroacetate. From the limited number of acute and chronic studies conducted with fluorocitrate it does not appear to be as potent as fluoroacetate by either the oral or parenteral routes of administration. This decreased level of toxicity is thought to be due to the larger molecular weight of fluorocitrate which would not be as readily absorbed by tissues. Central nervous system toxic manifestations (i.e., tremors, convulsions) are characteristic in many animals poisoned with fluoroacetate. Fluorocitrate administered directly into the brain was found to be 100 times more toxic than fluoroacetate. The accumulation of citrate in organs is characteristic of fluorocitrate poisoning; from a quantitative point of view the liver is less affected than the brain, heart, kidney, or spleen. Fluorocitrate causes extensive kidney damage, but the testes are most sensitive to sublethal doses. Testicular damage may be either reversible or irreversible, depending upon the dose. Several plants have the ability to metabolize both fluoroacetate and fluorocitrate from either inorganic or atmospheric fluoride.

INTRODUCTION

Compound 1080 (sodium monofluoroacetate) is the synthetic sodium salt of fluoroacetic acid (fluoroacetate) which was first identified in nature as the main toxic component in the South African poisonous plant, gifblaar (Dichapetalum cymosum) by Marais (1944). Its mode of action remained unknown for several years because investigators could not find any biochemical changes. Studies with in vitro test systems from rat tissues showed that it did not affect oxidative enzymes (i.e., cytochrome oxidase, succinoxidase, isocitric oxidase) in the tricarboxylic acid cycle (Bartlett and Barron 1947), nor did it have any effect on aconitase from pigeon liver (Liebecq and Peters 1949) or aconitase from pigeon breast and rat heart muscle (Buffa and Peters 1950). Since fluoroacetate did not inhibit the activity of these and other isolated enzymes, it cannot be classified as a toxic chemical. But fluoroacetate is the active ingredient for controlling rodents and other vertebrate pests, so from a practical point of view fluoroacetate is a toxic chemical but its toxicity results from its metabolism to fluorocitric acid (fluorocitrate).

For ecotoxicological reasons much of the recent research with Compound 1080 as a pesticide concerns environmental hazards including primary toxicity to target and nontarget animals; secondary toxicity; effective concentrations in baits or delivery systems; operational control methods; and analytical methods development (Rammell and Fleming 1978, Wade and Connolly 1980, Okuno and Meeker 1980, Hegdal et al. 1981, Connolly 1982, Okuno et al. 1982). Although these investigations have provided data to advance and aid in the operational use of 1080, studies about 1080 metabolism have been largely neglected. For instance, it is noteworthy that the metabolic fate of 1080 in target species such as coyotes (Canis latrans), prairie dogs (Cynomys spp.) and ground squirrels (Spermophilus spp.) has not been studied. Most of what is known about the metabolism of 1080 has been studied in albino mice and rats using either in vivo, but primarily in vitro test conditions. These data are then extrapolated to indicate what may occur in other animals.

Metabolism of Fluoroacetate to Fluorocitrate and Mode of Action

The tricarboxylic acid (Kreb's cycle) metabolic pathway and its coupling with cytochrome oxidase is the major route of energy production in most aerobic animals, and disruption of this pathway at key enzymatic steps can lead to death.

A simplified tricarboxylic acid cycle is depicted in Figure 1 with the enzyme aconitase shown as the enzyme which catalyzes the conversion of citrate to cis-aconitic acid.

The classical explanation of 1080's toxicity is that fluorocitrate inhibits the activity of aconitase (Peters 1963). When aconitase is inhibited, production of energy diminishes resulting in cellular death and ultimately death of the whole organism. Hence 1080 is classified as a nonselective toxicant. But the acute LD50 (lethal dose that kills 50% of a test population) of 1080 varies considerably in different animals from a low of 0.066 mg/kg, orally, in the domestic dog (Tourtellotte and Coon 1950) to over 500 mg/kg, intraperitoneally, in the South African clawed toad (Xenopus laevis) (Quin and Clark 1947).

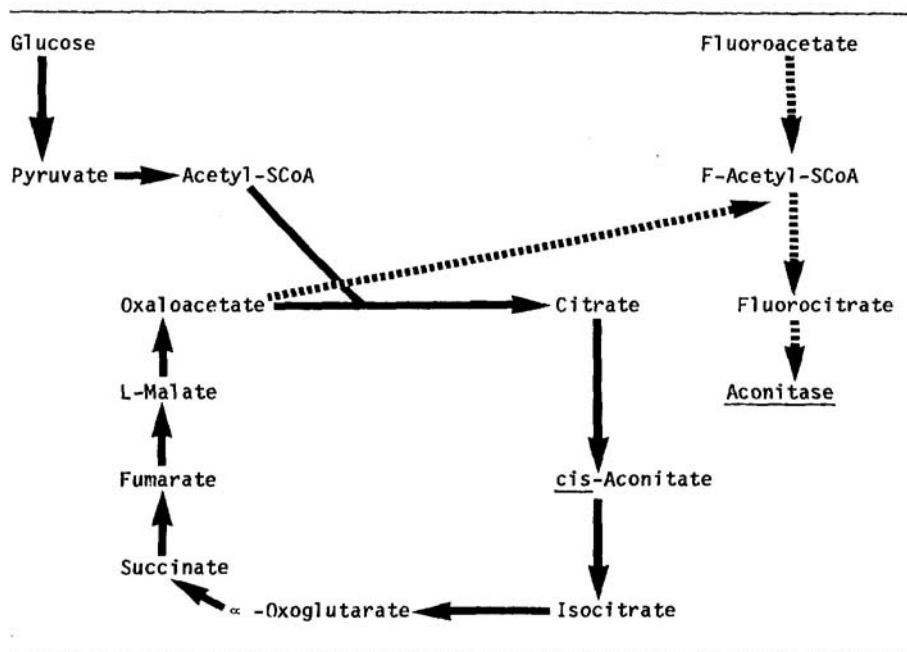


Figure 1. Diagram of the metabolism of fluoroacetate to fluorocitrate in the tricarboxylic acid cycle and inhibition of the enzyme aconitase by fluorocitrate (adapted from Egekeze and Oehme 1979).

The phrase "lethal synthesis" was coined by Peters (1952) to describe the biotransformation of fluoroacetate to fluorocitrate. A main feature of this conversion is that synthesis and not degradation is involved and depends upon fluoroacetate being so stereochemically similar to acetic acid that it undergoes changes by enzymes in the tricarboxylic acid pathway until it is converted to fluorocitrate. This involves the synthesis of fluorocitrate, having six carbon atoms, from fluoroacetate which has two carbon atoms.

Identification of the active toxic metabolite of fluoroacetate has not been easy. Studies of its isolation and properties have been described (Elliott and Kalnitsky 1950, Peters, et al. 1953a). Small amounts of the toxic metabolite were formed but it was tentatively identified as fluorocitrate. Because it has two asymmetric carbon atoms, four isomers are possible. Rivett (1953) and Brown and Saunders (1962) have synthesized fluorocitrate; and Peters et al. (1953b) found by infra-red spectra comparisons that the enzymatically synthesized fluorocitrate from rat kidney homogenates and synthetic fluorocitrate were identical, thus supporting the hypothesis that the toxicity of fluoroacetate is due to fluorocitrate. Dummel and Kun (1969) isolated the active isomer and identified it as L-erythrofluorocitric acid which inhibited aconitase activity of rat kidney mitochondria in vitro.

Although fluorocitrate has four isomers, biochemical reactions usually do not utilize them all, and in recent years investigators conducting enzymatic studies with the active isomer have data which indicate that inhibition of aconitase is not the primary mechanism of action. Kun (1982) reviewed the pharmacology and toxicology of 1080 and described in great detail the molecular toxicology of (-)-erythrofluorocitrate, identified by Stallings et al. (1980) as 2R, 3R(-)-erythrofluorocitric acid, which is the active isomer of fluorocitrate. Eanes et al. (1972) found that low concentrations of this active isomer failed to inhibit aconitase, but it could irreversibly prevent utilization of citrate and cis-aconitate by liver mitochondria. Inhibition of aconitase by fluorocitrate is reversible (Eanes and Kun 1974). In 1978, Kirsten et al. reported the active isomer was found on mitochondrial protein from rat kidney, heart, and brain which causes inhibition of citrate transport and prevents it from being metabolized in the tricarboxylic acid cycle. Regardless of the exact mode of action of fluorocitrate, the end result is that energy production is inhibited and death occurs after sufficient amounts of fluoroacetate have been metabolized to fluorocitrate.

It appears that only small amounts of fluorocitrate are metabolized from fluoroacetate in animals. Using intact rats injected intraperitoneally with fluoroacetate-2-C¹⁴, Gal et al. (1961) conducted several experiments and found only small amounts of fluorocitrate. Of the total amount of radioactivity administered, 32% was excreted in the urine, and 3% was exhaled as CO₂, and about 65% of the radioactivity was retained over four days. Fluorocitrate in urine accounted for only about 3% of the radioactivity. The major radioactive component in the urine did not inhibit aconitase activity. Another experiment by these authors provided data to suggest "...that indeed the liver of male rat very poorly converts fluoroacetate to fluorocitrate in vivo." The average radioactivity recovered as

fluorocitrate in the liver was 0.16% and in kidney it was 1.6%. Further evidence that fluorocitrate is formed in only very small amounts was reported by Schaefer and Machleidt (1971). Mice were dosed orally with [2-¹⁴C] fluoroacetate, and organs such as heart, spleen, kidney, and liver were found to contain amino acids as the major metabolites. It was calculated that if fluorocitrate was formed, it was less than 2.5%.

Acute and Chronic Toxicity of Fluorocitrate

As compared to the studies conducted on the acute and chronic oral toxicity of fluoroacetate (Chenoweth 1949), there are not many data for such studies with fluorocitrate. Limited data suggest that fluorocitrate administered orally is not as toxic as fluoroacetate. Peters and Shorthouse (1971) reported that 40-60 mg synthetic sodium fluorocitrate/kg intraperitoneally killed rats but that 40 mg/kg single oral doses of fluorocitrate... "which would be toxic by the intraperitoneal route do not kill most of the rats, LD20." The above doses probably do not represent the active isomer of fluorocitrate because in another publication it is stated that 40 mg fluorocitrate/kg is equivalent to about 4.6 mg "... of the active isomer of fluorocitrate..." (Peters et al. 1972a). The most extensive study on the oral toxicity of fluorocitrate was conducted by Peters et al. (1972a). Four-week-old male rats were given sublethal amounts of synthetic sodium fluorocitrate in their drinking water for seven months. Consumption was as much as 185 mg fluorocitrate per rat (equivalent to about 21 mg of the active isomer) which is several times the intraperitoneal injection lethal dose. In two of the three experiments animals grew and appeared normal after seven months. In the third experiment rats weighed less than controls, but they looked well. Organs such as the liver and kidney from fluorocitrate-fed and control rats examined by light and electron microscopy appeared normal and no abnormalities were found in x-ray examination of the bones. It was also determined that rats on fluorocitrate treatment had not become resistant. It was concluded that there was no toxicity in these chronically dosed rats, in contrast to fluoroacetate which has been described as a moderately chronic toxicant (Tucker and Crabtree 1970). Data from another study also indicate a low chronic toxicity of synthetic fluorocitrate (Dietrich and Shapiro 1956). These investigators observed no mortality and very little signs of toxicity in mice given daily intraperitoneal doses of 10 mg/kg twice daily (about 1.1 mg/kg of the active isomer) or 30 mg/kg daily (about 3.3 mg/kg of the active isomer) for as long as 17 days.

Effect of Fluorocitrate on the Central Nervous System

Many animals poisoned by fluoroacetate exhibit neurotoxic manifestations (i.e., tremors, convulsions), but the role of fluorocitrate in the brain remains to be defined. Gal (1972) administered either [2-¹⁴C] fluoroacetate or [¹⁴C] fluorocitrate intraperitoneally to rats and found a significant difference in the distribution of radioactivity of each chemical four hours later. Nineteen (19)% of the radioactivity of fluoroacetate and 52% of the radioactivity of fluorocitrate was recovered in the following organs: (% recovery of fluoroacetate listed first; fluorocitrate second) brain - 2.3, 0.1; liver - 12.0, 1.2; kidney - 2.5, 0.3; respiratory CO₂ - 1.8, 0.5; and urine - 0.5, 50.0. The high amount of fluorocitrate excreted in the urine is noteworthy and probably represents (since fluorocitrate is a larger molecule than fluoroacetate) the inability of fluorocitrate to be absorbed by tissue. The small amount of fluorocitrate in the brain (0.1%) indicates neurotoxicity can be caused by a small proportion of a given dose. In fact, when rats convulsed after intracerebral injection into the brain, the concentration of fluorocitrate was calculated to be about 25 ng/mg mitochondrial protein (1ng=1/1,000,000 mg).

Evaluating the role of fluorocitrate in the brain has been difficult because earlier experiments failed to demonstrate that brain tissue could metabolize fluoroacetate to fluorocitrate. In vitro tests with preparations of rat and pigeon brain tissue indicated little, if any, synthesis of fluorocitrate from fluoroacetate (Liebecq and Peters 1949, Peters and Wakelin 1957, Peters and Shorthouse 1966). The accumulation of citrate in tissues is one metabolic change attributed to the inhibition of aconitase by fluoroacetate. Buffa and Peters (1950) reported high increases of citrate levels in the heart, kidney, spleen, and brain of rats dosed intraperitoneally with fluoroacetate. There was also an increase of citrate in blood and liver but quantitatively it was smaller. Accumulation of citrate after fluoroacetate poisoning also occurs in brain, heart, and kidney of pigeon and guinea pig. Again the increase found in the liver from both species was also quantitatively less than the other organs. From these data it was concluded that the citrate was produced within the cells of the respective organs, including brain, and this is indirect evidence that fluorocitrate can be formed from fluoroacetate in vivo. Direct injections of fluorocitrate into rat brain or into the lumbar subarachnoid space of the cat spinal cord increased the citrate content of both these central nervous system structures (Patel and Koenig 1971). Later, Cheng et al. (1972) found that in vitro rat brain tissue slices did indeed accumulate citrate after fluoroacetate treatment, indicating that metabolism of fluoroacetate to fluorocitrate occurred in the brain. Peters and Shorthouse (1975) reported difficulty in detecting fluorocitrate synthesis in brain tissue in vitro, because of the small amount and slow activity of acetyl CoA synthetase in brain which converts fluoroacetate to F-acetyl-S-CoA and then into fluorocitrate. (cf. Fig. 1). A long delay in the onset of neurotoxic symptoms after fluoroacetate administration could be accounted for by the slow metabolism to fluorocitrate.

Fluorocitrate is a very potent toxicant when injected directly on or into nervous tissue. Morselli et al. (1968) found that as little as 0.56 g of the active fluorocitrate isomer was lethal to 200 g rats when injected into various areas of the brain including nucleus medialis septi, gyrus dentatus, nucleus reuniens thalami, and midbrain. Convulsions were observed in 24/24 of the rats tested and 19/24 died. Rather surprisingly it was found that 100 g fluoroacetate injected into the brain did not kill any rats. From this experiment and others conducted by these investigators it was concluded that fluorocitrate was "at least 100 times more toxic" than fluoroacetate when injected into the brain.

Koenig (1969) injected 3 to 50/ μ g of the active fluorocitrate isomer directly into the lumbar subarachnoid space of cats and observed convulsions in the trunk, hindlimbs, and tail after a latent period of one to two hours. Microscopic examination revealed pathological conditions consisting of mitochondrial swelling in the neurons and an extrusion of organelles such as mitochondria and multi-tubular lysosomes into axons.

Effect of Fluorocitrate on the Kidney

Pathological conditions were observed in various parts of the rat kidney after single intraperitoneal doses of 15 or 60 mg/kg of synthetic sodium fluorocitrate (about 1.65 or 6.6 mg/kg of the active isomer) (McDowell 1972a, 1973). Doses of 15 mg/kg caused gross behavioral depression in rats up to two hours after dosing, but after four hours they appeared normal. Rats given 60 mg/kg were moribund, but none died during the two-hour observation period, at which time they were killed for tissue examination. Damage was dose-dependent with morphological changes in the proximal convoluted tubules first appearing within one to two hours after dosing. At 15 mg/kg most damage was reversible and the only abnormality apparent after 24 hours was high matrix densities in several mitochondria of the proximal convoluted tubules. The 60 mg/kg dose, however, led "...to widespread necrosis" in the proximal convoluted tubules. Contrary to the dose-dependent pathological changes in the proximal convoluted tubules, morphological changes consisting of increased vacuolation and multivesicular bodies in the pars recta tubules were not readily apparent with these two doses. Pathological changes seen in these various parts of the kidney are thought to be related to the physiological, functional, and metabolic differences between these segments. Fluoroacetate also causes damage to the proximal convoluted tubules of rat kidney but, unlike fluorocitrate, the damage was not dose-dependent (McDowell 1972b).

Effect of Fluoroacetate on the Testes

Although the brain may be the primary organ for producing fluorocitrate toxicity, data suggest that the reproductive system, particularly the testes, may be the most sensitive organ. Mazzarti et al. (1964, 1965) found that doses of fluoroacetate, and fluoroacetamide which is metabolized to fluoroacetate, inhibited sperm production and caused testicular atrophy in rats. More recently Sullivan et al. (1979) found elevated citrate levels and morphological damage in the testes of rats receiving sublethal doses of 2.2, 6.6, or 20 ppm fluoroacetate in their drinking water for seven days. Cellular damage consisted of depletion of spermatids and "...formation of spermatid and spermatocyte giant cells." Seminiferous tubule atrophy resulted from the two higher concentrations but at the lower concentration regeneration of the seminiferous tubules was complete seven days after treatment, but was not at the two higher concentrations 21 days after treatment. No morphological changes were noted in the liver or kidneys. These results are interpreted to the formation of fluorocitrate which inhibits energy production in the testes. Severe damage to the testes, including absence of sperm, has also been reported in rats maintained on drinking water containing 26 ppm fluoroacetate for 126 days (Smith et al. 1977).

Fluorocitrate in the Environment

Cheng et al. (1968) provided the first evidence that some plants under appropriate conditions have a general property to synthesize fluoroacetate and fluorocitrate. These investigators showed that soybean plants (*Glycine max*) fumigated with hydrogen fluoride or grown in nutrient media containing either sodium fluoride or fluoroacetate could produce both fluoroacetate or fluorocitrate. The fluorocitrate produced by these plants was inhibitory to aconitase extracted from either soybean leaves or pig heart.

Under environmental conditions forage crops including alfalfa (*Medicago sativa*) and crested wheat grass (*Agropyron cristatum*) from a pasture with a high atmospheric fluoride content accumulate both fluoroacetate and fluorocitrate (Lovelace et al. 1968). Both of these chemicals were identified by chromatographic techniques, aconitase inhibition, and infra-red spectrometric analysis. Horses grazing on this pasture contained more citrate in their blood than control animals and this indicates that fluorocitrate intoxication had occurred.

When lettuce plants were incubated with either sodium [$1-^{14}$ C] acetate or sodium fluoro [$1-^{14}$ C] acetate, radioactivity was found in both fluoroacetate and fluorocitrate (Ward and Huskisson 1969). Single cell cultures of soya bean (*Acacia georginae*) and tea (*Thea sinensis*) grown in the presence of inorganic fluoride can also synthesize fluoroacetate and fluorocitrate (Peters and Shorthouse 1972). Small amounts of fluorocitrate, considered to be of nontoxic significance, were also detected in commercial samples of tea and oatmeal.

Although the exact mode of action of the active isomer of fluorocitrate has not been conclusively identified, there is no doubt that it inhibits the function of the tricarboxylic acid cycle causing dire toxicological manifestations in animals. The central nervous system is probably the target organ for producing mortality seen with acute lethal doses. Pathological changes are readily apparent in the kidney and may contribute to the chronic toxicity of fluoroacetate. Toxic effects with sublethal doses of fluoroacetate, presumably mediated via fluorocitrate, are seen in the testes without causing harm to other organs.

There does not appear to be much conversion of fluorocitrate from fluoroacetate, and the fluorocitrate concentrations in animal tissues poisoned by Compound 1080 are most likely to be much lower than fluoroacetate.

The acute and chronic toxicity of fluorocitrate appears to be much less than fluoroacetate, and leads to the hypothesis that the secondary toxicity hazard potential of Compound 1080 is probably due to the unmetabolized fluoroacetate remaining in tissue and not fluorocitrate.

Finally, under certain environmental conditions where there are high fluoride concentrations, plants can synthesize both fluoroacetate and fluorocitrate. In unusual cases of suspected Compound 1080 poisoning (i.e., livestock grazing on this type of pastureland) this source of fluoroacetate should be investigated.

LITERATURE CITED

- BARTLETT, G. R., and E. S. G. BARRON. 1947. The effect of fluoroacetate on enzymes and on tissue metabolism. Its use for the study of the oxidative pathway of pyruvate metabolism. *J. Biol. Chem.* 170:67-82.
- BROWN, P. J., and B. C. SAUNDERS. 1962. A new synthesis of monofluorocitric acid. *Chem. Ind. (London)*, 307-308.
- BUFFA, P., and R. A. PETERS. 1950. The *in vivo* formation of citrate induced by fluoroacetate and its significance. *J. Phys.* 110:488-500.
- CHENG, S. C., S. KUMAR, and G. A. CASELLA. 1972. Effects of fluoroacetate and fluorocitrate on the metabolic compartmentation of tricarboxylic acid cycle in rat brain slices. *Brain Res.* 42:117-128.
- CHENG, J. Y., M. H. YU, G. W. MILLER, and G. U. WELKIE. 1968. Fluoroorganic acids in soybean leaves exposed to fluoride. *Environ. Sci. Technol.* 2:367-370.
- CHENOWETH, M. B. 1949. Monofluoroacetic acid and related compounds. *Pharmacol. Rev.* 1:383-424.
- CONNOLLY, G. 1982. U.S. Fish and Wildlife Service coyote control research. Pages 132-149 In: *Proc. 5th Great Plains Wildl. Conf.*, R. M. Timm and R. J. Johnson, Eds. Lincoln, Nebraska.
- DIETRICH, L. S., and D. M. SHAPIRO. 1956. Fluoroacetate and fluorocitrate antagonism of tumor growth. Effect of these compounds on citrate metabolism in normal and neoplastic tissue. *Cancer Res.* 16: 585-588.
- DUMMEL, R. J., and E. KUN. 1969. Studies with specific enzyme inhibitors. XII. Resolution of DL-erythro-fluorocitric acid into optically active isomers. *J. Biol. Chem.* 244:2966-2969.
- EANES, R. Z., and E. KUN. 1974. Inhibition of liver aconitase isozymes by (-)-erythro-fluorocitrate. *Mol. Pharmacol.* 10:130-139.
- EANES, R. Z., D. N. SKILLETER, and E. KUN. 1972. Inactivation of the tricarboxylate carrier of liver mitochondria by (-)-erythrofluorocitrate. *Biochem. Biophys. Res. Comm.* 46:1618-1622.
- EGEKEZE, J. O., and F. W. OEHME. 1979. Sodium monofluoroacetate (SMFA, Compound 1080): A literature review. *Vet. Hum. Toxicol.* 21:411-416.
- ELLIOTT, W. B., and G. KALNITSKY. 1950. Mechanism of fluoroacetate inhibition. *Fed. Proc.* 9:168-169.
- GAL, E. M. 1972. Effect of fluoro compounds on metabolic control in brain mitochondria. Pages 77-93 In: *Carbon-Fluorine Compounds. Chemistry, Biochemistry and Biological Activities.* Ciba Foundation Symposium. Elsevier, New York.
- GAL, E. M., P. A. DREWES, and N. F. TAYLOR. 1961. Metabolism of fluoroacetic acid-2-C¹⁴ in the intact rat. *Arch. Biochem. Biophys.* 93:1-14.
- HEGDAL, P. L., T. A. GATZ, and E. C. FITE. 1981. Secondary effects of rodenticides on mammalian predators. Pages 1781-1793 In: *Worldwide Furbearer Conference Proceedings; Volume III*, J. A. Chapman and D. Pursley, Eds. August 3-11, 1980. Frostburg, Maryland.
- KIRSTEN, E., M. L. SHARMA, and E. KUN. 1978. Molecular toxicology of (-)-erythro-fluorocitrate. Selective inhibition of citrate transport in mitochondria and the binding of fluorocitrate to mitochondrial proteins. *Mol. Pharmacol.* 14:172-184.
- KOENIG, H. 1969. Acute axonal dystrophy caused by fluorocitrate. The role of mitochondrial swelling. *Science*, 164:310-312.
- KUN, E. A. 1982. Monofluoroacetic acid (Compound 1080), its pharmacology and toxicology. *Verte. Pest Conf.* 10:34-41
- LIEBECQ, C., and R. A. PETERS. 1949. The toxicity of fluoroacetate and the tricarboxylic acid cycle. *Biochem. Biophys. Acta*, 3:215-230.
- LOVELACE, J., G. W. MILLER, and G. W. WELKIE. 1968. The accumulation of fluoroacetate and fluorocitrate in forage crops collected near a phosphate plant. *Atmos. Environ.* 2:187-190.
- MARAI, J. S. C. 1944. Monofluoroacetic acid, the toxic principle of "gifblaar" *Dichapetalum cymosum*, (Hook) Engl. *Onderstepoort J. Vet. Sci. Anim. Ind.* 20:67-73.
- MAZZARTI, L., M. LOPEZ, and M. G. HERTI. 1964. Selective destruction in testis induced by fluoroacetamide. *Experientia*, 20:492-493.
- MAZZARTI, L., M. LOPEZ, and M. G. HERTI. 1965. Atrofia del testicolo prodotta dal monofluoroacetato sodico vel ratto albino. *Experientia*, 21:446-447.
- MCDOWELL, E. M. 1972a. Light- and electron-microscope studies of the rat kidney after administration of inhibitors of the citric acid cycle *in vivo*. Changes in the proximal convoluted tubule during fluorocitrate poisoning. *J. Pathol.* 108:303-318.
- MCDOWELL, E. M. 1972b. Light and electron microscopic studies of the rat kidney after administration of inhibitors of the citric acid cycle *in vivo*. I. Effects of sodium fluoroacetate on the proximal convoluted tubule. *Amer. J. Path.* 66:513-530.
- MCDOWELL, E. M. 1973. Light and electron microscopic studies of rat kidney after administration of inhibitors of the citric acid cycle *in vivo*. Changes in the pars recta during fluorocitrate poisoning. *Virchows Arch.* 13:321-340.

- MORSELLI, P. L., S. GARATTINI, F. MARCUCCI, E. MUSSINI, W. REWERSKY, L. VALZELLI, and R. A. PETERS. 1968. The effect of injections of fluorocitrate into the brains of rats. *Biochem. Pharmacol.* 17: 195-202.
- OKUNO, I., and D. L. MEEKER. 1980. Gas-liquid chromatographic determination of sodium fluoroacetate (Compound 1080). *J. Assoc. Off. Anal. Chem.* 63:49-55.
- OKUNO, I., D. L. MEEKER, and R. R. FELTON. 1982. Modified gas-liquid chromatographic method for determination of Compound 1080 (sodium fluoroacetate). *J. Assoc. Off. Anal. Chem.* 65:1102-1105.
- PATEL, A., and H. KOENIG. 1971. Some neurochemical aspects of fluorocitrate intoxication. *J. Neurochem.* 18:621-628.
- PETERS, R. A. 1952. Lethal synthesis. *Proc. Royal Soc. (London) B*, 139:143-170.
- PETERS, R. A. 1963. *Biochemical lesions and lethal synthesis*. Macmillan, New York. 312 pp.
- PETERS, R. A., and M. SHORTHOUSE. 1966. Note upon the behavior of rat brain tissue treated with fluoroacetate *in vitro*. *Biochem. Pharmacol.* 15:2130-2131.
- PETERS, R. A., and M. SHORTHOUSE. 1971. Oral toxicity of fluoroacetate and fluorocitrate in rats. *J. Physiol.* 216:40P-41P.
- PETERS, R. A., and M. SHORTHOUSE. 1972. Fluorocitrate in plants and food stuffs. *Phytochem.* 11: 1337-1338.
- PETERS, R. A., and M. SHORTHOUSE. 1975. Brain tissue and fluorocitrate synthesis. *Biochem. Pharmacol.* 24:1199-1201.
- PETERS, R. A., M. SHORTHOUSE, P. F. V. WARD, and E. M. MCDOWELL. 1972a. Observations upon the metabolism of fluorocitrate in rats. *Proc. Roy. Soc. (London) B*. 182:1-8.
- PETERS, R. A., and R. W. WAKELIN. 1957. The synthesis of fluorocitric acid and its inhibition in acetate. *Biochem. J.* 67:280-286.
- PETERS, R. A., R. W. WAKELIN, D. E. A. RIVETT, and L. C. THOMAS. 1953b. Fluoroacetate poisoning. Comparison of synthetic fluorocitric acid with the enzymatically synthesized fluorotricarboxylic acid. *Nature* 171:1111-1112.
- PETERS, R., R. W. WAKELIN, and L. C. THOMAS. 1953a. Biochemistry of fluoroacetate poisoning. The isolation and some properties of the fluorotricarboxylic acid inhibitor of citrate metabolism. *Proc. Royal Soc. (London) B*, 140:497-507.
- QUIN, J. I., and R. CLARK. 1947. Studies on the action of potassium monofluoroacetate (CH₂F COOK) *Dichapetalum cymosum* (Hook) Engl. toxin on animals. *Onderstepoort J. Vet. Sci. Animal Ind.* 22: 77-90.
- RAMMELL, C. G., and P. A. FLEMING. 1978. Compound 1080-Properties and use of sodium monofluoroacetate in New Zealand. Animal Health Division, Ministry of Agriculture and Fisheries, P.O. Box 2298, Wellington, New Zealand. 112 pp.
- RIVETT, D. E. A. 1953. The synthesis of monofluorocitric acid. *J. Chem. Soc.* 3710-3711.
- SCHAEFER, H., and H. MACHLEIDT. 1971. Conversion of fluoroacetic acid to amino acids in the mammal. *Biochem. Biophys. Acta* 252:83-91.
- SMITH, F. A., D. E. GARDNER, C. L. YUILE, O. H. DE LOPEZ, and L. L. HALL. 1977. Defluorination of fluoroacetate in the rat. *Life Sci.* 20:1131-1138.
- STALLINGS, W. C., C. T. MONTE, J. F. BELVEDERE, R. K. PRESTON, and J. P. GLUSKER. 1980. Absolute configuration of the isomer of fluorocitrate that inhibits aconitase. *Arch. Biochem. Biophys.* 203:65-72.
- SULLIVAN, J. L., F. A. SMITH, and R. H. GARMAN. 1979. Effects of fluoroacetate on the testis of the rat. *J. Reprod. Fert.* 56:201-207.
- TOURTELLOTTI, W. W., and J. M. COON. 1950. Treatment of fluoroacetate poisoning in mice and dogs. *J. Pharmacol. Exptl. Ther.* 101:82-91.
- TUCKER, R. K., and D. G. CRABTREE. 1970. *Handbook of toxicity of pesticides to wildlife*. Bureau of Sport Fisheries and Wildlife. Resource Publication No. 84, 131 pp.
- WADE, D. A., and G. E. CONNOLLY. 1980. Coyote predation on a Texas goat ranch. *Texas Agric. Progress*, 26:12-16.
- WARD, P. F. V., and H. S. HUSKISSON. 1969. The metabolism of fluoroacetate by plants. *Biochem. J.* 113:9P.