REPORT 4

MONOHALOACETIC ACIDS

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16. Abstract (Limit: 200 words) The monohaloacetic acids were reviewed, including information on occupational exposure, physical properties, toxicity, and structure/activity relationships. A detailed review and analysis was conducted of the biological effects of chloroacetic-acid (79118), sodium-chloroacetate (3926623), fluoroacetic-acid (144490), sodium-fluoroacetate (62748), iodoacetic-acid (64697), sodium-iodoacetate (305533), and bromoacetic-acid (79083). Topics included: human effects; epidemiologic studies; animal toxicity; diagnosis; antidotes; absorption, distribution, metabolism, and excretion; biochemistry; mutagenicity; carcinogenicity; and teratogenicity. Accurate information on the number of workers potentially exposed to these compounds was not available. Sodium-fluoroacetate has been widely used as a mammalian pest control agent. Although these compounds have different modes of action, all of them inhibit various metabolic pathways. Based on the acute toxicity to rats, fluoroacetate was the most toxic.

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I. SUMMARY

Introduction

The monohaloacetic acids are extremely toxic substances. Although structurally very similar to one another, these compounds have quite different modes of action. For example, fluoroacetic acid very specifically inhibits the enzyme aconitase in the tricarboxylic acid (TCA) cycle, while iodoacetic acid reacts with and inhibits sulfhydryl groups necessary for the function of many enzymes.

The specifics of the toxic effects of the monohaloacetic acids differ depending on the particular compound. The only apt generalization is that these substances inhibit various metabolic pathways, resulting in the progressive metabolic "turning off" of the organism until death occurs.

The exposure of workers to these compounds is difficult to document. The National Occupational Hazard Survey (NOHS) estimated almost 700,000 occupational exposures to chloroacetic acid. Only about 5,000 potential exposures were estimated when only actual or tradename ingredients were considered. Fluoroacetic acid and its salt, sodium fluoroacetate, are sold worldwide as compound 1080, yet accurate information on exposure is currently minimal.

Historical Perspective

The history of man's use of the monohaloacetic acids was relatively uneventful until World War II. Man's first synthesis of the monohaloacetic acid compounds was carried out during the late 19th century (N01524, N01467).

During World War II, the belligerent governments conducted extensive research in attempts to find effective pest control and chemical warfare agents. One of the compounds found to be the most lethal was sodium fluoroacetate, which is in many ways a perfect poison. The results of this research were published as they were declassified by the various governments (N01541). Research delving into the mechanism of sodium fluoroacetate poisoning occupied the immediate postwar research effort on the monohaloacetic acids. By the mid-1950's it was found that the fluoroacetate ion mimicked the acetate ion to the degree that the halogenated compound would enter the tricarboxylic (TCA) acid cycle. A metabolic synthesis converted fluoroacetate into fluorocitrate, a potent inhibitor of the enzyme aconitase.

Near the end of World War II fluoroacetate was discovered to be the toxic agent of the poisonous plant gifblaar (Dichopetalum cymosum). Gifblaar is a serious threat to cattle grazing in South Africa (N01467). A search for an effective antidote to fluoroacetate poisoning has also been conducted, but with little success. During the late 1970's the Environmental Protection Agency (EPA) placed severe restrictions on the

use of sodium fluoroacetate (commercially known as compound 1080) as a rodenticide.

Iodoacetic acid is a well recognized inhibitor of sulfhydryl (-SH) groups, which are essential for the activity of many enzymes. Accordingly, this property of iodoacetic acid has made it a popular experimental tool for selectively inhibiting glycolysis and examining the role of -SH groups in various enzymes. The ability of bromoacetic acid to inhibit free $-NH_2$ groups has led to its usage in inhibiting specific enzymes in biochemical experimentation.

Chloroacetic acid is used extensively as a precursor to a variety of defoliants, drugs, and pesticides. Until recently very little research on the mechanism of toxicity was known. Hayes et al (NO1274) recently discovered that chloroacetic acid is unique in its toxic action. However, the exact mechanism remains to be elucidated.

Extent of Exposure

Table IV-1 lists actual and tradename exposure to bromoacetic and chloroacetic acid as estimated by the National Institute for Occupational Safety and Health (NIOSH) from the NOHS study. However, the actual extent of exposure of the working population to monohaloacetic acids is difficult to determine. For instance, although large amounts of chloroacetic acid are imported to the US, transportation workers are not listed in the NOHS study.

Three of the compounds included in the scope of this document, bromoacetic acid, chloroacetic acid, and sodium fluoroacetate, were included in the National Occupational Hazard Survey. Chloroacetic acid had the highest estimated number of exposures, approximately 677,547. This estimate included generic, actual, and tradename exposures. However, when the data are restricted to the actual compound and tradenames for which the contents are known to contain chloroacetic acid, only 4,391 exposures were identified, or 0.65% of the NIOSH 1976 NOHS estimate. The remainder of the estimated generic exposure is due to the classification of chloroacetic acid, along with 64 other chemicals, as a potential component of disinfectants (K Kreitel, telephonic communication, May 1980). However, chloroacetic acid is not used as a disinfectant. The estimated exposures vary over two orders of magnitude, indicating that an accurate estimate of the number of exposures will be difficult to determine.

Table IV-2 lists US import figures for chloroacetic acid during the last 5 years. Since 1976 the import poundage has increased by 57% (11,330,000 lbs). In light of these figures, the potential exposure to chloroacetic acid may include workers involved in its unloading and shipping. These categories of workers were not included as exposures in the NOHS data. No information is currently available on ports of entry or the number of workers exposed to chloroacetic acid.

The NOHS study provides far better estimates of exposure for the haloacetic compound, bromoacetic acid, which is identified by either its

actual name or by a tradename. A total of 42 exposures was estimated by the survey.

NOHS data on sodium fluoroacetate, one of the most effective mammalian pest control agents known, is undoubtedly inaccurate. Only 31 exposures were estimated and all the information was derived from generic names. Potential occupational and accidental exposure of the work force to sodium fluoroacetate is unquestionably larger than the estimate in the NOHS study.

Sodium fluoroacetate is sold worldwide. Mr. Tull Allen, President of Tull Chemical Company (Oxford, Alabama), stated that he sells sodium fluoroacetate (compound 1080) to 3,500 customers in all 50 states and in 33 countries (telephonic communication, March 28, 1980). Within the US sodium fluoroacetate is shipped by commercial trucking firms in sealed containers.

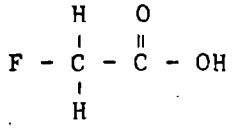
Data provided by EPA indicate that sodium fluoroacetate is widely used in the US, especially in the West. In 1979 33 county agricultural commissioners in the Southwest applied for permits to produce small mammal baits containing sodium fluoroacetate. In regions of southern California, airplanes spread bait containing sodium fluoroacetate; the bait reduces the small-rodent population which harbors bubonic plague. For authorized use of compound 1080 in California, the average number of exposure man-hours per county per year in 1979 averaged 154.21 hrs (range 3.0-1,050) for persons mixing the bait; the number of exposure man-hours per county per year averaged 2,634.33 hrs (range 8.0-12,000) for persons

applying the bait (N02498). The Montana Department of Agriculture (Federal Register 45:15647, March 11, 1980) has applied for an exemption to use sodium fluoroacetate to control Columbian ground squirrels. According to EPA, there are over 1,165,000 licensed private users of pesticides and 170,000 commercial users (J McDonald, written communication, April 2, 1980). The vast majority of the private pesticide users are farmers.

Despite EPA's restrictions on sodium fluoroacetate use, the possible exposures to the compound are widespread. Workers involved in the shipping, handling, and application of the compound apparently include truckers, agricultural pilots, longshoremen, and licensed pesticide applicators. The potential for exposure to sodium fluoroacetate is no doubt much larger than the NOHS occupational data indicate.

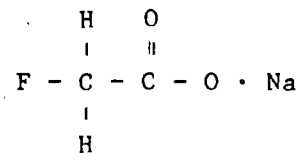
Physical Properties

The monohaloacetic acids are a group of compounds derived from acetic acid with a hydrogen replaced by a halogen: bromine, chlorine, fluorine, or iodine. For example, the compound fluoroacetic acid has the structure:



Sodium chloroacetate, sodium fluoroacetate, and sodium iodoacetate, the commonly produced sodium salts of the monohaloacetic acids, are

structurally similar to their respective acids. However, hydrogen in the hydroxyl group is absent, giving the molecule sufficient charge so that it is ionically bonded to the Na^+ ion:



The physical properties of the monohaloacetic acids are very similar to one another (see Table IV-3). The melting points of the monohaloacetic acids are fairly high, with a maximum of 83 C. The salts have much higher melting points than the acids, but they tend to decompose before a boiling point can be attained. The densities of the monohaloacetic acids and salts are greater than that of water.

The unique physiologic actions of these groups of compounds require that they be discussed singly in the remainder of this report. The three groups are: chloroacetic acid and sodium chloroacetate; fluoroacetic acid and its salt, sodium fluoroacetate; and iodoacetic acid, sodium iodoacetate, and bromoacetic acid.

Chloroacetic Acid and Sodium Chloroacetate

(a) Human Effects

Human effects of exposure to these two compounds are not documented in the primary literature. This reflects the fact that human exposure to

these compounds is quite limited when compared to fluoroacetic acid (see Table IV-4). An exception to this lack of information occurs in the Soviet literature, which contains two reports (N01195, N01257) of epidemiologic surveys of workers chronically exposed to chloroacetic acid, trichloroethylene, tetrachloroethane, and perchloroethylene. Unfortunately, the effects observed cannot be attributed to chloroacetic acid alone. The only reported gross human effects of exposure appear in The Merck Index (N00896), which states that chloroacetic acid is irritating.

(b) Epidemiologic Studies

Two epidemiologic studies of worker populations simultaneously exposed to chloroacetic acid, tricholoroethylene and a number of other raw materials, intermediates, and byproducts were found in the Soviet literature (N01195, N01257). Symptoms of intoxication included listlessness, changes in the gastrointestinal tract, insomnia, pain in the epigastric region, dyspeptic disorders, and catarrhal manifestations of the mucous membranes of the nasopharnyx. However, because the population studied was exposed to a number of different chemicals, it would be inaccurate to assume that all of the observed pathologic symptoms were caused by exposure to chloroacetic acid.

(c) Animal Toxicity

The toxicity of chloroacetic acid (Table IV-7) to rats varies from a reported LD_{50} of 277.5 mg/kg (oral) (N01238) to an LD_{50} of 5 mg/kg

(subcutaneous) (N01520 Abst). Cysteine, administered subcutaneously to rats in doses of 200 mg/kg, was found to be an effective antidote for chloroacetic acid poisoning.

Chloroacetic acid is eliminated primarily through the urine (88%) and expired air (8%) (N01186). The principal metabolites are S-carboxymethyl-L-cysteine, thiodiacetic acid, and a minor metabolite, glycolic acid.

(d) Biochemistry

The toxic activity of the chloroacetic acid molecule is poorly understood. Apparently, -SH groups are affected and acetate oxidation is inhibited, but the kinetics of the reactions are different from that which would be expected if iodoacetate or fluoroacetate was the inhibitor (N01274). Hayes et al (N01274) concluded that chloroacetate ions act by a mechanism different from that of fluoroacetate or iodoacetate.

(e) Mutagenicity, Carcinogenicity, and Teratogenicity

The ability of chloroacetic acid to cause mutation in the bacteria Salmonella typhimurium has been explored (using the Ames test). The results demonstrated no mutagenic activity in bacteria exposed to chloroacetic acid (N01254, N01232, N01271).

Fluoroacetic Acid and Sodium Fluoroacetate

(a) Human Effects

Scientific reports on the exposure of humans to monohaloacetic acids and their salts are limited, with the exception of the widely used sodium fluoroacetate (compound 1080).

The effects of fluoroacetic acid and sodium fluoroacetate on humans are well documented by case histories of accidental and willful poisonings (Table IV-4). The effects of poisoning by these compounds are related primarily to the central nervous system (CNS) and the heart. CNS effects include agitation, depressed consciousness, seizures, and coma; heart effects include tachycardia, irregular rhythm with premature ventricular contractions, and ventricular tachycardia and fibrillation--which generally lead to death. More often than not, death is attributed to cardiovascular (CVS) effects as opposed to CNS effects, and in poisoned children death is usually attributed to heart failure and cardiac standstill (N01495, N01516, N02891). It has been extrapolated from data collected in animal studies that 5 mg/kg of sodium fluoroacetate is lethal to humans (N01495, N02891). The Merck Index (N00896) reports that the oral human lethal dose of the sodium salt of fluoroacetic acid is 2-5 mg/kg. Merck also reports that fluoroacetic acid is a skin irritant (N00896).

(b) Epidemiologic Studies

No epidemiologic studies on either fluoroacetic acid or sodium fluoroacetate have been published.

(c) Animal Toxicity

Fluoroacetic acid and its salt, sodium fluoroacetate, are very toxic to warm-blooded animals (Tables IV-6 and IV-9). The LD_{50} for these agents in albino rats is 5.0 mg/kg (N01516). After poisoning, a latent period occurs that is seldom less than 2 hours long (N01516). Although the site of toxicity varies from one species to another, the central nervous system and the heart are the main target organs for fluoroacetate toxicity (N01501). Cases of the accidental poisoning of domesticated animals exposed to low levels of sodium fluoroacetate have been reported (N02852).

Fluoroacetate inhibits the tricarboxylic acid (TCA) cycle at the stage catalyzed by the enzyme aconitase (N01276). Although no antidote exists for fluoroacetic poisoning, monoacetin is promising. Monoacetin provides an available supply of acetate that competes with the fluoroacetate ion for incorporation into the TCA cycle (N01775).

(d) Biochemistry

The mode of the toxic action of sodium fluoroacetate and fluoroacetic acid is through the inhibition of the tricarboxylic acid

cycle. The TCA cycle takes place in the mitochondria and is essential to the storage of energy in the form of ATP. The cycle also provides the initial building blocks for many cellular macromolecules (see Figure I-1) (N02813).

The toxic agent of sodium fluoroacetate and fluoroacetic acid is the fluoroacetate ion, which physiologically mimics the acetate ion. The mimicry is possible because fluorine is a compact atom with roughly the same diameter as a hydrogen atom. In fact, fluoroacetate can be activated to fluoroacetyl-CoA, the analogue of acetyl-CoA, and thus enter the TCA cycle. Fluoroacetyl-CoA is converted to fluorocitric acid in the TCA cycle. However, this is where any resemblance between the metabolism of the acetate and that of the fluoroacetate ion ceases. Apparently fluorocitric acid forms an irreversible combination with the next enzyme in the TCA cycle, aconitase. Aconitase is the enzyme that catalyzes the addition of water to the double bond of the metabolic intermediate cis-aconitic acid, forming isocitric acid.

It seems likely that the resemblance of fluorocitric acid to citric acid allows fluorocitric acid to bind to the active site of aconitase. However, the electrochemical properties of the carbon-fluorine bond apparently inhibit the dislodgement or further breakdown of the fluorocitric acid molecule, rendering the enzyme inoperative. The TCA cycle is therefore blocked, resulting in a decrease of energy within the cell. The cell's permeability barriers are destroyed, cellular functions cease, and cellular death follows (N01467, N01155).

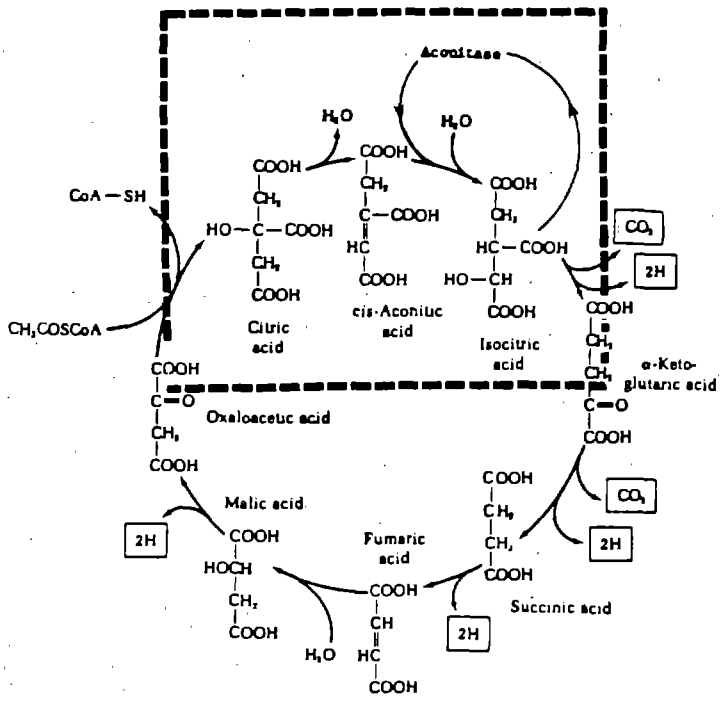


FIGURE I-1. TRICARBOXYLIC ACID CYCLE

The tricarboxylic acid cycle provides essential building blocks for the macromolecules of a cell and is essential in the production of ATP. The enzyme affected by the fluorocitrate ion is aconitase. Aconitase catalyzes the conversion of citric acid to isocitric acid as the enzyme adds water to the double bond in cis-aconitic acid.

(e) Mutagenicity, Carcinogenicity, and Teratogenicity

No information is currently available on the mutagenicity, carcinogenicity, or teratogenicity of either sodium fluoroacetate or fluoroacetic acid.

Iodoacetic Acid, Sodium Iodoacetate, and Bromoacetic Acid

(a) Human Effects

No gross human effects resulting from exposure to iodoacetic acid have been reported in the scientific literature; however, the literature does contain a sizable amount of information on the ability of iodoacetic acid to inhibit various human enzymes and induce or inhibit various biochemical reactions and growth of human cell cultures. For a review of the enzymatic inhibitions and the biochemical and cellular effects caused by iodoacetic acid, see Table IV-5.

Bromoacetic acid is both irritating and corrosive to the skin and mucous membranes (N00896). Also, bromoacetic acid has been shown to reversibly inactivate the enzyme carbonic anhydrase B, which is found in human erythrocytes (N01223) (Table IV-5).

(b) Epidemiologic Studies

No epidemiologic studies on iodoacetic acid or sodium iodoacetate are currently available.

(c) Animal Toxicity

The acute toxicity of iodoacetic acid ranges from an LD_{50} of 55.5 mg/kg in mice and 45.3 mg/kg in dogs to 108 mg/kg in rats (N01666). Iodoacetic acid also can cause cataracts in rabbits (N01543, N01172, N01201). The cataractogenic effect is intensified by simultaneous exposure to ultraviolet radiation (N01259). Retinal degeneration can also be caused by iodoacetic acid (N01273, N01269). Smooth muscle effects, such as depression of contractile activity due to exposure to iodoacetic acid, have been noted in rabbit detrusor muscles (N01215), rat uterus (N01222, N01199), and rat aorta (N01166, N01213, N01153). Increased mineralization of bone has also been noted (N01198) after iodoacetic acid exposure.

(d) Biochemistry

Iodoacetic acid inhibits sulfhydryl groups (-SH) that act as proton donors in enzyme catalyzed reactions (N02813). Iodoacetic acid does not compete with an enzyme's normal substrate for a particular active site. Instead, the action of iodoacetic acid affects a much broader spectrum of enzymes; all that is necessary for inhibition of the enzyme is the presence of -SH groups vital to the enzyme's function.

Since iodoacetic acid inactivates sulfhydryl groups, a great variety of enzymes and metabolic pathways is affected (Table IV-8). An example of an enzyme affected is phosphoglyceraldehyde dehydrogenase

(N01188, N01543), an enzyme vital to glycolysis. Iodoacetic acid is also suspected of drastically inhibiting the enzyme triisophosphate dehydrogenase in the retinae of rats, causing severe retinal degeneration (N01273). Consequences of the block of glycolysis by iodoacetic acid include depression of contractile activity in rat and frog hearts (N01164, N01154) and the breakdown of the mitotic processes (N01263).

The toxic activity of bromoacetic acid is due to its inhibition of enzymes by its reaction to $-NH_2$ groups that are essential for the enzyme's activity. An example of such an enzyme is guinea pig ileum monoamine oxidase (N01174).

(e) Mutagenicity, Carcinogenicity, and Teratogenicity

The mutagenic activity of iodoacetic acid is apparent in conjunction with electromagnetic radiation such as gamma or x-rays (N01264, N01268). The effect is likely due to the iodoacetate inhibition of glycolysis, which provides energy for aerobic repair and the general inhibition of enzymes with active -SH groups.

The carcinogenic activity of the iodoacetic ion is questionable. Tagashira (N01514) claimed that iodoacetic acid caused fibrosarcomas in rats. However, controls were not provided, a hybrid strain of rat was used, and on 3 of 20 rats a fibrosarcoma developed but no tumor appeared until the animals were 450 days old. These considerations weaken the case for iodoacetic acid's oncogenicity. Gywnn and Salaman (N01665) determined that iodoacetic acid may be a weak co-carcinogen in

combination with 9,10-dimethyl-1,2-benzanthracene. Further research is necessary to determine the possible carcinogenicity of iodoacetic acid.

Iodoacetic acid is teratogenic in mice. Miller (N01159) showed that injection of pregnant mice during days 11-13 of gestation increased the proportion of cleft palates in the offspring. Skeletal deformities were also increased by the injection of iodoacetic acid (N01508). No data are currently available on primates.

No information on the mutagenic ability of bromoacetic acid has been discovered.

(f) Current Research

Research is being conducted using iodoacetic acid to study the adhesion of eye membranes and neuromuscular diseases. Pilkerton et al (N01282 Abst) used iodoacetate to examine the electrostatic adhesion between the retina and the pigment epithelium, and are preparing to publish results. Bromback (N01281 Abst) will study the effects of the inhibition of glycolysis on rat muscles to simulate human muscle phosphorylase deficiency and phosphofructokinase deficiency. These studies again illustrate the usefulness of iodoacetic acid and iodoacetate as a tool for studying the metabolism and physiology of tissues.

Comparative Toxicity of Monohaloacetic Acids

Hayes et al (N01274) compared the toxicity of chloroacetate, fluoroacetate, and iodoacetate in rats. The 24-hour LD_{50} values for chloroacetate, fluoroacetate, and iodoacetate were 108, 5, and 60 mg/kg, respectively. The haloacetates, in LD_{90} doses (162 mg/kg for chloroacetate, 7.1 mg/kg for fluoroacetate, and 72 mg/kg for iodoacetate) were administered to rats and the time until death (LT) was determined. The LT_{50} for chloroacetate, fluoroacetate, and iodoacetate was 130, 310, and 480 minutes, respectively. Based upon these results, it seems that fluoroacetate is the most toxic of the three, chloroacetate is the least toxic, and iodoacetate is of intermediate toxicity. Relative potency ratios were 12 (iodoacetate/fluoroacetate), 1.8 (chloroacetate/iodoacetate), and 21.6 (chloroacetate/fluoroacetate).

Structure-Activity Relationships among the Monohaloacetic Acids

Although the monohaloacetic acids have similar chemical properties and structure, the unique properties of the halogen cause very different physiologic effects. Figure I-2 is a spatial representation of the four monohaloacetic acids and acetic acid. As shown in the figure, fluoroacetic acid and acetic acid are very similar in configuration. The small size of the fluorine atom enables fluoroacetic acid to mimic acetic acid (in the tricarboxylic acid cycle) to the point where fluorocitric acid is synthesized in the place of citric acid. However, the enzyme aconitase is inhibited by fluorocitric acid. Aconitase accepts the molecule into its active site but the strong electronegativity of the

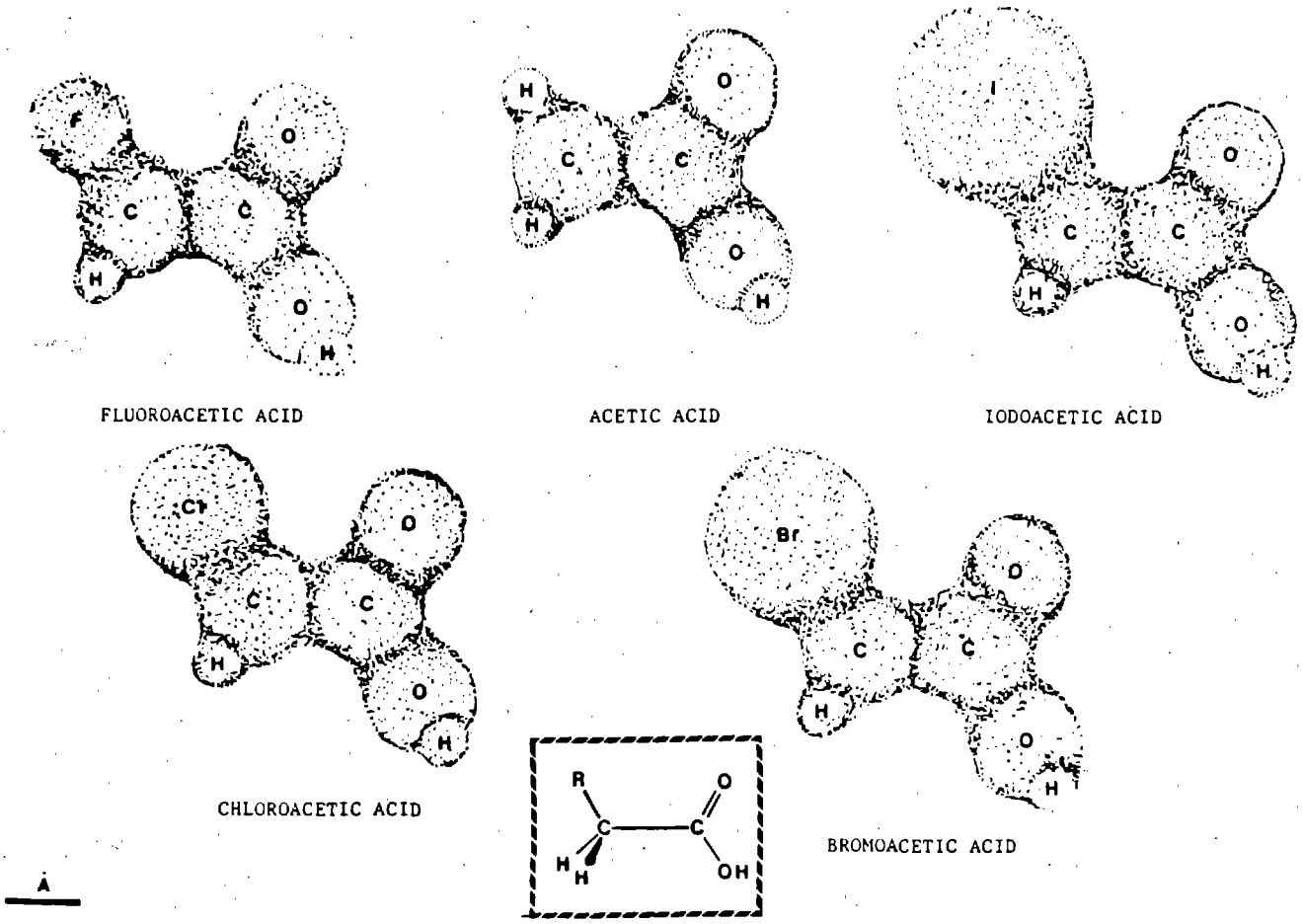


FIGURE I-2. RELATIVE SIZES OF ACETIC ACID AND THE MONOHALOACETIC ACIDS BASED ON THE COVALENT RADIUS OF THE ATOMS

fluorine prevents the enzyme from catalyzing the reaction or dislodging the molecule. (See Fluoroacetic Acid and Sodium Fluoroacetate, Biochemistry, p 37.)

Iodoacetic and bromoacetic acids inhibit enzymes by alkylating sulfhydryl (-SH) and amino ($-NH_2$) groups. This involves replacement of the hydrogen atom by the acetic acid group $-CH_2COOH$. This prevents the hydrogen molecules from acting as proton donors in the biochemical reactions which the various enzymes containing these two groups catalyze. (See Iodoacetic Acid, Sodium Iodoacetate and Bromoacetic Acid, Biochemistry, p 48.) Iodoacetic and bromoacetic acid are unable to enter the tricarboxylic acid cycle, however, because of the large structural differences between these compounds and acetic acid.

Chloroacetic acid may be an intermediate case. Apparently -SH groups and acetate oxidation are affected (N01274). Because of the relative size of the chlorine atom, chloroacetic acid may be able to partially enter the TCA cycle and at the same time alkylate some -SH groups. Further research is warranted and may shed light on the structure-activity relationships of other groups of compounds.

II. IN DEPTH REVIEW AND ANALYSIS OF THE BIOLOGIC EFFECTS OF MONOHALOACETIC ACIDS

Chloroacetic Acid and Sodium Chloroacetate

(a) Human Effects

Data on the human effects of exposure to both chloroacetic acid and sodium chloroacetate are limited. Unlike fluoroacetic acid and its sodium salt, no case histories of human exposure to the above compounds were found. The Merck Index (N00896) reports that chloroacetic acid is irritating. Documentation of these effects on humans was not found in any of the primary sources reviewed.

Only two papers (N01195, N01257) addressing the human effects of exposure to chloroacetic acid were found. These papers reported on two Soviet studies which examined workplace exposure to this compound from an epidemiologic viewpoint; these studies are discussed below.

(b) Epidemiologic Studies

Two epidemiologic studies of worker populations exposed to monochloroacetic acid appear in the Soviet literature (N01195, N01257). Unfortunately, the workers examined in these two studies were employed in the manufacture of both chloroacetic acid and trichloroethylene, and were

therefore exposed to a handful of various raw materials, intermediates, and byproducts used and produced by these manufacturing processes.

The first of these studies, conducted and written by Sukhotina (N01195), appeared in 1969. Sukhotina examined the urine of 166 workers for trichloroacetic acid and trichloroethanol content. All of the workers were known to have been exposed to trichloroethylene, tetrachloroethane, perchloroethylene, and monochloroacetic acid. An interrelationship was suggested between urinary trichloroethanol and metabolite concentrations (of trichloroacetic acid and trichloroethanol) and the state of the nervous system in workers with specific intoxication signs. The indicated intoxication signs included listlessness, changes in the gastrointestinal tract, and catarrhal manifestations in the mucous membranes of the nasopharynx. It must be noted that it would be inaccurate to assume that chloroacetic acid played a major part in inducing these symptoms.

The second study, conducted by Sukhotina et al (N01257), was published in 1973. Clinical observations were made of 26 patients suffering from chronic poisoning by chlorinated hydrocarbons, including trichloroethylene and chloroacetic acid. These observations revealed complaints of general weakness, increased fatigue, headaches, impairment of sleep in the form of drowsiness during the day and insomnia at night, increased perspiration, pain in the epigastric region, and dyspeptic disorders. Objective investigation revealed autonomic dysfunction with asthenia and, more rarely, hyperasthenic syndrome, with a predominance of a parasympathetic direction of autonomic reactions. Again, it must be

stressed that it would be inaccurate to assume that these symptoms are the result of monochloroacetic acid exposure.

(c) Animal Toxicity

The acute toxicity of chloroacetic acid has been determined by various authors (see Table IV-7). Kurchatov and Vasilleva (N01238) reported an LD_{50} of 277.5 mg/kg when chloroacetic acid was given orally to rats. Maksimov and Dubinina (N01250) found that the LD_{50} of chloroacetic acid (sodium salt solution) is 580 mg/kg when given by lavage to rats. Given intravenously, the LD_{50} of chloroacetic acid sodium salt was found to be 55 mg/kg. Earlier studies by Hayes et al (N01520 Abst) showed that it is highly toxic, with the LD_{50} of chloroacetic acid (given subcutaneously to rats) reported to be 5 mg/kg. Rats exposed to chloroacetic acid by inhalation showed signs of irritation and the LC_{50} was found by Maksimov and Dubinina (N01250) to be 180 mg/m^3. Cysteine administered subcutaneously to rats in doses of 200 mg/kg was found by Kurchatov and Vasilleva (N01238) to be an effective antidote for chloroacetic acid poisoning.

Based on LD_{50} values, chloroacetic acid was found to be 21.6 times less toxic than the closely related compound, fluoroacetic acid (N01520 Abst).

(1) Absorption, Distribution, Metabolism and Excretion

Studies by Yllner (N01186) showed that chloroacetic acid given to female albino mice is eliminated mainly via urine. Radioactive chloroacetic-1-^{14}C acid was injected intraperitoneally in a dose of 2 mg (radioactivity of 2-4 μCi), and radioactivity was followed for 3 days after the administration. Eighty-two to 88% of the radioactivity was found in the urine, 8% in expired air, 0.2 to 3% in feces (contaminated with urine), and about 2 to 3% remained in the animal. Examination of urine showed that 6 to 22% of the radioactivity in urine was due to chloroacetic acid, 33 to 43% due to free- and 1 to 6% due to conjugated-S-carboxymethyl-L-cysteine, 33 to 42% due to thiodiacetic acid, 3 to 5% due to glycolic acid, and 0.1 to 0.2% due to oxalic acid. Two metabolic pathways were suggested for chloroacetic acid: a major route that entails the formation of S-carboxymethyl glutathione which is then converted to S-carboxymethyl-L-cysteine and ultimately to thiodiacetic acid; and a route that involves enzymatic hydrolysis of chloroacetic acid to glycolic acid and ultimately to carbon dioxide.

(d) Biochemistry

The toxic action of chloroacetic acid is not fully understood. Hayes et al (N01274) have compared the physiologic activity of fluoroacetate, iodoacetate, and chloroacetate in rats. Chloroacetate ions did not significantly alkylate -SH groups of cysteine in vitro. However, tests with rat liver and kidney indicated a marked inhibition of total sulfhydryls. Acetate oxidation in vitro was inhibited by

chloroacetate ions but the kinetics of inhibition were different from those of fluoroacetate poisoning. Hayes et al (N01274) concluded that chloroacetate acts by a mechanism different from that of either fluoroacetate or iodoacetate.

(e) Mutagenicity, Carcinogenicity, and Teratogenicity

Testing of chloroacetic acid for possible mutagenic or carcinogenic activity has occurred in conjunction with testing metabolites of polyvinyl chloride for mutagenic activity. Chloroacetic acid is a metabolite of vinyl chloride (N01244). The tests are basic Ames tests, exposing chloroacetic acid to Salmonella typhimurium. Bartsch et al (N01254) used a microsomal fraction added to the plates of S typhimurium treated with chloroacetic acid. No increase in the number of bacterial revertants was observed. Only low concentrations (1.1×10^{-6} M/plate) (M = molar) could be tested because of the toxicity of chloroacetic acid to the bacteria. Lambach et al (N01232) tested chloroacetic acid for mutagenic activity in S typhimurium (strain TA100) and B subtilis, and detected no reaction. Chloroacetic acid also did not cause a direct or tissue mediated response in the S typhimurium strain TA1530 (N01271).

Fluoroacetic Acid and Sodium Fluoroacetate

(a) Human Effects

Case history reports on fluoroacetic acid and sodium fluoroacetate poisonings abound in the scientific literature. Six of these reports

(three fatal and three nonfatal poisonings) have been collected and reviewed in a monograph by Pattison on industrial toxic agents (N01467). In his review Pattison stated that it is apparent that the major toxic effects of the fluoroacetates in man involve the CNS and the heart. Specific CNS poisoning symptoms include epileptiform convulsions which alternate with coma and depression. Heart related symptoms include cardiac irregularities and sudden cardiac arrest. These severe symptoms are usually preceded by a latent period of up to six hours during which time there may be nausea, vomiting, excessive salivation, numbness, tingling sensations, epigastric pain, and mental apprehension. According to Pattison, other signs or symptoms which may develop subsequent to the latent period include muscular twitching, low blood pressure, and blurred vision. Pattison quantified all of these symptoms, stating that convulsions are often severe and death can result from cardiac arrest, which may occur suddenly along with ventricular fibrillation, and/or from asphyxia during a convulsion or respiratory failure. He also warned that secondary infection (especially of the lungs) or shock may play a part in fatal cases, but the primary cause of death is considered to be cardiac difficulties.

Pattison (N01467) reported that as of 1959 there had been at least 30 cases of fluoroacetate poisoning, of which at least 16 had been fatal. Some of the poisonings had been the result of acts of suicide but most were caused by accidental ingestion of compound 1080, the sodium salt of fluoroacetic acid. One poisoning occurred when a gust of wind blew sodium fluoroacetate into the face of a US Naval Sanitation Officer conducting field tests with the substance (N02890).

As mentioned above, Pattison (N01467) reported in symptomatic detail case histories of three fatal and three nonfatal human exposures to sodium monofluoroacetate (N02893, N02811, N02892, N02891, N02890). In these six cases, all patients were male and ranged in age from 13 months to 40 years. Pattison did not review the methods of treatment for every case because they were generally symptomatic and sometimes valueless. Similarly, he concluded that reports of pathologic and microscopic examinations contained no characteristic signs indicative of fluoroacetate poisoning.

Pattison (N01467) also discussed the therapy of poisoned individuals and made recommendations for first aid and clinical treatment. On the basis of monkey experiments Pattison wrote that intramuscular injection of large doses of monoacetin (glycerol monoacetate and glyceryl monoacetate) may be beneficial because the monoacetin acts as a specific antagonist to fluoroacetate. Pattison noted that although some pain and edema may be expected as a result of such treatment, the toxicity of monoacetin is very low and the side effects which may occur need not cause alarm.

In 1975 Reigart et al (N01495) reported in considerable detail a case of sodium fluoroacetate poisoning in which the patient was an 8-month-old girl who was found chewing on a rat baitcup that had been placed in her home 10 months earlier. According to the authors this nonfatal case was unusual because of the mild nature of the poisoning and the remarkably delayed onset of serious CNS symptoms. With respect to

the latter point, the authors stated that most investigators have emphasized that this symptomatic delay usually lasts 1 to 2 hours and can be as short as 30 minutes. In this particular case, however, definitive symptoms did not occur until about 20 hours after ingestion of the poison.

In the same paper Reigart et al (N01495) discussed the applicability and practical use of monoacetin as an antidote for sodium fluoroacetate poisoning. The authors considered monoacetin because it had been the subject of extensive animal experiments conducted by Chenoweth et al (N02898) and because, after careful review of a gamut of acetate compounds, monoacetin proved to be the least toxic in animals. Reigart et al (N01495) reported that although the animal studies of Chenoweth et al (N02898) indicated that monoacetin would probably prove useful in treating acute poisonings, the effective dose appears to be quite close to the toxic dose. Unfortunately, monoacetin in pharmaceutical dosage form is unavailable commercially; instead the substance is available as a 95% active ingredient with no assay on the remaining 5%. This presents the problem of ensuring that the monoacetin is sterile so that it can be administered intramuscularly without danger of secondary infection or other pathogenic effects. Since sterilization by filtration of practical grade monoacetin is difficult, due to the compound's viscous nature, and because autoclaving may result in hydrolysis, Reigart et al (N01495) recommend that an aseptically collected sample from the sealed commercial container be cultured in an appropriate medium to test for pathogenic microorganisms. Unfortunately, time usually does not allow for an adequate examination of the sterility of monoacetin using standard culture methods. However, if a secondary infection does occur, a

microbiology lab should be able to identify the pathogen responsible for the infection, ipso facto. Reigart et al (N01495) suggested that the following therapy and management, as recommended by Chenoweth et al (N02898), be utilized in cases of fluoroacetate poisoning:

1. Administer monoacetin intramuscularly in repeated hourly doses of 0.1 to 0.5 ml/kg as soon after ingestion as possible, and continue until a clinical response is noted.
2. Conduct continuous cardiac monitoring.
3. Protect against and control seizures by administration of anticonvulsant medications.
4. Avoid infusion of calcium or potassium salts as well as sodium chloride, bicarbonate, or acetate.
5. Replace fluid with plasma in a cautious manner.
6. Avoid cardiac glycosides.

The rationale for points 4-6 is that Chenoweth et al (N02898) have shown through their animal research that the above-mentioned salts and cardiac glycosides enhance the toxicity of sodium fluoroacetate.

In 1978 Guynn and Faillace (N01277) stated that the chronic effects of low concentrations of fluoroacetic acid are unknown but perhaps deserve attention. Their reasoning was that there is a possibility that fluoroacetic acid may be formed in minute amounts by the biodegradation of the anesthetics, halothane and fluoroxene, and that these compounds have been implicated in an increased incidence of subtle neurologic and psychiatric symptoms among anesthesiologists. Of course, such reasoning is purely speculative and there is no scientific evidence to link chronic, low-level exposure to fluoroacetic acid or fluoroacetate with

the observed neurologic and psychiatric disturbances noted in anesthesiologists.

(b) Epidemiologic Studies

No epidemiologic studies on either fluoroacetic acid or sodium fluoroacetate have been published.

(c) Animal Toxicity

Because of its use in pest control, sodium fluoroacetate (also known as compound 1080) has been widely investigated. Investigations of its toxicity have been summarized in two reviews: the first (by Chenoweth) appeared in 1949 and included 124 references (N01516), and the second (by Atzert) appeared in 1971 and included 54 references (N01501).

The toxicity of sodium fluoroacetate salt to various species is summarized in Table IV-6. The prominent features of sodium fluoroacetate toxicity are as follows:

1. Route of Administration: There is no major difference in toxicity when sodium fluoroacetate is administered by various routes of administration. For instance, the LD_{50} in albino rats is 5.0 mg/kg after subcutaneous, intraperitoneal, or intramuscular administation (see Table IV-9). The LD_{50} in mice is 19.3 and 17.0 mg/kg when the compound is administered subcutaneously or orally, respectively. This phenomenon is

quite uncommon, and is attributable to the fact that sodium fluoroacetate is very soluble in aqueous solutions and is stable.

2. Latent Period: Toxicity is manifested after a long and irreducible latent period which is independent of the route of administration (N01501, N01516). This latent period is seldom less than 2 hours (N01516). An increase in the administered dose of sodium fluoroacetate brought about a shortening of the refractory period but failed to induce an immediate response. For instance, Chenoweth (N01516) injected 0.5 mg/kg (LD_{95}) of sodium fluoroacetate intravenously in white rabbits; ventricular fibrillation and death ensued 125 minutes later. Increasing the dose to 250 mg/kg (500 times the LD_{95}) reduced the latent period by approximately one-sixth (20 minutes).

   Prior administration of sodium chloride, bicarbonate, or fumarate appreciably shortened the latent period but did not abolish it completely. Neostigmine (0.25 mg/kg) greatly shortened the latent period of fluoroacetate in mice but not in dogs and rabbits (N01516).

   The latent period is related to the mechanism of action of fluoroacetate. It was explained by Chenoweth (N01516) on the basis of the following biochemical actions: (a) the time needed to hydrolyze sodium fluoroacetate to fluoroacetic acid; (b) the time necessary for the accumulation of a sufficient amount of sodium fluorocitrate; and (c) the time required for the

disruption of the delicate intracellular balance to be manifested as gross organ dysfunction.

3. Site: The site of toxicity varies from one species to the other. The central nervous system and the heart are the main target organs for fluoroacetate toxicity. With the exception of the guinea pig, herbivores seem to manifest cardiac effects, whereas carnivores show CNS convulsions or depression. Death by fluoroacetate poisoning is due to: (a) gradual depression of the heart that culminates in ventricular fibrillation, (b) respiratory failure, or (c) progressive CNS depression that ends in respiratory or cardiac failure (N01501).

4. Species Sensitivity: Cold-blooded vertebrates are generally less sensitive to fluoroacetate poisoning than the warm-blooded species. Thus, an LD_{50} of more than 500 mg/kg was reported for the South African clawed toad, whereas that for a dog was 0.06 mg/kg (N01516). There is also a great variation in toxicity among the warm-blooded animals. For instance, an intraperitoneal injection of 0.05 mg/kg of fluoroacetate was lethal to the Texan pocket gopher, while 10 mg/kg was needed to kill an albino mouse (N01516).

5. Effect of Sex and Temperature: A difference in toxicity of fluoroacetate that is attributable to sex differences was noticed only in certain wild ducks, but not in other species (N01516). An increase in the environmental temperature was

found to increase the sensitivity of mice to fluoroacetate toxicity (N01516).

6. Tolerance: The administration of sublethal doses of sodium fluoroacetate to certain animal species resulted in tolerance to subsequent larger doses. This effect was observed in golden eagles, rats, mice, and possibly rhesus monkeys (N01501), but not in dogs and rabbits (N01516).

Conversely, the administration of several sublethal doses at short intervals might lead to the accumulation of sodium fluoroacetate until it reaches a lethal level (N01501). Interestingly, this response was noticed in species that do not develop tolerance, such as dogs and rabbits; those that develop tolerance, such as mice and rats, do not exhibit this cumulative response (N01501).

Tolerance is a time-dependent phenomenon. Chenoweth (N01516) stated that rats that received 0.5 mg/kg of sodium fluoroacetate became resistant to the toxic effects of 5.0 mg/kg of the same substance, if the latter dose was given within 4 to 24 hours after the first one. This increase in resistance lasted only 48 hours.

(1) Absorption, Distribution, Biotransformation, and Excretion

Fluoroacetic acid and its sodium salt are readily absorbed

through the gastrointestinal tract, mucous membranes, and pulmonary epithelium (N01516). Intact skin is quite impervious to these compounds, although they can be absorbed through open wounds (N01501). As mentioned above, there is no noteworthy difference between the toxicity of sodium fluoroacetate after oral, subcutaneous, intramuscular, or intravenous administration (N01516), nor is the toxicity affected by the type of vehicle used (water, oil, gum acacia suspension, meat, grain, or gelatin capsule) (N01501).

Chenoweth (N01516) assumed that the water soluble acetate is evenly distributed throughout body water. However, in the absence of actual determination of fluoroacetate in tissues, the author questioned whether the distribution of fluoroacetate is different in those species in which the heart or the central nervous system is primarily affected.Experiments performed by Gal et al and cited by Atzert (N01501) revealed that radioactive sodium monofluoro-2-^{14}C-acetate injected intraperitoneally in rats was found in highest concentrations in the brain, liver, heart, and kidney.

Fluoroacetate is partially metabolized to fluorocitrate and is excreted mostly unchanged in urine (N01516).

(2) Mechanism of Fluoroacetate Toxicity

Fluoroacetic acid is metabolized in the body to fluorocitrate, which blocks the TCA at the citrate stage (N01276, N01516). This leads to the inhibition of citrate and succinate metabolism (N01501). In the

TCA cycle, acetic acid combines with coenzyme A (CoA) in the presence of adenosine-5'-triphosphate (ATP) to form acetyl-CoA, which then reacts with oxaloacetate and water to form citrate. Likewise, fluoroacetate will follow the same pattern, resulting in the formation of fluorocitrate. But, whereas citrate continues through the TCA cycle, fluorocitrate does not; in fact, it inhibits several enzymes such as aconitase and succinic dehydrogenase by competing with the citrate molecule. The inhibition of these enzymes results in the accumulation of citrate which in turn blocks glucose metabolism by inhibiting phosphofructokinase. This ultimately leads to the interruption of energy supply to cells; when the energy shortage reaches a certain level, cellular permeability barriers are destroyed, resulting in loss of function and cellular death.

(3) Antidotes for Fluoroacetate Poisoning

So far there is no specific antidote for fluoroacetate poisoning; treatment is largely symptomatic. The objective of first aid treatment is to prevent further absorption of fluoroacetate from the gastrointestinal tract. This could be achieved by gastric lavage followed by a cathartic, such as sodium or magnesium sulfate.

Investigations with fluoroacetate poisoned animals showed that ethanol (800 mg/kg) injected subcutaneously (10% by volume in normal saline) within 30 minutes of poisoning with fluoroacetate significantly reduced mortality among mice, guinea pigs, and rabbits (N01512). The authors speculated that ethanol acts by catalyzing the oxidation of

acetate by fluoroacetate poisoned cells. Although ethanol was not effective in treating dogs poisoned by fluoroacetate, light pentobarbital anesthesia maintained for 18 to 24 hours significantly reduced mortality among animals poisoned by 0.1 mg/kg of fluoroacetate (N01512).

In another study (N01775), monoacetin was found to provide protection against the lethality of fluoroacetate. Monoacetin provides a readily available supply of intracellular acetate ions to inhibit the lethal synthesis of fluoroacetate to fluorocitrate. Arena (N02897) suggested the use of monoacetin (100 ml administered orally, repeated every hour) and/or slow, intravenous injection of procainamide (to restore normal rhythm of the heart in ventricular fibrillation) to treat fluoroacetate poisoning.

(4) Diagnosis of Fluoroacetate Poisoning in Animals

Egyed and Shlosberg (N01497) have identified a method to diagnose the cause of accidental poisoning of livestock that ingest poison baits or poisoned animal carcasses. The method involves the injection into guinea pigs of an aqueous extract of the heart and kidney from suspected animals or of suspected bait. Examination of the citrate level of the kidneys of guinea pigs showed an elevated citrate level in 80 of the 143 suspected poisonings. Kirson et al (N01498) found an increase in the citric acid contents of blood, heart, brain, and kidney of rabbits and cats poisoned by sodium fluoroacetate. An increase in brain citric acid content was also found by Goldberg et al (N02784). The differential diagnosis in the pathogenesis and symptomatology of

fluoroacetate poisoning and of acute and chronic fluoride intoxication in cattle was discussed by Grander (N01255). Stevens et al (N01240) described a rapid method for the extraction and identification of fluoroacetic acid from tissues by gas chromatography.

(5) Organ Toxicity

Chenoweth (N01516) described in 1949 the toxicity of fluoroacetate to various systems such as the cardiovascular system and the central nervous system. Since then only a few articles have appeared that describe the toxic effects of fluoroacetate on other organs. Articles by Yates and Yates (N01760 Abst, N01272) included the results of experiments designed to study alterations in the endoplasmic reticulum of rat hepatocytes after fluoroacetate administration. Animals injected with 5 mg/kg of sodium fluoroacetate and killed after 3 hours exhibited an increase in the amount of tubular agranular endoplasmic reticulum, and aberrant shaped mitochondria were noted.

(d) Biochemistry

The biochemical action of sodium fluoroacetate and fluoroacetic acid and its elucidation have been reviewed by Pattison (N01467). According to Pattison: Liebecq and Peters, Marcus and Elliott, and Kalnitsky suggested that the fluoroacetate ion was not responsible for the toxic properties of the compounds and that the ion was converted to fluorocitrate. The fluorocitrate was responsible for the deactivation of the TCA cycle. The evidence was primarily the finding that citric acid

accumulation occurred after poisoning with fluoroacetate, suggesting that the citric acid oxidation was blocked (N02877, N03242). Elliott and Kalnitsky (N02804) demonstrated the synthesis of fluorocitric acid during fluoroacetate poisoning. Peters et al (N02881) showed that a fluorotricarboxylic compound, with properties suggesting that it was fluorocitric acid, was responsible for the toxic effects of fluoroacetic acid poisoning. Judah and Rees (N02879), Morrison and Peters (N02880), Buffa and Peters (N02878), Peters and Wilson (N02819), and Lotspeich (N02808) isolated aconitase and showed that fluorocitrate is a competitive inhibitor of aconitase.

Aconitase catalyzes the addition of water as citric acid converts to the metabolic intermediate cis-aconitic acid, forming isocitric acid. The deactivation of aconitase is due to the size and electronegativity of the fluorine atom as compared with hydrogen.

The CH_3- and FCH_2- radicals are spatially very similar. Acetic acid and fluoroacetic acid therefore bear a strong structural resemblance to each other, and fluoroacetic acid can mimic acetic acid in undergoing activation and incorporation into the TCA cycle. Interestingly, there is evidence that the activation of fluoroacetic acid to fluoroacetyl-CoA may be a process different from that of acetic acid (N03240). After fluoroacetyl-CoA enters the cycle, fluorocitric acid is formed. The mimicry ceases as fluorocitric acid inhibits aconitase. The structure of fluorocitrate allows the compound to enter the enzyme matrix, but the physiochemical properties of the fluorine atoms hinder the dislodgement of the substrate. The inhibition of aconitase blocks the TCA cycle;

energy to the cell is decreased; permeability barriers are destroyed; and cellular death occurs (N01467, N01155). Berlinguet and Laliberte (N01209) and Benjamin and Quastral (N01169) have examined the inhibition of amino acid metabolism caused by fluoroacetate in pancreatectomized dogs and diabetic rats, respectively. Berlinguet and Laliberte (N01209) found that levels of N-acetyl-L-aspartic acid in brain tissue increased after treatment with fluoroacetate. Benjamin and Quastral (N01169) found that when brain slices from rats were poisoned by fluoroacetate, the content of glutamine decreased and that of glutamate and gamma-aminobutyrate increased. Interestingly, Maude (N01203) found that fluoroacetate did not inhibit proximal tubular fluid transport within the rat renal cortex in the presence of oxaloacetate. Apparently the rate of ATP production from oxaloacetate remained sufficient for transport across the cell membrane to occur.

A decrease in the rate of DNA synthesis in mouse lymphosarcoma LS/BL cells exposed to fluorocitrate was observed by Novak and Juraskova (N01502). Inhibition of DNA synthesis by injection of sodium fluoroacetate was also noted in vitro and in cells cultured in the abdominal cavity of host mice. DNA synthesis requires ATP as an energy source. The decrease of ATP production due to the inhibition of the TCA cycle was the likely cause of the decrease in the rate of DNA synthesis.

(e) Mutagenicity, Carcinogenicity, and Teratogenicity

No material has been published on the mutagenic, carcinogenic, or teratogenic properties of sodium fluoroacetate or fluoroacetic acid.

Iodoacetic Acid, Sodium Iodoacetate, and Bromoacetic Acid

(a) Human Effects

No case histories of human exposure to iodoacetic acid, sodium iodoacetate, or bromoacetic acid and no primary documentation of gross or symptomatic effects resulting from exposure were found. The only reported gross human effects resulting from iodoacetic acid exposure appear in Sax's Dangerous Properties of Industrial Materials (N00919), which states that monoiodoacetic acid is highly irritating to skin, eyes, and mucous membranes. The Merck Index (N00896) reports that bromoacetic acid is both irritating and corrosive to skin and mucous membranes.

A considerable amount of data has been collected on the ability of bromoacetic and iodoacetic acid to inhibit various human enzymes and inhibit or induce various biochemical reactions. These biochemical effects are summarized in Table IV-5. Several examples of the effects of bromoacetic and iodoacetic acid follow.

In 1967 Whitney et al (N01223) reported that bromoacetic acid in 5 mM concentrations, incubated with human erythrocytes for 0.87 hours, caused a 50% reversible inactivation of the erythrocyte carbonic anhydrase B. According to the authors, this inactivation was caused by reaction at the 3'-imidazole nitrogen of a histidine residue. When the enzyme was altered by the replacement of a zinc atom with a cobalt atom, the rate of inactivation of the apoenzyme was found to be only 1 to 2% of

the native-enzyme inactivation rate. Because of this reduction and because the rate of inactivation of the native-enzyme is directly proportional to the fraction of the enzyme which is reversibly inhibited by the bromoacetate, the authors postulated that the enzyme's metal atom seems to be involved in the inhibitor binding process.

In 1967 Yamada (N01224) studied the effects of several inhibitors, including iodoacetic acid, on the metabolism and transfer of glucose in the human term placenta. He found that placenta tissue, when incubated for 20 minutes in a nutrient medium containing 10^{-4} M iodoacetic acid, increased its glucose uptake slightly and increased its fructose production slightly.

In 1969 Murer (N01214) examined the effects and mechanisms of action of a number of metabolic inhibitors on the retraction of human blood clots and the energy metabolism of human platelets. He found that iodoacetic acid, when placed in a nutrient solution at 0.1 M concentration, almost completely inhibited the retraction of human blood clots incubated for a period of 5 minutes.

In 1970 Prasad and Callaghan (N01197) investigated the influence of glucose metabolism on ouabain-induced changes in the transmembrane potential and contraction of the human heart in vitro. They utilized the inhibiting effect of iodoacetate as an investigative tool in their research, and found that iodoacetate in concentrations of 10^{-5} M caused partial to complete inhibition of the positive inotropic effects of

ouabain. Monoiodoacetate in 10^{-5} M concentrations also enhanced the ouabain-induced shortening of action potential duration.

In 1971 Feddersen and Gormsen (N01194) investigated the plasmin digestion of stabilized and nonstabilized fibrin. They found that monoiodoacetate in 10^{-2} M concentrations inhibited the stabilization of human fibrin and reduced the maximal amplitude of fibrin in thrombelastography.

(b) Epidemiologic Studies

No reports of epidemiologic studies on iodoacetic acid, sodium iodoacetate, or bromoacetic acid have been discovered in the literature.

(c) Animal Toxicity

No acute toxicity information on bromoacetic acid from primary sources is currently available.

Like iodoacetic acid, bromoacetic acid produces cataracts when injected into the eyes of male albino rabbits. Saline controls and injections of chloroacetate and fluoroacetate showed no cataract producing ability (N02837). Also like iodoacetic acid, bromoacetic acid increases the radiosensitivity of rabbit red blood cells (N02849).

The acute toxicity of iodoacetic acid has been studied by various authors. The LD_{50} values were determined in various species via

different routes of administration. The LD_{50} values are 55.5 mg/kg when given intraperitoneally to mice, 45.3 mg/kg in dogs (route of administration unreported), and 108 mg/kg when given subcutaneously to rats (N01666).

The toxicity of iodoacetic acid is discussed below under the following topics: ocular toxicity, toxicity to smooth muscles, hemotoxicity, and toxicity to bone.

(1) Oculotoxicity

The cataractogenic effect of iodoacetic acid is well documented (N01543, N02837). Usually, the development of a cataract following exposure to iodoacetic acid is delayed for a few weeks to a few months, and is similar to that produced by irradiation (N01543).

Normally, the lens contains high concentrations of ascorbic acid and glutathione, which suggests that these two compounds are essential for the normal function of the lens. Iodoacetic acid acts by combining with the sulfhydryl group in -SH-containing enzymes (see Biochemistry section, p 48). Iodoacetic acid's cataractogenic effect can be predicted in light of the high concentration in the lens of glutathione, an -SH group amino acid.

Several biochemical changes are known to occur in the later stages of the development of a cataract: (a) irreversible change in the constituents of lens proteins, (b) progressive decrease in the glutathione content of the lens, and (c) change in the cation

distribution of the lens; normally the lens contains high potassium and low sodium concentrations.

To investigate the cataractogenic effect of iodoacetic acid, Ikemoto (N01172) used an in vitro rabbit lens preparation. Various concentrations of iodoacetic acid were incubated with lens homogenates for 15 hours. An increase in the potassium efflux and sodium influx, as well as swelling of the lens, were observed. Lactate formation was inhibited under the influence of iodoacetic acid (N01172). An in vivo study by Milano et al (N01201) was conducted in which 25 mg of iodoacetic acid was injected into the carotid artery of rabbits. However, the experiment failed to demonstrate a decrease in the lactic acid content of the crystalline lens isolated at various times before the appearance of cataracts.

An iodoacetate-induced cataract can be intensified by simultaneous exposure to ultraviolet radiation (N01259). Inhibition of lens metabolism by iodoacetic acid renders the lens less resistant to the deleterious effect of ultraviolet radiation. In fact, Kuck (N01259) considered exposure to ultraviolet light over many decades, potentiated by environmental toxicants, to be a factor in human senile cataractogenesis.

The ocular effects of iodoacetic acid involve not only the lens but also the visual cells of the retina. The retina appears to be selectively affected by low doses of iodoacetic acid compound. As in the case of the cataractogenic effect on the lens, the effect on the retinal

cell was attributed to the interference of iodoacetic acid with some -SH-dependent enzymes that are necessary to retinal metabolism (N01273). Furthermore, a difference was found between the effect of iodoacetic acid upon the rods and cones of the retina, with the rod system being more susceptible to poisoning than the cones (N01269).

(2) Effect on Smooth Muscles

Iodoacetate, when added to rabbits' isolated detrusor muscles, brought about depression of the contractile response of the muscle to acetylcholine (N01215). Because this depressant effect was reversed (although incompletely) by pyruvate, the observed effect may be due at least partially to inhibition of glycolysis.

A similar effect of iodoacetic acid was observed on the smooth muscles of the rat uterus. Paton and Daniel (N01222) showed that exposure of the uterine horns to 10^{-3} M of iodoacetic acid for 5 minutes abolished the contractile response induced by acetylcholine and prostaglandin E_1. In a later study from the same laboratory (N01199), it was found that incubation of rat uterus in 10^{-3} M of iodoacetic acid resulted (in the first hour) in the loss of potassium and a gain in the sodium content; there was no change in either calcium or water content. After 2 hours, the calcium and water content was increased.

The effect of iodoacetic acid on the smooth muscles of the aorta was studied by various authors. Balansard et al (N01166) found that iodoacetic acid partially suppressed adrenaline-induced contractions of

isolated rabbit aorta. Byts and Korkach (N01213) found that intravenous injection of iodoacetic acid (20 mg/kg) in dogs induced a decrease in the rate of glycolysis and in the oxygen tension in the vascular walls.

In another study, Sidorenkov and Sharaev (N01153) injected iodoacetic acid (7 mg/kg/d) either intravenously or subcutaneously into rabbits for 3 months, producing an increase in the concentration of hexosamine and hexuronic acid in the aortic wall.

The above studies demonstrate the various effects of iodoacetate on smooth muscles. However, the studies are all linked by the property of iodoacetate to inhibit a broad range of enzymes. In every case the effect observed in the study was due to inhibition of glycolysis.

(3) Hemotoxicity

Mason (N01275) studied the effect of iodoacetic acid on the blood of rabbits and sheep. A 0.05 M solution of iodoacetate in a dose of 19.5 to 26.5 mg/kg was injected intravenously in rabbits; sheep received between 18.5 and 22.5 mg/kg of iodoacetate intravenously. No effect on the rabbits' erythrocytes was seen for 10 days after the administration of iodoacetate, although retinal degeneration due to the iodoacetate poisoning was observed on ophthalmoscopic examination. Sheep, on the other hand, developed profound hemolytic anemia and died. The author attributed this effect to changes in red cell membrane.

Bianchi et al (N02849) discovered that iodoacetic acid increased the radiosensitivity of rabbit red blood cells in vitro by up to 4 times. This increase in radiosensitivity occurred only when the iodoacetic acid was present at the time of irradiation. The sensitivity effect apparently is not due to the alkylating ability of iodoacetic acid. Experiments with labelled iodoacetic acid-1-^{14}C demonstrated that a significant amount of iodoacetic acid binds to the red blood cells (N02849). After irradiation with x-rays the amount of labelled compound attached to the red blood cell membrane was markedly reduced.

(4) Effect on Bone

Conceptually, there seems to be a functional membrane separating bone extracellular fluid (ECF) from blood ECF. The cellular membrane acts as a controlling system for the ionic composition of bone ECF. This membrane concentrates potassium and decreases sodium, calcium, and magnesium concentrations in the bone ECF. Disruption of the function of this membrane could result in a change in the composition of bone ECF and hence mineralization of bones.

Experiments conducted to study the factors affecting mineralization of bone in tissue culture showed that treatment of bones with iodoacetic acid caused a marked increase in bone minerals and severe depression of lactate production, nitrogen incorporation, and potassium retention by the bones. Iodoacetic acid is a powerful inhibitor of glycolysis, and bone is quite dependent on this pathway for its energy needs. Ramp and Neuman's experiments (N01198), in which the mineral content of the

iodoacetic acid-treated bones more than doubled, strongly support the argument that living cells are necessary to control mineralization in bone. Similar studies performed on guinea pigs and dogs by Urist (N01167) showed that undemineralized bone pretreated in iodoacetic acid has osteoinductive properties after implantation in muscle in allogeneic animals.

(5) Miscellaneous Effects

Inhibition of glycolysis by iodoacetic acid leads to a variety of pharmacologic responses, such as inhibition of norepinephrine release from postganglionic sympathetic nerves (N01208), decrease in the vasopressor response due to renin (N01245), and blockade of transmission of fast axoplasmic transport in mammalian nerve (N01189). The inhibitory effect of iodoacetic acid on the rate of afferent discharges from muscle fibers was, however, attributed to its effect on the sodium-pump in fibers of nerve terminals (N01239).

(d) Biochemistry

The toxic action of bromoacetic acid is probably due to its ability to react with $-NH_2$ free residues. It has been shown that bromoacetic acid inhibits the enzyme monoamine oxidase in guinea pig ileum (N01174).

Iodoacetic acid is a well known inhibitor of sulfhydryl groups (-SH). Sulfhydryl groups are essential to the activity of many enzymes, as they are proton donors. Iodoacetic acid acts directly on the -SH

group and not on the enzyme's active site. The reaction of the sulfhydryl group of the enzyme (E) with the iodoacetic acid molecule renders the enzyme inactive (N02812):

$$E\text{-}SH + ICH_2COOH \longrightarrow E\text{-}S\text{-}CH_2COOH + HI$$

Active form Inactive form

Iodoacetate may also deactivate -SH groups in a photochemical reaction that has not yet been elucidated (N02783). Iodoacetic acid does not compete with a specific enzyme's normal substrate for the active site, but the compound inhibits a broad variety of enzymes in various metabolic pathways (see Table IV-8). Researchers often use iodoacetic acid to examine the presence of -SH groups in an enzyme, creating a wealth of data on the effect of iodoacetate on various metabolic pathways (see Table IV-8). A cross section of these studies is presented below.

Cox and Gunburg (N01164) examined the effect of iodoacetate on isolated 12-day rat embryo hearts. Iodoacetate at a concentration of 3×10^{-5} M completely depressed heart activity. However, the introduction of pyruvate (10^{-2} M) reversed the effect. This result suggests a very specific action on glycolysis.

de Boer et al (N01154) also examined the effect of iodoacetate on hearts, but used the adult frogs Rana temporaris and R esculenta. Iodoacetic acid was introduced at a concentration of 10^{-6} M and depression of heart activity occurred.

Laszt (N02802), in a 1936 paper, used iodoacetic acid administered at sublethal doses to young rats to simulate Gee-Herter's disease. Anemia, hypertrophy of the adrenal cortex, demineralization of the bone, and overall stunting of growth were observed.

Wilson and Morrison (N01263) used the mitotic process as an indication of chemical effect on Pisum root tips. In this study iodoacetate markedly inhibited the movement of chromosomes from prometaphase to metaphase. The effect of iodoacetate on the movement of the chromosomes was dose dependent. No specific target of the mitotic apparatus except perhaps the kinetochore was affected by iodoacetate. Apparently a general lack of energy due to the blockage of glycolysis caused the lack of chromosomal movement.

(e) Mutagenicity, Carcinogenicity, and Teratogenicity

The mutagenic activity of iodoacetic acid has been examined in conjunction with gamma and x-rays in unicellular organisms. Nair and Pradhan (N01264) found that iodoacetic acid (concentration: 10^{-4} M) slowed the repair of DNA that had been damaged by gamma irradiation under aerobic conditions, in Escherichia coli. The inhibition of glycolysis apparently reduced the effectiveness of the DNA repair system.

No inhibition of the slow repair process under anaerobic conditions was observed. However, under anaerobic conditions the radiation-induced cellular lethality was increased by the presence of iodoacetic acid during irradiation. Apparently, iodoacetic acid either increases the

attack on the DNA by the radiolytic products produced by the gamma radiation or inhibits either the ultra-fast or fast cellular repair systems.

Kimball et al (N01268) examined the effect of iodoacetic acid on the mutation rate of x-ray irradiated Paramecium tetraurelia. Surprisingly, the number of mutational effects decreased with the addition of iodoacetic acid (concentration: 10^{-4} M). This was due to the slowing of the rate of fission of the paramecia, which allowed more of the damage to be repaired before being permanently incorporated into the genome. Apparently the decrease in the rate of the the pathways necessary for fission to occur was greater than that of the DNA repair system, allowing fewer mutations than the controls.

Few reports exist on the carcinogenicity of iodoacetic acid. Tagashira (N01514) claimed that iodoacetic acid caused tumors in rats. In two sets of experiments with a combined total of 20 rats, 3 animals developed fibrosarcoma. The rats did not develop the tumors before 450 days after the beginning of the experiment. The rats used in the study were hybrid strains and neither a spontaneous rate of tumor formation nor adequate controls were provided. Therefore, the results of the experiments are inconclusive. Gwynn and Salaman (N01665) found that iodoacetic acid may be a co-carcinogen in mice when applied dermally after treatment with 9,10-dimethyl-1,2-benzanthracene. Eight of the 10 mice surviving the duration of the experiment developed tumors. Apparently iodoacetic acid may have a weak cancer-causing ability in rodents, but further research is necessary.

Iodoacetic acid can also cause cleft palate in mice. Miller (N01159) injected pregnant mice with iodoacetic acid during days 11-13 of gestation. Significant increases in cleft palate formation were noted in the rats that were injected with iodoacetic acid. The likely mechanism is the inhibition of glycolysis during palate formation by iodoacetic acid. If the multiplication and growth of the cells forming the embryonic palate is slowed by the lack of energy due to the inhibition of glycolysis, a cleft palate can result.

Skeletal deformities of embryos in strains of 129/RrJ mice have been induced by injection of 1.0 mg of iodoacetic acid on the ninth day of pregnancy. Sixty-two to 66% of the fetuses in the experiments developed some type of skeletal abnormality (N01508).

While iodoacetic acid has a teratogenetic effect in mice, data on higher primates are not currently available. Considering the mechanism of enzyme inhibition employed by iodoacetic acid, it could be postulated that teratogenic effects would be observed in primates.

No data on the mutagenicity, carcinogenicity, or teratogenicity of bromoacetic acid has been published.

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IV. TABLES

TABLE IV-1

NOHS EXPOSURE SUMMARY BY OCCUPATION
Actual and Trade Name

Substance (Hazard Code)	SIC CODE	Description	Estimated Exposures
Bromoacetic acid (83731)	692	Machine operatives	42
Chloroacetic acid (18070)	045	Chemists	117
"	071	Podiatrists	1,711
"	080	Clinical laboratory technologists and technicians	15
"	151	Chemical technicians	21
"	392	Weighers	19
"	441	Foremen, N.E.C.	10
"	641	Mixing operatives	77
"	692	Machine operatives, not specified	497
"	694	Miscellaneous operatives	84
"	695	Not specified operatives	5
"	785	Not specified laborers	124
"	922	Health aides, except nursing	1,711
		Total	4,391
		Total Actual and Trade Name Exposures to the Monohaloacetic Acids	4,433

Adapted from reference N00957

TABLE IV-2

CHLOROACETIC ACID IMPORTS TO THE US

Year	lbs	kg
1975	24,929,263	11,307,724
1976	19,818,176	8,989,373
1977	19,884,317	9,019,374
1978	27,564,058	12,502,846
1979	31,148,179	14,128,576

Source: Dept of Commerce, Bureau of the Census

TABLE IV-3

PHYSICAL PROPERTIES OF THE MONOHALOACETIC ACIDS AND DERIVATIVES

Substance	CAS #	Molecular Formula	Molecular Weight	Density (STP)	Melting Point (C)	Boiling Point (C)	Solubility*			
							Water	Alcohol	Benzene	Ether
Bromoacetic acid	79-08-3	$CH_2BrCOOH$	138.96	1.9335	50	208	+	+	-	-
Chloroacetic acid	79-11-8	$CH_2ClCOOH$	94.50	1.4043	63	187.85	+	+	+	+
Sodium chloroacetate	3926-62-3	$CH_2ClCOO \cdot Na$	116.48	-	-	-	-	-	-	-
Fluoroacetic acid	144-49-0	CH_2FCOOH	78.04	1.3693	35.2	165	+	-	-	-
Sodium fluoroacetate	62-74-8	$CH_2FCOO \cdot Na$	100.03	-	200-202	Decompose	+	+	-	-
Iodoacetic acid	64-69-7	CH_2ICOOH	185.96	-	82-83	Decompose	-	-	-	-
Sodium iodoacetate	305-53-3	$CH_2ICOO \cdot Na$	160.94	-	-	-	+	+	-	+

* + = soluble
- = not soluble

Adapted from references N00807, N00808, N00896

TABLE IV-4

EFFECTS AND SYMPTOMS OF HUMAN POISONINGS BY MONOHALOACETIC ACIDS

Chemical	System	Effect/Symptom	Comments	Reference
Fluoroacetic acid	Central Nervous System (CNS)	Epileptiform convulsions		N00896, N01277
"	CNS	CNS excitation		N01277
"	"	Facial twitching		N01277
"	"	Coma		N01277
"	Cardiovascular system (CVS)	Ventricular fibrillation		N00896
"	Skin	Local irritant		N00896
"	--	Vomiting		N01277
"	--	Mental apprehension		N01277
Sodium fluoroacetate	CNS	Numbness of face	During latency period (lasting up to 6 hours)	N01467, N02890
"	"	Tingling of face and extremities	"	N01467, N02890
"	Gastrointestinal tract (GIT)	Epigastric pain	"	N01467, N02893
"	--	Nausea	"	N01467, N02892
"	--	Vomiting	"	N01467, N02891, N02892, N02893
"	--	Excessive salivation	"	N01467, N02890
"	--	Mental apprehension	"	N01467
"	CNS	Muscular twitching	Spasmodic contraction of voluntary muscles	N01467, N02890, N02892
"	--	Comatose		N02890, N02891, N02892, N02893
"	"	Epileptiform convulsions	Stiffening and jerking of body, tetanic convulsions, tonic-clonic convulsions	N01467, N01495, N01516, N02890, N02892, N02893

TABLE IV-4 (CONTINUED)

EFFECTS AND SYMPTOMS OF HUMAN POISONINGS BY MONOHALOACETIC ACIDS

Chemical	System	Effect/Symptom	Comments	Reference
Sodium fluoroacetate	CNS	Carpopedal spasms		N01467, N01495, N01516, N02890, N02893
"	"	Loss of speech		N01467, N02890, N02891, N02892, N02893
"	"	Dilation and inactivation of pupils to light	During convulsive spasms	N01467, N02892
"	"	Rolling of eyeballs		N01467
"		Nystagmus		N01467, N02890
"	"	Cutaneous hyperesthesia		N01467
"	CVS	Rapid pulse	Rising and irregular, often too rapid to count; 200+	N01467, N01495
"	"	Increase in amplitude of T waves followed by ST elevation		N01495, N01516
"	"	Low blood pressure		N01467
"	"	Diffuse myocardial abnormality		N01467, N01516, N02892
"	"	Cardiac arrhythmia		N01467, N01495
"	"	Ventricular premature contractions		N01467, N01495, N02892
"	"	Venticular fibrillation		N01467, N01495
"	"	Paroxysmal tachycardia		N01467
"	"	Sinus tachycardia		N01495, N02892
"	"	Cardiac arrest, asystole		N01467, N01495, N02892
"	Respiratory System (RS)	Apnea		N01467

TABLE IV-4 (CONTINUED)

EFFECTS AND SYMPTOMS OF HUMAN POISONINGS BY MONOHALOACETIC ACIDS

Chemical	System	Effect/Symptom	Comments	Reference
Sodium fluoroacetate	RS	Pulmonary edema	Possibly caused by secondary infection	NO1467
"	RS	Irregular respiration		NO2890
"	--	Vomiting blood		NO2890
"	--	Excessive mucous secretions		NO2890, NO2893
"	--	Foaming and frothing at the mouth		NO2890
"	--	Cyanotic skin, nailbeds, and lips		NO2890, NO2893
"	--	Clenching of jaws		NO2890
"	--	Inability to sit up		NO2890
"	--	Fecal incontinence		NO2890, NO2893
"	--	Increased perspiration		NO2890, NO2891
"	--	Blurred vision and inability to focus		NO2890
"	--	Depression		NO2890
"	--	LDlo (oral) = 2-5 mg/kg		NO0896
"	--	LDlo = 2-10 mg/kg		NO1467
Chloroacetic acid	--	Irritating to the skin and mucous membranes		NO0896, NO0919
"	--	Irritating to the eyes		NO0919

TABLE IV-4 (CONTINUED)

EFFECTS AND SYMPTOMS OF HUMAN POISONINGS BY MONOHALOACETIC ACIDS

Chemical	System	Effect/Symptom	Comments	Reference
Chloroacetic acid	--	Weakness and fatigue		NO1257, NO1195
"	--	Sleep disorder		NO1257
"	--	Headaches		NO1257
"	--	Epigastric pain		NO1257, NO1195
"	--	Dyseptic disorders		NO1257, NO1195
Bromoacetic acid	--	Irritating and corrosive		NO0919
Iodoacetic acid	--	Highly irritating to skin, eyes, and mucous membranes		NO0919

TABLE IV-5

HUMAN BIOCHEMICAL AND CELLULAR EFFECTS OF BROMOACETIC AND IODOACETIC ACIDS

Chemical	Tissue	Method	Concentration	Effects	Reference
Bromoacetic acid	Erythrocyte	Incubation in medium for 0.87 hrs	5×10^{-3} M	Reversible 50% inactivation of carbonic anhydrase B	N01223
Sodium iodoacetate	Fibrin	Incubation in urea medium	10^{-2} M for 1 hr	Inhibition of the stabilization of fibrin. Reduced maximum amplitude in thrombelastography and prolonged k-values	N01194
"	Papillary (heart)	Incubation in Krebs-Ringer solution	10^{-5} M	Partial to complete inhibition of the positive inotropic effects of ouabain. Enhancement of ouabain produced shortening of action potential duration.	N01197
"	Blood	Blood mixture; 4 hrs	0.5-10% IAA and blood	The disappearance of glucose was inhibited by iodoacetate, but glycolysis was never completely stopped. As glucose was lost, levels of lactic acid rose.	N02811
Iodoacetic acid	Fibrinogen Platelets Bovine thrombin	Incubation in medium for 5 min	10^{-1} M	Near complete inhibition of clot retraction	N01214
"	Placenta	Incubation in medium for 20 min	10^{-4} M	Increased glucose uptake slightly and increased fructose production slightly	N01224
"	Adipocytes	Incubation in medium for 3 hr	10^{-3} M	Increased lipolysis in isolated adipocytes	N01246
"	Platelets	Incubation in medium for 30 min	10^{-3} M	Hindrance of phosphorylation of pyridoxine	N01170
"	Foreskin	Tissue culture in medium for 14 d	0.1 g/ml	Markedly inhibited epithelial cell growth	N01157

TABLE IV-5 (CONTINUED)

HUMAN BIOCHEMICAL AND CELLULAR EFFECTS OF BROMOACETIC AND IODOACETIC ACIDS

Chemical	Tissue	Method	Concentration	Effects	Reference
Iodoacetic acid	Blood	Blood serum mixture	0.05 M	Iodoacetic acid led to inactivation of immune hemolysis at the second component of complement. The chemical groups with which it reacts are as yet undetermined.	N02851

TABLE IV-6

TOXIC EFFECTS OF SODIUM FLUOROACETATE, FLUOROACETIC ACID, AND RELATED IONS

Substance	Species	Route of Exposure and/or Tissue Type	Concentration of Dose	Number Exposed	Effects	Reference
Sodium fluoroacetate	Rat	Incubation; liver slices	$0.1\text{-}100 \times 10^{-3}$ M 20 min	--	Hypothetical sex difference was established between male and female rats. Females accumulated more citrate than males when fluoroacetate was present. Addition of malate caused a greater absolute increase than pyruvate or oxaloacetate.	N02844
"	"	"	1.0×10^{-3} M 10-160 min	--		
"	Rat	Incubation; myocardial cells	1, 10, 100 mg percent	--	Cytoplasmic vacuolization and mitochondrial swelling and clumping were observed with ultrastructural alteration. The morphologic effect was more variable than fibrillation as a dose response.	N02780
"	Wistar rat	Aqueous solution; kidney cell culture	1-10 mg/ml 100 µg/ml 15-30 min	--	Sodium fluoroacetate did not interfere with the growth rate of cells 48 hours past treatment, suggesting that no residual cell damage was present.	N01492
"	Mice	Intraperitoneal; blood, spleen, kidney, heart, liver, duodenum	8 mg/kg	--	Significant increases in the citric acid content of the organs when a heat killed S typhimurium suspension was injected into the mice. Aerobater aerogenes produced no change in the same tissues.	N02823
"	Wild Norway rat	Oral	0.1-5.0 mg/kg	55	Established a medium lethal dosage of 0.22 ± 0.01 mg/kg, and a survival time of 45-240 min	N02817

TABLE IV-6 (CONTINUED)

TOXIC EFFECTS OF SODIUM FLUOROACETATE, FLUOROACETIC ACID, AND RELATED IONS

Substance	Species	Route of Exposure and/or Tissue Type	Concentration of Dose	Number Exposed	Effects	Reference
Sodium fluoroacetate	Swiss Webster mice	Intraperitoneal	100 mg/kg	--	After citrate level had increased over three-fold, change occurred in levels of the other Krebs cycle members. The rise in glucose 6-phosphate and fall in pyruvate suggest inhibition of glycolysis at the phosphofructokinase step had taken place.	N02784
"	Rabbit Dog Monkey	Intraperitoneal " "	0.5 mg/kg 0.1 mg/kg 15.0 mg/kg	140 46 36	Commercially available monoacetin containing about 60% glycosol monoacetate was superior to any other substance yet tested for use against fluoroacetate poisoning (1950). An outline which may be helpful for guidance in treating humans was presented.	N02898
"	Rabbit	Incubation; kidney mitochondria	0.01-0.0033 M	--	An experimental arrangement allowed formation of the active inhibitor, fluorocitrate, so that when citrate was added, an immediate inhibition of its oxidation was always observed. Below concentrations of 0.0033 M citrate, the inhibition was noncompetitive.	N02879
Fluoroacetate	Rat	Intraperitoneal	80 µg/100 g	26	Depressed the intestinal absorption of vitamin B_{12} in the female rat, had no effect on absorption of coenzyme B_{12}. It is highly probable that vitamin B_{12} is converted to the coenzyme during intestinal absorption since both are absorbed by the same pathway.	N02839

TABLE IV-6 (CONTINUED)

TOXIC EFFECTS OF SODIUM FLUOROACETATE, FLUOROACETIC ACID, AND RELATED IONS

Substance	Species	Route of Exposure and/or Tissue Type	Concentration of Dose	Number Exposed	Effects	Reference
Fluoroacetate	Wistar rat	Intraperitoneal; liver tissue	5 mg/kg	--	In presence of fumarate the mitochondrial system of either sex was able to accumulate citrate; this effect was abolished by pyruvate. A time lag for inhibitory effect of fluorocompounds on respiration noted. Testosterone did not abolish effects on citrate accumulation, progesterone reversed it only in male liver mitochondria. Fluoroacetate in combination with progesterone inhibited respiration. Irradiation in normal rats did not significantly increase citrate accumulation in liver mitochondria of male rats.	N02834
"	Wistar rat	Intraperitoneal; liver tissue	20 mg/kg	--	Blocks the TCA cycle in vivo; would be of considerable interest to study alternate pathways in which hydrogen may be supplied to the respiratory chain independently of the TCA cycle in striated muscles. Other suggested pathways are the glycerol 1-phosphate cycle and the oxidation of glutamate either via glutamate dehydrogenase or via transamination to aspartate.	N02845
"	Rabbits	Intraperitoneal	1 mg/kg	--		
"	Wistar rat	Intraperitoneal; heart tissue	20 mg/kg	--	Results suggest that although the initial effect of fluoroacetate is to give rise to fluorocitrate, the inhibition of phosphofructokinase by accumulated citrate is actually lethal since it deprives the cell of pyruvate which would eventually overcome the inhibition of aconitase.	N02848
"	Rat	Oral (drinking water)	sublethal doses 7 mo	--	Normal growth; increased resistance to previous toxic levels	N01276
Fluoroacetic acid	Rabbit (M)	Intralenticular injection	0.01 M	--	Little effect on lens transparency and on PAEE-activity	N02837

TABLE IV-6 (CONTINUED)

TOXIC EFFECTS OF SODIUM FLUOROACETATE, FLUOROACETIC ACID AND RELATED IONS

Substance	Species	Route of Exposure and/or Tissue Type	Concentration of Dose	Number Exposed	Effects	Reference
Sodium iodoacetate	Rabbits	Injection; ear	20-25 mg/kg	18	Disruption of spermatogenesis, lesions of seminal vesicles.	NO2830
"	Albino rats (M)	Intraperitoneal	0.215-10 mg/kg	60	LD50 = 1.58 mg/kg	NO1775
"	Maple Grove mice (M&F)	Subcutaneous	10 ml/kg	77	Hyperirritable, convulsions; LD50 = 19.3 mg/kg	NO1512
"	Guinea pig	Intraperitoneal	1.0 ml/kg	52	Hyperirritable, convulsions; LD50 = 0.376 mg/kg	NO1512
"	Dog	Intravenous	0.1 ml/kg	--	Convulsive seizures, respiratory failure	NO1512
"	Wistar SW 69 rat (F)	Intraperitoneal	--	--	LD50 = 2.2 mg/kg	NO1504
"	Mice	Intraperitoneal	--	--	LD50 = 6.6 mg/kg	NO1511
Fluorocitrate	--	Incubation	1.6×10^{-4} M; 2.4×10^{-5} M	--	Competitive inhibition of aconitase by natural fluorocitrate was established. Synthetic fluorocitrate inhibits aconitase in both a competitive and an irreversible fashion.	NO2880
"	Rat	Intraperitoneal; liver	2.5 mg/kg	--	The turnover of blood citrate was rapid. Fluoroacetate resulted in a decreased, and fluorocitrate an increased urinary excretion of citrate-C^{14}. Fluoroacetate is also an inhibitor of the condensing enzyme. Although distribution of citrate in the subcellular fractions of liver differed from the kidney, the localization in each of the tissues was the same.	NO2838
"	Rat	Intraperitoneal; kidney	20 and 40 mg/kg			

TABLE IV-6 (CONTINUED)

TOXIC EFFECTS OF SODIUM FLUOROACETATE, FLUOROACETIC ACID, AND RELATED IONS

Substance	Species	Route of Exposure and/or Tissue Type	Concentration of Dose	Number Exposed	Effects	Reference
Fluorocitrate	Rat	Intraperitoneal	3 mg/kg	--	The C_4 members of Krebs cycle increased citrate in heart tissue but not kidney. C_2 members may, in appropriate doses, overcome the fluoroacetate block. In nonpoisoned rats, both C_4 and C_{12} members increased the citrate level in the kidneys.	NO2838

TABLE IV-7

TOXIC EFFECTS AND METABOLISM OF CHLOROACETIC ACID

Substance	Species	Route of Exposure and/or Tissue Type	Concentration or Dose	Number Exposed	Effects	Reference
Chloroacetic acid	Sprague-Dawley rat (M)	Rat liver homogenates	10^{-6} M	--	Displayed uncompetitive (coupling) inhibition; LD50 established at 5 mg/kg.	NO1520 (Abst)
"	Mice	Intraperitoneal	0.5 mM	--	Traced metabolic pathway: 82-88% excreted in urine; 8% expired in air; 0.2-0.3% remained in the animal.	NO1186
"	Rats	Oral	277.5 mg/kg	--	Dose given is the established LD50; 200 mg/kg cysteine was found to be the most effective antidote.	NO1238
"	Rabbit (M)	Intralenticular	0.01 M	--	Little effect on lens transparency and on PAEE-activity	NO2837
Sodium chloroacetate	Rat	Intravenous	117 mg/kg/d	2	As a thiol reagent proved a negative inhibitor of the sulphydryl enzyme systems. Retinal degeneration was not apparent.	NO2829
"	Rabbit	Intravenous	82 mg/kg for 2 d	3		
"	Rat	Stomach lavage and intravenous	--	--	LD50 = 580 mg/kg, when given by lavage. Intravenous LD50 = 55 mg/kg.	NO1250
Chloroacetic acid	Mice	Incubation; liver slices	0.005 M	--	Produced marked depression in oxygen consumption of liver slices. Chloroacetic acid within a range of 0.001 M to 0.03 M was found to be the most effective. An order of reactivity was established: chloro- the greatest, dichloro-, and trichloroacetic acid, the least reactive.	NO2815

TABLE IV-8

METABOLISM, BIOCHEMISTRY, AND TOXIC EFFECTS OF IODOACETIC AND BROMOACETIC ACIDS

Substance	Species	Route of Exposure and/or Tissue Type	Concentration of Dose	Number Exposed	Effects	Reference
Iodoacetic acid	Rabbit	Incubation; aorta	0.3 mg/ml 0-80 min	--	Suppressed the contractile response to adrenaline	N01166
"	Rabbit	Lens homogenates	25 mg	--	No lactic acid increase prior to *cataract development*	N01201
"	New Zealand rabbit	Detrusor muscle strips	$0.1-1.0 \times 10^{-3}$ M	24	Inhibition acetylcholine contraction; partially prevented pyruvate contraction	N01215
"	Rabbit (M & F)	Eye lens culture	--	--	Inhibited Na^+, K^+ transport system; swelled lenses	N01172
"	Rabbit	Ventrical slices	10^{-3} M	--	Metaraminol transport across membrane was not affected.	N01202
"	Rabbit	Intravenous	19.5-26.5 mg/kg	6	No erythrocyte effects; retinal degeneration; no effect on GSH levels; swelled lenses; increased free GSH	N01275
"	Rabbit (M) chinchilla	Intraperitoneal (5 mg/ml NaCl sol)	0.5-50 mg/kg	--	No erythroprotein fiber increase; suppression of oxygen consumption with cyanide	N01177
"	Rabbit	Subcutaneous or intraperitoneal;	7 mg/kg/d 3 mo	--	Reduced duration of action potential without a reduction of resting potential	N01153
"	Sheep	Intravenous	22.5 mg/kg	--	Caused hemolytic anemia; maintained GSH pathway by the hexose monophosphate pathway	N01275
"	Rat	Epididymal fat	10^{-3} M	--	Increased the levels of AMP and lipolysis; the inhibition of glycolysis produced a decrease in aerobic generated ATP.	N01171
"	Albino rat	Antemolar palate	$10^{-5}-10^{-6}$ M	--	Epithelial migration stopped; effects are reversible.	N01175
"	Albino rat	Antemolar palate	$10^{-2}-10^{-4}$ M	--	Epithelial migration stopped; effects are irreversible.	N01175
"	Rat	Thymus nuclei	5×10^{-5} M	--	Prevented respiration stimulation of glucose and inosine.	N01211

TABLE IV-8 (CONTINUED)

METABOLISM, BIOCHEMISTRY, AND TOXIC EFFECTS OF IODOACETIC AND BROMOACETIC ACIDS

Substance	Species	Route of Exposure and/or Tissue Type	Concentration of Dose	Number Exposed	Effects	Reference
Iodoacetic acid	Wistar rat female	Incubation; uterus	10^{-3} M 5 min	--	Inhibited prostaglandin E contraction 100%	NO1222
"	Sprague-Dawley rat (M)	Epididymal fat	$0.2\text{-}2.0 \times 10^{-3}$ M	--	Suggests action of glycolysis inhibitors and oxidative phosphorylation inhibitors is similar.	NO1225
"	Wistar rat (F)	Incubation; uterus	10^{-3} M (0-5 hr)	--	Caused H_2O, Ca^{++}, and Na^{+} increase in tissue; decrease K^{+}. Ca^{+} has a different transport system from Na^{+} and K^{+}.	NO1199
"	Rat	Lenses	10^{-4} M	--	Complete opacification of (actively cataractogenic) lenses.	NO1259
"	Rat (M & F)	Intraperitoneal	40 mg/kg	--	Decreased sensitivity to angiotensin, noradrenaline, reduced pressor response to hog renin.	NO1245
"	Rat	Bone implant	2×10^{-3} M	--	Dense nonhaversian bone was low in osteo-induction.	NO1167
"	Wistar rat (M)	Intraperitoneal	0.5-50 mg/kg	--	Hypoxia induced	NO1177
"	Rat	Intraperitoneal (w/ 1 mg thiamine)	3×10^{-4} M	--	Increased blood thiamine, decreased urinary thiamine	NO1219
"	Rat	Intraperitoneal (30 min later, w/ 800 rads radiation)	20 mg/kg	--	Caused radiosensitization leading to higher mortality; cysteine removed toxic effect.	NO1216
"	Wistar rat albino	Retina (in vivo)	$0.5\text{-}5 \times 10^{-5}$ M	--	No significant effect on retinal formation of latic acid	NO1273
"	Rat (thiamine deficient)	Intraperitoneal	3×10^{-4} M/kg	--	Increased phosphorylation of thiamine in liver	NO1221

TABLE IV-8 (CONTINUED)

METABOLISM, BIOCHEMISTRY, AND TOXIC EFFECTS OF IODOACETIC AND BROMOACETIC ACIDS

Substance	Species	Route of Exposure and/or Tissue Type	Concentration of Dose	Number Exposed	Effects	Reference
Iodoacetic acid	Dog	Bone implant; abdominal wall	2×10^{-3} M	--	Gave osteoinduction properties to undemineralized bone; suggests SH groups are essential for BMP-ase activity but not BMP activity.	N01167
"	Dog	Intravenous	20 mg/kg	--	Increased oxygen tension in blood compared to that in vascular wall and in muscle.	N01213
"	Pig	Blood platelets	--	--	Reduced sediment ATP and ADP levels	N01206
"	Pig	Heart; malate dehydrogenase	3×10^{-3} M	--	No effect on enzyme mitochondrial malate dehydrognase.	N01200
"	Cat	Spleen	5×10^{-4} M	--	Irreversibly blocked NE release both by nerve stimulation and potassium.	N01208
"	Cat	Sciatic nerve	$2.5\text{-}20 \times 10^{-3}$ M	--	Diminished fast axoplasmic transport system, complete block in 2 hr. Pyruvate and L-lactate reversed iodoacetic acid (IAA) block.	N01189
"	Cat	Sciatic nerve	5×10^{-3} M	--	Irreversible GAPD activity inhibitor	N01188
"	Immature mice (M)	Duodenum crypt cells	--	10	Mitochondrial swelling, cristae disruption; endoplasmic reticulum fragmentation; interstitial space inclusions	N01182
"	Albino mice (M)	Liver slices	10^{-4} M	--	Reduced uptake of decamethonium	N01207
"	Swiss mice	Brain tissue	$0.3\text{-}1 \times 10^{-3}$ M	--	Decreased ATP levels; inhibited amino acids, lysine glutamate	N01190
"	Snells dwarf mice	Pituitary	^{214}C-iodoacetic acid used to carboxymethylate methionine residues	--	Leading to loss of carboxymethyl bovine growth hormone	N01176

TABLE IV-8 (CONTINUED)

METABOLISM, BIOCHEMISTRY, AND TOXIC EFFECTS OF IODOACETIC AND BROMOACETIC ACIDS

Substance	Species	Route of Exposure and/or Tissue Type	Concentration of Dose	Number Exposed	Effects	Reference
Iodoacetic acid	Chick embryo	Tibias	1×10^{-3} M	--	Increased bone mineral, depressed Na^+,K^+, and lactic acid production	N01198
"	Guinea pig	Ileum muscle (2-40 min)	3×10^{-3} M	--	Increased tissue uptake of ^{45}Ca	N01165
"	Rat (M & F)	Subcutaneous injection	25 or 50 mg/kg	--	Hypoglycemia observed; neither karyometric nor histologic findings revealed damage to either alpha- or beta- cells in the islets of *Langerhans*. Blood sugar levels not permanent. Nuclei of both alpha and beta underwent some increase in size.	N02833
"	Rat	Tyrode's solution organ bath; diaphram	2.7×10^{-3}M	--	Caused contracture which was complete in 4 hr. As long as contracture developed, the membrane potential remained constant. It was concluded that IAA prolongs the action potential by an effect on membrane permeability during activity rather than by changing ionic gradients between intra- and extra-cellular space.	N02832
"	Cattle	Ribonuclease	0.02 M	--	Enzyme inactivation in bovine pancreatic ribonuclease is a single chemical process and was shown to be caused by alkylation of the sulfhydryl groups by iodoacetic acid.	N02840
"	Guinea pig	Tyrode's solution organ bath; ileum	1×10^{-4}M	--	Iodoacetic and bromoacetic acid were among amino acid residues which inhibit guinea pig ileum histamine and acetylcholine receptors. Noncompetitive antagonism was observed.	N01196

TABLE IV-8 (CONTINUED)

METABOLISM, BIOCHEMISTRY, AND TOXIC EFFECTS OF IODOACETIC AND BROMOACETIC ACIDS

Substance	Species	Route of Exposure and/or Tissue Type	Concentration of Dose	Number Exposed	Effects	Reference
Iodoacetic acid	Tumor tissue slices	Tissue bath; Ringer glucose bicarbonate medium	Ranges from $3x10^{-5}$ - $1x10^{-3}$M	--	IAA primarily inhibited aerobic glycolysis in a direct relationship accompanied by a smaller indirect inhibition of respiration. Certain concentrations had reversible inhibitions after a period of 1 hr. High concentrations produced irreversible damage, though glycolysis had not completely stopped.	N02787
"	Rabbit	Subcutaneous injection	10-20 mg/kg	--	Blood sugar rose, death within 1.5 hr; extreme rigor was apparent. After production of insulin hypoglycemia, iodoacetate caused blood sugar to rise and convulsions to cease, but iodoacetic-poisoning symptoms soon supervened.	N02792
"	Rat	Oral	1-2 mg/d	--	After 8-14 days, dermatitia and loss of hair. Gastrointestinal tract enlarged. Anemia, red blood corpuscle 30% less than normal count. Erythrocyte count increased, then continued to fall until death. Phosphorous content in blood down 33%. Adrenal cortex hypertrophied to double weight, some medulla increase. Dry yeast seemed to stimulate healing after poisoning, riboflavin appears to be the active ingredient. An important relationship to Gee-Herter disease was established. Cause suggested is secondary B_2-avitaminosis from insufficient adrenal gland secretions.	N02802
"	Dog	Intravenous	1-2 mg/kg	--	Lactic acid and blood sugar levels lowered by injections. Decrease related to size of dose; 2-4 hours later sugar concentration rose almost to original levels. Lower levels lactic acid explained by glycolysis-inhibitory effect of IAA.	N02812

TABLE IV-8 (CONTINUED)

METABOLISM, BIOCHEMISTRY, AND TOXIC EFFECTS OF IODOACETIC AND BROMOACETIC ACIDS

Substance	Species	Route of Exposure and/or Tissue Type	Concentration of Dose	Number Exposed	Effects	Reference
Iodoacetic acid	Rabbit	Injection; carotid artery	20-25 mg/5 ml 5 min	--	Unilateral retinal lesions ophthalmoscopically visible after 12 hr. Triosle - phosphate dehydrogenase inhibited at an early stage, activity later returns.	N02847
"	Rabbit	Intravenous	15-25 mg/kg	--	ERG and optic nerve impulses rapidly ceased within 2-4 min. IAA impaired the processes which resisted the reduction of the oxidative metabolism by low oxygen tensions. Anaerobic glycolysis was reduced, suggesting that, in the mammalian retina, aerobic glycolysis predominates over respiration in furnishing energy for generation of electrical potentials.	N02807
"	Cat	"	"	--		
"	Frog	Injection; isolated spinal cord	0.02 ml of 2% MIA/Ringer solution	--	Loss of reflex irritability of spinal cord, gas exchange near normal while utilization of sugar almost totally inhibited (glycolytic metabolic pathway of carbohydrates). Greater concentration and longer periods of exposure eventually affect respiration. Repiratory inhibition could be relieved temporarily with lactate .	N02791
"	Snells dwarf mice	Pituitary	^{214}C-iodoacetic acid used to carboxymethylate methionine residues	--	Leading to loss of carboxymethyl bovine growth hormone	N01176
"	Rabbit (M)	"	"	--	The glycolytic system was most likely blocked, producing opacities in lens within a few days. This was usually followed by complete cataract formation. There was no immediate drop in PAEE-activity in vivo. Later, when marked opacities developed, a significant drop in the rate of PAEE was noted.	N02837

TABLE IV-8 (CONTINUED)

METABOLISM, BIOCHEMISTRY, AND TOXIC EFFECTS OF IODOACETIC AND BROMOACETIC ACIDS

Substance	Species	Route of Exposure and/or Tissue Type	Concentration of Dose	Number Exposed	Effects	Reference
Iodoacetatic acid	Guinea pig	Ileum muscle	3×10^{-3} M (2-40 min)	--	Increased tissue uptake of ^{45}Ca	N01165
"	Guinea pig	Ileal longitudinal muscle, taenia coli	--	--	Decreased 5-hydroxy tryptamine $-^{14}C$ uptake	N01193
"	Guinea pig	Papillary muscle	10^{-5} M	--	Reduced duration of action potential without a reduction in resting potential	N01212
"	Guinea pig	Bone implant abdominal wall	2×10^{-3} M	3	Gives osteoinduction properties to undemineralized bone, suggests SH groups are essential for BMP-ase activity but not BMP activity.	N01167
"	Rat	Oral	7.4×10^{-3} M	--	Calcium ash and water content in bones of chronically poisoned rats proved equal to that of normal rats in same weight class, but not same age group. Partial growth inhibition values also corresponded to normal animals of the same weight. Calorie undernourishment did not prevent calcium deposit with age; water content was found to be reduced, as in the normal aging process of rats.	N02803
Sodium iodoacetate	Rabbit	Subcutaneous	80 mg/kg	--	Carbohydrate metabolism inhibitor. There occurred consistently an increase in serum organic phosphate. Increase noted in blood glucose and lactic acid. No acetone bodies were detected in plasma. Acidotic hyperpnea appeared and a few suffered convulsions.	N02816

TABLE IV-8 (CONTINUED)

METABOLISM, BIOCHEMISTRY, AND TOXIC EFFECTS OF IODOACETIC AND BROMOACETIC ACIDS

Substance	Species	Route of Exposure and/or Tissue Type	Concentration of Dose	Number Exposed	Effects	Reference
Iodoacetate	Clostridium acetobutylicum	Incubation	2.07×10^{-2}M-1.89×10^{-4}M	--	Destruction of enzymatic activity because photo-chemical oxidation caused the inactivation of acetoacetate decarboxylase; it occurs only under illumination and is ineffective except in air, and thiolsulfate prevents activation. Destruction did not result from carboxymethylation or iodination of the enzyme. A cysteine molecule is oxidized to cysteic acid. The details of the sulfhydryl group in the activity of this enzyme are unknown but may be applicable to other systems.	N02783
"	Rat	Incubation; heart mitrochondrial suspension	0.01, 0.10, and 10^{-3} M (10 min)	--	Oxygen uptake of heart mitochondria, distinct inhibition, strongest being oxidation of pyruvate and alpha-ketoglutarate and possibly involving systems utilizing coenzyme A and lipoic acid.	N02828
Iodoacetate	Rabbit	Injection; eye	20 mg/kg, single dose	--	Lesions on outer segments of retina; disorganization, vesiculation, lysis of rod sacs, synaptic vesicles, mitochondria of ellipsoid flake have tendency to disintegrate. No visible changes involving cones, some fusing of membranes	N02831
"	"	"	Additional dose of 20 mg/kg	--	Complete destruction of rod cells and cone cells. Alterations of submicroscopic membranes suggest locus; of action widely dispersed, and related in some way to the maintenance of lipoprotein structures.	
Bromoacetic acid	Horse	Blood serum	--	--	In the serum-antiserum flocculation reaction, sodium monobromoacetate inhibits the flocculation reaction of antibodies and antigens.	N02797

TABLE IV-8 (CONTINUED)

METABOLISM, BIOCHEMISTRY, AND TOXIC EFFECTS OF IODOACETIC AND BROMOACETIC ACIDS

Substance	Species	Route of Exposure and/or Tissue Type	Concentration of Dose	Number Exposed	Effects	Reference
Bromoacetic Acid	Cattle	Carbonic anhydrase	0.5, 1, 2, 5, 20, and 100 M	--	In the presence of bromoacetic acid, the bovine enzyme, carbonic anhydrase B, was not inactivated, or significantly reactive with bromoacetic acid.	N01218
"	Rabbit (M)	Intralenticular injection	0.01 M	--	Changes were less marked than those obtained with iodoacetic acid. Bromo- did lead to both loss of transparency and some reduction of PAEE-activity.	N02837
Bromoacetic and iodoacetic acids	Rabbit	Erythrocyte binding (in vitro)	Not specified	12	Tested compounds, which normally bound readily with the erythrocytes, were considerably reduced after irradiation with 79 kr of x-rays. Results were consistent, whether the samples were irradiated under 1 atm oxygen-tension or after flushing with oxygen or nitrogen. Activity is independent of alkylating ability of compounds used.	N02849
Sodium iodoacetate and sodium bromoacetate	Rat; rabbit	Intravenous	29-32 mg/kg	13	Bromoacetate and iodoacetate in sublethal doses present similar injuries to retina as inhibitors of sulfhydryl enzyme systems in the rabbit. In rat, only iodoacetate had an effect. Retinal degeneration cannot be related to systemic toxicity alone.	N02829

TABLE IV-9

LD_{50} VALUES FOR SODIUM FLUOROACETIC ACID

Species	Route of Exposure*	LD50 (mg/kg)	Target Organ Heart	Target Organ CNS	Reference
Primates					
Man (Homo sapiens)	Oral	2.5-5.0 (estimated)	+	+	N01516
"	Oral	0.7-2.1 (estimated)			N01501
Rhesus monkey (Macaca mulatta)	iv	4.0	+	+	N01516
Spider monkey (Ateles geoffroyi)	iv	15.0	+		N01516
Marsupials					
Opossum (Didelphis marsupialis)	Oral	60.0			N01501
Ungulates and Ruminates					
Goat	im	0.6	+		N01516
Sheep	Oral	2.0		+	N01516
"	Oral	0.25-0.05			N01501
Horse	Oral	1.0	+		N01516
Horse (male & female)	Oral	0.35-0.55			N01501
Swine (young)	ip	0.4	+	+	N01516
Swine (adult)	Oral	1.0	+	+	N01516
Cow (adult, female)	Oral	0.393			N01501
" (young, male & female)	Oral	0.221			N01501
Mule	Oral	0.22-0.44			N01501
Mule deer (Odocoileus h heminonus)	Oral	0.3-1.0			N01501

TABLE IV-9 (CONTINUED)

LD_{50} VALUES FOR SODIUM FLUOROACETIC ACID

Species	Route of Exposure*	LD50 (mg/kg)	Target Organ Heart	Target Organ CNS	Reference
Carnivores					
Canines:					
Dog (Mongrel)	iv	0.06		+	N01516
"	iv	0.10 (LD_{100})		+	N01516
Coyote (Canis latrans nebracensis)	ip	0.10	+		N01516
Bear (Ursus sp)	Oral	0.5-1.0			N01501
Grey fox (Urcocyon cinereoargenteus scotti)	ip	0.3			N01501
Badger (Taxidea taxus berlandieri)	ip	1.0-1.5			N01501
Domestic ferret (Mustela putorious)	Oral	1.41			N01501
Marten (Martes americana)	Oral	1.0			N01501
Mink (Mustela vison)	Oral	1.0			N01501
Cat (Felis domesticus)	iv	0.2	+	+	N01516
Bobcat (Lynx rufus baileyi)	ip	0.66			N01501
Rodents					
Rats:					
Albino rats (male)	ip	1.58		+	N01775
Albino rats	im, ip, sc	5.0			N01516
"	sc	2.0-3.0			N01516
"	Oral	2.5			N01516
Cotton rats (Sigmodon hispidus liltoralis)	sc Oral	108.0 0.1			N01520 (Abst) N01516

TABLE IV-9 (CONTINUED)

LD_{50} VALUES FOR SODIUM FLUOROACETIC ACID

Species	Route of Exposure*	LD50 (mg/kg)	Target Organ Heart	Target Organ CNS	Reference
Rodents (cont'd)					
Wood rat (Neotoma intermedia)	Oral	1.5			N01516
White-throated wood rat (Neotoma a albigula)	ip	0.8			N01516
Norway rat (males R r horuegicus)	Oral	2.1			N01501
Norway rat (female) Norway wild rat	Oral	2.2			N01501
Alexandria rat (R r alexandricus)	Oral	0.5			N01516
Black rat (R r subsp)	Oral	0.1			N01516
Mice:					
Albino (Maple Grover)	sc	19.3		+	N01512
" (Carworth)	Oral	17.0			N01516
Albino (others)	ip	10.0			N01516
"	sc	16.0			N01516
"	sc	5.0			N01516
Albino (Female)	ip	2.2			N01504
Meadow mouse (Microtus haydeni)	Oral	0.5			N01516
Meadow vole (Microtus pennsylvanicus)	Oral	0.92			N01501
Deer mouse (Peromyscus sp)	Oral	4.0			N01516
House mouse (Mus musculus)	Oral	8.0			N01516
Hamsters	ip	3.0		+	N01516

TABLE IV-9 (CONTINUED)

LD_{50} VALUES FOR SODIUM FLUOROACETIC ACID

Species	Route of Exposure*	LD50 (mg/kg)	Target Organ Heart	Target Organ CNS	Reference
Rodents (cont'd)					
Guinea pigs	ip	0.35		+	N01516
"	sc	0.25 (LD_{100})			N01516
Ground squirrels:					
Apache spotted (Citellus spilosoma cavesceus)	ip	10.4			N01516
Columbian (Citellus columbianus columbianus)	ip	0.91	+	+	N01516
Fisher (Citellus b fisheri)	Oral	0.3		+	N01516
Pocket gophers:					
Breviceps-Texas (Geomys breviceps sp)	ip	0.05 (LD_{100})			N01516
Tuza-Florida (Geomys floridanus)	ip	0.2			N01516
Kangaroo rats:					
Bannertail (Dipodmys s spectabilis)	ip	0.1			N01516
Merriam (Dipodomys m merriami)	ip	0.15			N01516
Miscellaneous:					
Nutria (Myocastor coypus)	Oral	0.056			N01501
Prairie dog (Cynomys-ludoviciarus)	Oral	0.3			N01501
Lagomorphs					
Rabbits	ip	0.25		+	N01541
New Zealand white rabbit	iv	0.25	+		N01516

TABLE IV-9 (CONTINUED)

LD_{50} VALUES FOR SODIUM FLUOROACETIC ACID

Species	Route of Exposure*	LD50 (mg/kg)	Target Organ: Heart	Target Organ: CNS	Reference
Lagomorphs (cont'd)					
Pigmented	iv	0.5	+		N01516
Dutch & others	sc	0.28			N01512
"	ip	0.38			N01512
Black-tailed jack rabbit	Oral	5.55			N01501
European rabbit	Oral	0.8			N01501
Birds					
Calliforms:					
White leghorn	Oral	7.5		+	N01516
Rhode Island red	Oral, iv	5.0	+	+	N01516
Chukars	Oral	3.51			N01501
Plymouth rock	Oral	5.5			N01516
Gambels quail (M)	Oral	20.0			N01516
Japanese quail (M)	Oral	17.7			N01501
Ring-necked pheasant (F)	Oral	6.46			N01501
Calumbiformes:					
Florida pigeon	Oral	9.0			N01516
Colorado pigeon	Oral	2.5			N01516
Domestic pigeon	Oral	4.24			N01501
Mourning dove	Oral	8.55-14.6			N01501
Passerines:					
English sparrow (M)	Oral	2.5			N01516
Magpie	Oral	0.6-1.3			N01501
Brewer's blackbird	Oral	2.0-3.0			N01516

TABLE IV-9 (CONTINUED)

LD_{50} VALUES FOR SODIUM FLUOROACETIC ACID

Species	Route of Exposure*	LD50 (mg/kg)	Target Organ Heart	Target Organ CNS	Reference
Birds (cont'd)					
Raptors and scavengers:					
Golden eagle	Oral	1.25-5.0			N01501
American rough-legged hawk	Oral	10.0			N01516
Ferruginous rough-legged hawk	Oral	10.0			N01501
Greek horned owl	Oral	10.0			N01501
Black vulture	Oral	15.0			N01516
Turkey vulture	Oral	20.0			N01501
Anseriformes:					
Mallard (adult male)	Oral	10.0			N01501
" (" female)	"	8.0			N01501
Pintail (" male)	"	10.0			N01501
" (" female)	"	8.0			N01501
Poikiliotherms					
Frogs:					
Leopard frog	sc	150.0		+	N01516
Toad	ip, sc	500.0			N01516
Bull frog (M)	Oral	54.4			N01501

*Definitions of abbreviations are as follows:

iv = intravenous
im = intramuscular
ip = intraperitoneal
sc = subcutaneous