TOXICOLOGICAL PROFILE FOR
FLUORIDES, HYDROGEN FLUORIDE,
AND FLUORINE

Prepared by:

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Agency for Toxic Substances and Disease Registry
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UPDATE STATEMENT

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333

FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987, on October 20, 1988, on October 26, 1989, on October 17, 1990, and on October 17, 1991. A revised list of 275 substances was published on October 28, 1992.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the lists. Each profile must include the following:

(A) The examination, summary, and interpretation of available toxicological information and epidemiological evaluations on a hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects.

(C) Where appropriate, identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.
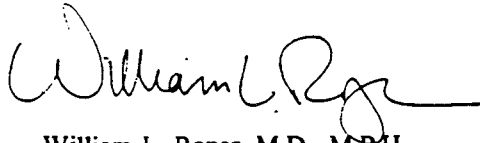
The ATSDR toxicological profile is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health will be identified by ATSDR and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

Foreword

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control and Prevention (CDC), and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures the consistency with ATSDR policy.

2. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying endpoints.

3. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

4. Quality Assurance Review. The Quality Assurance Branch assures that consistency across profiles is maintained, identifies any significant problems in format or content, and establishes that Guidance has been followed.

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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about fluorine, hydrogen fluoride, and fluorides, and to emphasize the human health effects that may result from exposure to them. The Environmental Protection Agency (EPA) has identified 1,334 sites on its National Priorities List (NPL) sites. Fluoride-containing compounds have been found at 130 of these sites. Fluorine has been found at 28 of these sites, and hydrogen fluoride or hydrofluoric acid have been found at 19 of the sites. However, we do not know how many of the 1,334 NPL sites have been evaluated for fluorine, hydrogen fluoride, or fluorides. As EPA evaluates more sites, the number of sites at which fluorine, hydrogen fluoride, and fluorides are found may change. The information in this profile is important for you because fluorine, hydrogen fluoride, and fluorides may cause harmful health effects and because these sites are potential or actual sources of human exposure to fluorine, hydrogen fluoride, or fluorides.

When a chemical is released from a large area such as an industrial plant, or from a container such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You are exposed only when you come into contact with the chemical. You can come into contact with it in the environment through breathing, eating, or drinking substances containing the chemical. Exposure may also result from skin contact with it.

If you are exposed to substances such as fluorine, hydrogen fluoride, or fluorides, several factors determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life style, and state of
health.

1.1 WHAT ARE FLUORINE, HYDROGEN FLUORIDE, AND FLUORIDES?

Fluorine is a pale, yellow-green, irritating gas that has a strong, sharp odor. It is so chemically reactive that it is nearly always found combined with metals as a salt. Fluorine is unlikely to be released from landfills as a gas because it rapidly combines with many earth materials to form fluoride compounds in the soil.

Hydrogen fluoride is a colorless gas that is made up of a hydrogen ion and a fluoride ion. It readily dissolves in water, where it is also colorless at room temperature. The dissolved form is called hydrofluoric acid. Hydrogen fluoride may be found at hazardous waste sites.

In this profile, the term fluorides will be used to refer to the common salts of the element fluorine. Examples of fluorides include sodium fluoride

and calcium fluoride. Sodium fluoride and calcium fluoride are white solids. Sodium fluoride dissolves easily in water, but calcium fluoride does not.

Fluoride salts as a group are properly called fluorides. However, because toxic effects are due to the fluoride ion, the word fluoride is used in discussing health effects. Certain fluoride-containing compounds can reasonably be expected to occur at hazardous waste sites. These may include sodium fluoride and calcium fluoride. Cryolite is a mineral that contains sodium, fluoride, and aluminum and is used in making aluminum metal. It may also be found at hazardous waste sites.

Fluorides are found in many natural materials such as coal, clay, and minerals. They also occur naturally in the earth's crust. Fluorides can be released to the air from these substances when they are heated to high temperatures, such as in aluminum smelters; glass, brick, and tile works; and plastic factories. The biggest natural source of fluorides released to the air is volcanic eruptions. Once released to the air, fluorides are carried by wind and rain onto nearby water, soil, and food sources.

The biggest natural source of fluorides in soil and water is the breakdown of rocks containing fluoride. Fluorides are removed from surface water, such as lakes and streams, when they attach to particles in the water. Some phosphorus fertilizers have fluorides in them. Use of these fertilizers may also cause fluorides to enter food and water supplies. Some plants, such as tea, accumulate fluorides and concentrate them in their leaves and stems.

Fluorine is used in rocket fuels, and in making glass, enamel, and bricks. Hydrogen fluoride is used mainly in making aluminum and in making chlorofluorocarbons (CFCs). Fluorides are used in making steel, chemicals, ceramics, lubricants, dyes, and plastics. They are also used as pesticides, mainly against ants and roaches. Fluorides are also added to some medicines and household products such as toothpaste and mouth rinses. Substances containing radioactive fluorine can be used to help visualize tumors in medical tests. Fluorides are added to drinking water to prevent cavities in many communities where the water supply is naturally low in fluoride. For more information on the chemical properties of fluorine, hydrogen fluoride, and fluorides, and their production, use, and fate in the environment, see Chapters 3, 4, and 5.

1.2 HOW MIGHT I BE EXPOSED TO FLUORINE, HYDROGEN FLUORIDE, OR FLUORIDES?

Because fluorides are part of the earth, you are exposed to small amounts of them in air, water, and soil. These amounts are called background levels. Fluorides are found in your body fluids, bones, and tissues. Fluorides are normally found in very small amounts in the air. Levels measured in areas around cities are usually less than 1 microgram of fluoride

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per cubic meter ($\mu g/m^3$) of air. Rural areas where few people live have even lower levels. Air around hazardous waste sites or factories that use or produce hydrogen fluoride or fluoride compounds may contain high levels of these chemicals.

Levels of naturally occurring fluorides in surface water such as rivers, streams, and lakes usually range from 0.01 to 0.3 parts of fluoride per million parts of water (ppm). Levels of fluorides in underground water are usually higher than those found in rivers, streams, and lakes (0.02-1.5 ppm). Sea water generally has more fluoride than fresh water. Levels in sea water range from 1.4 to 1.5 ppm. Surface and groundwater levels near industrial sites using fluorides may be higher than normal if fluorides are released. In areas near hazardous waste sites, you are most likely to be exposed to higher than normal levels of fluorides by drinking contaminated groundwater.

Workers may be exposed to high levels of hydrogen fluoride or cryolite in the air if their work involves certain machinery, air transportation, medical and other health services, textile and metal manufacturing, or petroleum and coal production. Workers in these jobs may breathe in levels as high as 2.5 milligrams of fluoride per cubic meter (mg/m^3) of air. Some hazardous waste sites contain containers of hydrofluoric acid. If material leaks from these containers, clean-up workers can be exposed to hydrofluoric acid. In areas near hazardous waste sites, you are not likely to be exposed to hydrofluoric acid because the acid will react with soil to form fluoride salts before it reaches you. Some hazardous waste sites may contain fluorine in pressurized containers. Fluorine reacts even faster than hydrofluoric acid. It is very unlikely that people living near a hazardous waste site would be exposed to fluorine.

The level of fluorides in soils is usually between 200 and 300 ppm. However, soils with high amounts of minerals may have higher amounts of fluorides. Some industrial processes, such as the removal of phosphorus from rocks during fertilizer manufacture or the smelting of aluminum, can release fluorides to the air. The released fluorides can then settle on the soil. Higher than normal levels of fluorides in soil have also been found at hazardous waste sites. You could be exposed to fluorides through contact with these soils.

Food grown in areas where soils have high amounts of fluorides or where fertilizers containing fluorides are used may have high levels of fluorides. Tea and some seafoods have been found to have high levels of fluorides. Food cooked in water with added fluorides may also have increased fluoride levels.

To prevent dental decay (caries), fluorides are sometimes added to drinking water to achieve levels of about 1 ppm. You may also come in contact with fluorides from using household items. Most of these are dental products, such as toothpastes, fluoride gels, and fluoride rinses. If you swallow the treated water, or these products, you will be exposed to fluoride. Swallowing

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toothpaste can account for a large percentage of the fluoride to which a small child might be exposed. Certain medicines used to treat some skin diseases and cancer contain fluorides, and using them also increases exposure. Skin contact with products such as lubricants and oils containing fluorides or hydrofluoric acid may also increase your exposure. The average daily fluoride intake from food and water is estimated to be about 1 milligram (mg) if you have water that is not artificially fluoridated, and about 2.7 mg if you have fluoridated water.

For more information on how you can be exposed to fluorine, hydrogen fluoride, or fluorides, see Chapter 5.

1.3 HOW CAN FLUORINE, HYDROGEN FLUORIDE, BODY, AND FLUORIDES ENTER AND LEAVE MY BODY?

When you breathe in air containing fluorine, fluoride can enter your bloodstream through your lungs, but it is not known how quickly this happens. Much of the fluoride leaves your body in urine, but some is stored in your bones and teeth.

When you breathe in air containing hydrogen fluoride or fluoride dusts, it enters your bloodstream quickly through your lungs. When hydrofluoric acid touches skin, most of it can quickly pass through the skin into the blood. How much of it enters your blood stream depends on how concentrated the hydrofluoric acid is and how long it stays on your skin. Almost all of the fluoride that enters the body in these ways is quickly removed from the body in the urine, but some is stored in your bones and teeth.

Generally, most of the fluoride in food or water that you swallow enters your bloodstream quickly through the digestive tract. However, the amount that enters your blood stream also depends on factors such as how much of the fluoride you swallowed, how well the fluoride dissolves in water, whether you ate or drank recently, and what you ate or drank. It is likely that you will vomit if you drink water that contains high levels of fluoride, and the vomiting will probably also reduce the amount of fluoride that enters your bloodstream. Things such as age, sex, and health status affect what happens to the fluoride ion once it is in your body. After entering your body, about half of the fluoride leaves the body quickly in urine, usually within several days. Most of the fluoride ion that stays in your body is stored in your bones and teeth.

For more information on how fluorine, hydrogen fluoride, and fluorides enter and leave your body, see Chapter 2.

1.4 HOW CAN FLUORINE, HYDROGEN FLUORIDE, AND FLUORIDES AFFECT MY HEALTH?

Fluorine. Fluorine gas is very irritating and very dangerous to the eyes, skin, and lungs. Fluorine gas at low concentrations makes your eyes and

nose hurt. At higher concentrations, it becomes hard to breathe. Exposure to high concentrations of fluorine can do so much damage to your lungs that it can kill you.

Hydrogen Fluoride. Hydrogen fluoride is also a very irritating gas. Hydrogen fluoride is not as dangerous as fluorine, but large amounts of it can also cause death. The actual amounts that cause death are not known because these measurements are hard to make. Breathing in a large amount of hydrogen fluoride with air can also harm the lungs and heart. The human health effects of breathing moderate amounts of hydrogen fluoride for several months are not well known, but rats that breathed hydrogen fluoride for several months had kidney damage and nervous system changes, such as learning problems. If you breathe hydrogen fluoride or fluoride-containing dust for several years, changes in your bones, called skeletal fluorosis, can happen. Skeletal fluorosis is further described below.

Hydrofluoric acid is dangerous to humans because it can burn the eyes and skin. The initial exposure to hydrofluoric acid may not look like a typical acid burn. Skin may only appear red and may not be painful at first. Damage to skin may happen over several hours or days, and deep, painful wounds may develop. When not treated properly, serious skin damage and tissue loss can occur. In the worst cases, getting a large amount of hydrofluoric acid on your skin can lead to death caused by the fluoride affecting your lungs or heart. The major public health concern regarding hydrofluoric acid is related to short-term exposure at work.

Fluoride. Several medicines that contain fluoride are used for treating skin diseases and some cancers. In addition, small amounts of sodium fluoride are added to toothpaste or drinking water to help prevent dental decay. In 1991, the Public Health Service (PHS) of the U.S. Department of Health and Human Services completed a report on the risks and benefits of exposure to fluorides in drinking water. The PHS report determined that 50 years of experience shows that adding fluorides to drinking water supplies (water fluoridation) has reduced tooth cavities. The PHS also noted that there are health and economic benefits of water fluoridation for people of all ages and social and economic groups, especially for children who do not get adequate dental care.

However, exposure to certain levels of fluoride can harm your health. The health effects depend on the type of fluoride you are exposed to, how long you are exposed, and how much gets into your body. In general, the more soluble the fluoride-containing substance is, the more toxic it is. Drinking or eating fluoride during the time teeth are being formed can cause visible changes in teeth. These changes increase in severity with increasing levels of fluoride. The condition is called dental fluorosis. In the most mild cases, there are a few almost invisible white spots on the teeth. In moderate cases, there are large white spots on the teeth (mottled teeth), and some brown spots. In severe cases, the teeth are pitted and have many brown

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stains. Symptoms are not identical for all children exposed to the same level of fluoride. In general, some children who drink water with 1 ppm fluoride may get a few small spots or slight discolorations on their teeth. Some children who drink water with 4 ppm fluoride in it for long periods before their permanent teeth are in place may get brown spots or pitting on their teeth. At these higher levels of fluoride, the teeth can become more fragile and sometimes develop a greater number of cavities.

Skeletal fluorosis can be caused by eating, drinking, or breathing large amounts of fluorides. This disease only occurs after long-term exposures and can cause denser bones, joint pain, and a limited range of joint movement. In the most severe cases, the spine is completely rigid. Skeletal fluorosis that severely limits movement is extremely rare in the United States. It is more common in places where people do not get proper nutrition. Although fluoride exposure results in denser bones, the bone appears to be weaker than normal bone. Fluoride has been used to treat women with osteoporosis. However, these women have a greater risk of breaking a bone if they take fluoride pills containing over 30 mg fluoride per day. Fluorides in drinking water may increase the risk of old women and men breaking a bone. If you eat relatively large amounts of sodium fluoride, it can cause stomach aches, vomiting, and diarrhea. Still larger amounts can cause death by damaging your stomach and affecting your heart.

It is not known whether fluoride affects reproduction in people. Certain animal species, such as cows and various birds, have reproductive problems when they eat or drink large amounts of fluoride. Some experiments have found reproductive effects of fluoride in laboratory animals, while others have not. The significance of these results to human health is unclear. It is also not known whether fluoride causes birth defects in people or animals. Fluoride does cross the placenta from the mother's blood to the developing fetus. However, no birth defects related to fluoride were seen in newborn humans in one study. No experiments have studied developmental effects of fluoride using standard testing methods. Some animal studies have found developmental effects of fluoride, while others have not. As with reproductive effects, cows may be more sensitive than laboratory animals.

Studies have been done to see if fluoride causes cancer in people who live in areas with fluoridated water or naturally high levels of fluoride in drinking water, or people who work in jobs where they may be exposed to fluorides. The studies that were well-designed have generally not found any association between fluoride and cancer in people. However, these studies may not have been sensitive enough to have detected very low cancer rates. A large study of fluoride conducted by the National Toxicology Program with both rats and mice found that a small number of male rats developed bone cancer after drinking water with high levels of fluoride in it throughout their lives. This was considered equivocal evidence that fluoride causes cancer in male rats. Fluoride did not cause cancer in mice or female rats. Another study found no evidence that fluoride causes cancer in rats. Both animal

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studies had problems that limited their usefulness in showing whether or not fluoride can cause cancer in humans. It is not known if the same effects would be seen in people exposed the same way. The bone cancer seen in the rat study is rare in humans, although its frequency has recently increased among males in counties with fluoridated water. In spite of this geographical association, a careful analysis by the National Cancer Institute indicates that exposure to fluoride in drinking water was not the cause of this increase.

For more information on the health effects of fluorine, hydrogen fluoride, and fluorides, see Chapter 2.

1.5 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO FLUORINE, HYDROGEN FLUORIDE, OR FLUORIDES?

Urine samples can be analyzed to find out if you have been exposed to fluorides. The fluoride level in the sample is compared to the level of fluoride usually found in urine. This will show if a person has been exposed recently to higher than normal levels of fluorides. However, this test cannot be used to predict any specific health effects that may occur after fluoride exposure. The urine test must be performed soon after exposure because fluoride that is not stored in the bones leaves the body within a few days. This test can be done at most laboratories that test for chemical exposure. Blood sampling does not provide as good a measure of exposure to fluoride as urine sampling. Bone sampling can be done in special cases to measure long-term exposure to fluorides. Because fluorine, hydrogen fluoride, and fluorides all enter the body as fluoride, these tests can not distinguish among exposure to these different chemicals. However, the tests are not normally used to monitor fluorine exposure.

For more information on medical tests to determine exposure to fluorine, hydrogen fluoride, and fluorides, see Chapters 2 and 6.

1.6 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

Fluorine, hydrogen fluoride and sodium fluoride have been named hazardous substances by EPA. Spills of more than 10 pounds of fluorine, 100 pounds of hydrogen fluoride, or 1,000 pounds of sodium fluoride must be reported to the National Response Center. The highest level allowed by the Occupational Safety and Health Administration (OSHA) for fluorine in air for an 8-hour work day, 40-hour work week is 0.2 milligrams of fluorine per cubic meter of air (mg/m^3); for hydrogen fluoride it is 2.5 mg/m^3. The highest level of fluoride allowed by OSHA for an 8-hour work day, 40-hour work week is 2.5 mg/m^3. The maximum amount of fluoride allowed in drinking water by EPA is 4 mg/L. EPA recommends that states limit the amount of fluoride in drinking water to 2 mg/L.

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Scientists within the PHS recently formed a committee to study the risks and benefits of exposure to fluoride. The committee prepared a report that states that fluoride in drinking water helps to prevent tooth decay. However, the scientists also said that there is a need to study fluoride further to find out more about other possible health effects in humans and animals exposed to fluoride in drinking water.

For more information on recommendations regarding exposure to fluorine, hydrogen fluoride, and fluorides, see Chapter 7.

1.7 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns not covered here, please contact your state health or environmental department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, E-29
Atlanta, Georgia 30333

This agency can also provide you with information on the location of the nearest occupational and environmental health clinic. Such clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of fluorine, hydrogen fluoride, and fluorides, and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for fluorine, hydrogen fluoride, and fluorides based on toxicological studies and epidemiological investigations.

Fluorine is a gaseous element that occurs only in very low concentrations in the environment in the absence of anthropogenic sources (see Chapter 5 for further discussion). Because it is strongly electronegative, it is rarely found in the environment in the elemental state, nor is it likely to be found in the environment near toxic waste sites as molecular fluorine. Hydrogen fluoride is also a gas and it is very water soluble. When hydrogen fluoride is dissolved in water it is called hydrofluoric acid.

Hydrogen fluoride is very water-soluble and dissolves readily in any water present in the air or other media. Although hydrofluoric acid is very corrosive and can etch glass, it is a weak acid, meaning that it can be present in water as an undissociated molecule. However, in dilute solutions it is almost completely ionized; salts are formed if cautions are available. Due to formation of complexes, very concentrated solutions of hydrofluoric acid are also largely ionic in nature. Therefore, a hydrogen fluoride or hydrofluoric acid spill would result in contamination with fluoride ion, but hydrogen fluoride or hydrofluoric acid would not be of concern outside the immediate vicinity of the spill. However, while members of the public are only likely to come into contact with fluoride contamination, clean-up workers could be exposed to hydrogen fluoride/hydrofluoric acid. In this profile, hydrogen fluoride is used to refer to the gas, while hydrofluoric acid is used to refer to the liquid form. When both forms are included, the word hydrogen fluoride is used.

The term fluoride properly refers to numerous natural and synthesized compounds that are derived from hydrofluoric acid. This class of chemicals is commonly referred to as fluorides. Some of these compounds, such as oxygen difluoride, are very reactive and highly toxic. Because of their reactivity, these compounds would not migrate unchanged from a hazardous waste site. Fluoride salts, such as sodium fluoride and calcium fluoride, are much less reactive and much less toxic. Since the fluoride ion is the toxicologically active agent, and discussion of water fluoridation uses the term fluoride, the term fluoride is used generically in this profile to refer to toxicology of fluoride salts. Because numerous different fluoride compounds exist naturally in the environment and have varying chemical properties, the term fluorides is used in the discussion of environmental media. Most of the available

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literature on fluoride toxicity concerns sodium fluoride. Additional toxicity literature is available on some other forms of fluoride, such as stannous fluoride. Other forms of fluoride are discussed only if exposure is likely to occur at a hazardous waste site. (Such exposure to stannous fluoride is not likely.) Wherever the form of fluoride exposure is known, that salt is identified in the profile.

Limited information also exists concerning occupational exposure to the mineral cryolite (Na_3AlF_6), sometimes with concomitant exposure to hydrogen fluoride. Because these exposures usually involve exposure to both hydrogen fluoride and cryolite, sometimes along with exposure to other fluoride dusts, they are discussed separately in the profile.

This profile will discuss data, or the absence of data, concerning the toxicity of inorganic compounds of fluorine which people could be exposed to at a hazardous waste site. Exposure and toxicity are discussed separately for fluorine, hydrogen fluoride/hydrofluoric acid, and fluoride. Toxic effects of occupational exposure in aluminum reduction plants, where exposure to hydrogen fluoride, fluoride dusts, and cryolite all occur, are also discussed separately. Because the toxic effects of fluorine are largely due to the action of the fluorine molecule on the respiratory tract or other exposed surfaces, fluorine exposure is reported as exposure to a level of diatomic fluorine. By contrast, systemic effects of hydrogen fluoride are due to the fluoride ion, so concentrations of hydrogen fluoride are converted to fluoride equivalents. All doses of fluoride are reported as amount of fluoride ion.

The primary routes and durations of concern vary with the different fluorine compounds. In general, the more soluble the fluoride is, the more that can be absorbed by oral ingestion, and the more toxic it is. The primary exposure routes and duration for hydrofluoric acid are by the inhalation or dermal routes, related to acute occupational exposure, while the primary exposure route and duration for fluoride is chronic exposure to fluoride in the drinking water (often as sodium fluoride) and in food. Therefore, most of the information for the inhalation and dermal routes comes from studies of acute exposure to fluorine or hydrofluoric acid, while most of the information regarding the oral route is based on sodium fluoride. The toxicity following inhalation or dermal exposure to other inorganic fluorine compounds differs from that of hydrofluoric acid. Similarly, oral exposure to various fluorides other than sodium fluoride may result in different toxic effects.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure--inhalation, oral, and dermal--and then by health effect--death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed

in terms of three exposure periods--acute (less than 15 days), intermediate
(15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented
in tables and illustrated in figures. The points in the figures showing noobserved-
adverse-effect levels (NOAELs) or lowest-observed-adverse-effect
levels (LOAELs) reflect the actual doses (levels of exposure) used in the
studies. LOAELs have been classified into "less serious" or "serious"
effects. These distinctions are intended to help the users of the document
identify the levels of exposure at which adverse health effects start to
appear. They should also help to determine whether or not the effects vary
with dose and/or duration, and place into perspective the possible
significance of these effects to human health.

The significance of the exposure levels shown in the tables and figures
may differ depending on the user's perspective. For example, physicians
concerned with the interpretation of clinical findings in exposed persons may
be interested in levels of exposure associated with "serious" effects. Public
health officials and project managers concerned with appropriate actions to
take at hazardous waste sites may want information on levels of exposure
associated with more subtle effects in humans or animals (LOAEL) or exposure
levels below which no adverse effects (NOAEL) have been observed. Estimates
of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of
interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (MRLs) have
been made, where data were believed reliable, for the most sensitive noncancer
effect for each exposure duration. MRLs include adjustments to reflect human
variability in the extrapolation of laboratory animal data to health effects
in humans.

Although methods have been established to derive these levels (Barnes et
al. 1988; EPA 1990), uncertainties are associated with these techniques.
Furthermore, ATSDR acknowledges additional uncertainties inherent in the
application of the procedures to derive less than lifetime MRLs. As an
example, acute inhalation MRLs may not be protective for health effects that
are delayed in development or are acquired following repeated acute insults,
such as hypersensitivity reactions, asthma, or chronic bronchitis. As these
kinds of health effects data become available and methods to assess levels of
significant human exposure improve, these MRLs will be revised.

2.2.1 Inhalation Exposure

Inhalation exposure most commonly occurs in an occupational setting. As
discussed above, most of the available information concerning toxic effects of
fluorine and its compounds following inhalation exposure comes from studies of
exposure to hydrogen fluoride or hydrofluoric acid. There are also a limited
number of useful studies concerning inhalation exposure to fluorine or

particulates of inorganic fluoride compounds. However, no animal studies were located regarding toxic effects of exposure to the particulate fluoride compounds. Toxic effects of hydrogen fluoride are discussed in all of the following sections. Where toxicity data exist for fluorine or fluoride, these substances are also discussed.

Fluorine gas is extremely irritating. The primary health effects of acute fluorine inhalation are nasal and eye irritation (at low levels), and death due to pulmonary edema (at high levels). In animals, renal and hepatic damage have also observed.

Acute inhalation of hydrogen fluoride following facial splashes with hydrofluoric acid can cause bronchiolar ulceration, pulmonary hemorrhage and edema, and death. In addition, renal and hepatic damage have been observed in animal studies. Many of the human studies regarding inhalation of hydrogen fluoride fumes also involved dermal exposure; in such cases, it is difficult to determine which effects are specific to the inhalation route. However, the respiratory effects of hydrogen fluoride appear to be inhalation-specific, since they have not been reported in cases where there was clearly no inhalation exposure. The effects of combined inhalation and dermal exposure to hydrofluoric acid are also discussed in Section 2.2.3.

The major health effect of chronic inhalation exposure to fluoride is skeletal fluorosis, which has been reported in cases of exposure to fluoride dusts and hydrogen fluoride, either individually or in combination.

2.2.1.1 Death

Both fluorine and hydrogen fluoride can cause lethal pulmonary edema, although cardiac effects also contribute to the toxicity of hydrogen fluoride. The reported LC_{50} values for hydrogen fluoride (in mg/m^3 as fluoride) in rats for a given duration are generally at least 3.5-fold the value for fluorine (as diatomic fluorine) in rats for the same duration. Although strain differences could account for some of this difference, the LC_{50} of hydrogen fluoride in Crl:CD®BR and Wistar-derived rats was very similar.

Fluorine. No information was located on death in humans caused by fluorine. Fluorine toxicity has been investigated in Osborne-Mendel rats, Swiss-Webster mice, New England guinea pigs, and New Zealand rabbits (Keplinger and Suissa 1968). Similar values for the LC_{50}, were calculated for the different species. In the rats, the LC_{50} for exposures of 5, 15, 30, and 60 minutes were 1,088, 606, 420, and 287 mg/m^3, respectively. At concentrations near the LC_{50}, few signs of intoxication were observed immediately after exposure, except for irritation of the eyes and nose. Several hours after exposure, the animals exhibited lethargy, dyspnea, and general weakness. Except at concentrations above the LC_{90}, death generally occurred 12-18 hours after exposure. Animals that survived for 48 hours generally survived for the duration of the observation period. Loss of body weight was also observed but was considered nonspecific and was attributed to anorexia.

2. HEALTH EFFECTS

Toxic effects of inhalation exposure to fluorine and hydrogen fluoride were compared in rats, mice, rabbits, and guinea pigs (Stokinger 1949). Lethal doses from fluorine exposure determined by this group are about 3-4 times those determined by Keplinger and Suissa (1968), but quantitative exposure level data from these experiments are not reliable due to technical problems in monitoring fluorine gas levels. However, qualitative results from these experiments are useful. These experiments also found that fluorine was more toxic than hydrogen fluoride.

There are some indications that pre-exposure to low levels of fluorine may provide resistance to lethal effects of fluorine. Increased survival times were seen in New Zealand rabbits when challenged 48 hours after a pre-exposure regimen (Keplinger 1969). For example, 4 weeks of exposure to 78 mg/m^3 for 30 minutes once/week increased the survival time following a 30-minute challenge with 622 mg/m^3 from a maximum of 18 hours to 48 hours. Small increases in the LC$_{50}$ were observed when mice were pre-exposed four times in 7 days to 39 mg/m^3 for 15 minutes/exposure, followed by a challenge exposure 24-168 hours later. No mechanism for the possible tolerance was suggested.

Repeated exposures of rats, mice, guinea pigs, and rabbits to 0.8, 3, 8, or 25 mg/m^3 fluorine were conducted for up to 178 hours over 35 days (Stokinger 1949). The exposure regimen was not stated, but appears to be 5-6 hours/day, 5 days/week. The exposure levels at these lower concentrations were considered fairly reliable. Guinea pigs and rats were less sensitive to lethal effects than were rabbits or dogs. All of the rabbits, mice, and dogs exposed to 25 mg/m^3 died, while only half of the rats and guinea pigs died. The highest exposure level at which some rabbits survived was 3 mg/m^3. Almost all animals of all species survived exposure to 0.8 mg/m^3.

Hydrogen Fluoride. Acute inhalation of hydrogen fluoride fumes in combination with dermal exposure to hydrofluoric acid has been reported to cause death in humans. Actual exposure concentrations are not known in any of these cases. Death was generally due to pulmonary edema (resulting from irritation and constriction of the airways), or cardiac arrhythmias with pronounced hyperkalemia, hypocalcemia, and hypomagnesemia.

The death of a chemist who sustained first-and second-degree burns of the face, hands, and arms when a vat containing hydrofluoric acid accidentally ruptured has been described (Kleinfeld 1965). This 29-year-old male died 10 hours after admission to the hospital. Postmortem examination revealed severe tracheobronchitis and hemorrhagic pulmonary edema. A petroleum refinery worker was splashed in the face with 100% anhydrous hydrofluoric acid (Tepperman 1980). The absorption of fluoride produced acute systemic fluoride poisoning with profound hypocalcemia and hypomagnesemia and cardiac arrhythmias. The patient died less than 24 hours after exposure; autopsy revealed pulmonary edema. A young woman splashed in the face with hydrofluoric acid died of respiratory insufficiency a few hours after exposure

2. HEALTH EFFECTS

(Chela et al. 1989). The autopsy revealed severe burns of the skin and lungs, with hemorrhagic pulmonary edema produced by hydrofluoric acid and its vapor.

The lethal concentration of hydrogen fluoride has been investigated in rats, mice, and guinea pigs. It appears that mice are more sensitive to the acute effects of hydrogen fluoride than are rats, and rats are more sensitive than guinea pigs. The 15-minute LC_{50} values for hydrogen fluoride were 3,362 mg fluoride/m^3 for guinea pigs and 2,090 mg fluoride/m^3 for Wistar-derived rats (Rosenholtz. et al. 1963). The 60-minute LC_{50} for hydrogen fluoride in ICR-derived mice was 266 mg fluoride/m^3 (Wohlslagel et al. 1976), while in rats it has been reported as 1,084 mg fluoride/m^3 for a Sprague-Dawley-derived strain (Wohlslagel et al. 1976) and 1,016 mg fluoride/m^3 for a Wistar-derived strain (Rosenholtz et al. 1963).

The LC_{50} values reported by Haskell Laboratory (1988) for Crl:CD®BR rats were much higher than the values reported by the above investigators, although the size of the discrepancy decreased with longer exposure durations. For example, the 15-minute LC_{50}, was reported as 5,144 mg/m^3, while the 60-minute LC_{50} was 1,251 mg/m^3. Although the concentration of hydrogen fluoride that produced death was reported to be lower when it was administered to rats in humid air (Haskell Laboratory 1988), the method for measuring fluoride in humid air may not have given accurate results. This limitation was recognized by the authors, who stated that the collection efficiency of the sampling train for aerosols was not evaluated.

Longer-term effects of hydrogen fluoride were investigated by exposing various species to 7 or 24 mg/m^3 hydrogen fluoride for 6 hours/day, 6 days/week, for 30 days (Stokinger 1949). Humidity was 47-97% at the lower concentration, and 48-66% at the higher concentration. Marked species differences were observed. All rats and mice exposed to 24 mg/m^3 died, but no guinea pigs, rabbits, or dogs exposed at this level died. No animal of any species died following exposure to 7 mg/m^3. In an experiment where five rabbits, three guinea pigs, and two Rhesus monkeys were exposed to 14.4 mg/m^3 for 6-7 hours/day, 5 days/week, for 50 days (309 hours total), the only deaths observed were two guinea pigs (Machle and Kitzmiller 1935). Exposure of one of these animals stopped after 134 hours' exposure, and exposure of the other one stopped after 160 hours, when marked weight loss was observed. Nevertheless, the animals died about 2 weeks later.

The LC_{50} values for each species and duration category of exposure to fluorine are recorded in Table 2-l and plotted in Figure 2-l. The LC_{50} values for each species and duration category of exposure to hydrogen fluoride are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.1.2 Systemic Effects

The predominant systemic effects of acute inhalation exposure to fluorine or hydrogen fluoride are respiratory, nasal, and ocular irritation.

TABLE 2-1. Levels of Significant Exposure to Fluorine - Inhalation

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (mg F_2/m^3)[b]	LOAEL (effect) Less serious (mg F_2/m^3)[b]	LOAEL (effect) Serious (mg F_2/m^3)[b]	Reference
ACUTE EXPOSURE							
Death							
1	Rat	1 d 5-60 min/d				1088 (5-minute LC50) 606 (15-minute LC50) 420 (30-minute LC50) 287 (60-minute LC50)	Keplinger and Suissa 1968
2	Rabbit	1 d 5-30 min/d				1275 (5-minute LC50) 420 (30-minute LC50)	Keplinger and Suissa 1968
3	Gn Pig	1 d 15-60 min/d				614 (15-minute LC50) 264 (60-minute LC50)	Keplinger and Suissa 1968
4	Mouse	1 d 5-60 min/d				932 (5-minute LC50) 583 (15-minute LC50) 350 (30-minute LC50) 233 (60-minute LC50)	Keplinger and Suissa 1968
Systemic							
5	Rat	1 d 5min/d	Resp	132	263 (dyspnea; mild congestion)		Keplinger and Suissa 1968
6	Rat	1 d 15min/d	Resp	75	147 (very mild congestion)		Keplinger and Suissa 1968
7	Rat	1 d 30min/d	Resp	53	105 (very mild congestion)		Keplinger and Suissa 1968
8	Rat	1 d 60min/d	Derm/Oc	71	144 (irritation of eye and nose)		Keplinger and Suissa 1968
9	Rat	1 d 60min/d	Resp	42	71 (very mild congestion)		Keplinger and Suissa 1968

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (mg F_2/m^3)[b]	LOAEL (effect)		Reference
					Less serious (mg F_2/m^3)[b]	Serious (mg F_2/m^3)[b]	
10	Mouse	1 d 5min/d	Resp	119	263 (dyspnea; mild congestion)		Keplinger and Suissa 1968
11	Mouse	1 d 5min/d	Resp	119	263 (dyspnea; mild congestion)		Keplinger and Suissa 1968
			Hepatic	263	303 (coagulation, necrosis, and cloudy swelling)		
			Renal	119	177 (coagulation, necrosis)		
12	Mouse	1 d 15min/d	Resp	98	131 (very mild congestion)		Keplinger and Suissa 1968
13	Mouse	1 d 15min/d	Resp	98	127 (dyspnea; mild congestion)		Keplinger and Suissa 1968
			Hepatic	199	224 (coagulation, necrosis, and cloudy swelling)		
			Renal	98	127 (coagulation, necrosis)		
14	Mouse	1 d 30min/d	Resp	79	127 (dyspnea; mild congestion)		Keplinger and Suissa 1968
			Hepatic	127	180 (coagulation, necrosis, and cloudy swelling)		
			Renal	79	127 (coagulation, necrosis)		
15	Mouse	1 d 30min/d	Resp	48	101 (very mild congestion)		Keplinger and Suissa 1968

2. HEALTH EFFECTS

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TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (mg F_2/m^3)[b]	LOAEL (effect)		Reference
					Less serious (mg F_2/m^3)[b]	Serious (mg F_2/m^3)[b]	
16	Mouse	1 d 60min/d	Resp	23	45 (very mild conges- tion)		Keplinger and Suissa 1968
17	Mouse	1 d 60min/d	Resp	45	75 (dyspnea; mild congestion)		Keplinger and Suissa 1968
			Hepatic	85	124 (coagulation, necrosis, and cloudy swelling)		
			Renal	75	85 (coagulation, necrosis)		

[a]The number corresponds to entries in Figure 2-1.

[b]All concentrations expressed as mg fluorine/m^3 for consistency with ACGIH guidelines.

d = day(s); Derm/oc = dermal/ocular; Gn pig = guinea pig; LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; min = minute(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory

FIGURE 2-1. Levels of Significant Exposure to Fluorine - Inhalation

ACUTE
(≤14 Days)

Systemic

Death   Respiratory   Hepatic   Renal   Dermal/Ocular

(mgF_2/m^3)

10,000

1,000

■ 2h
■ 4m ■ 1r
■ 3g ■ 4m ■ 1r
              ■ 1r ■ 2h
■ 3g ■ 4m ■ 1r
■ 3g ■ 4m

100

◐ 10m ◐ 11m   ◐ 5r   ◐ 11m
                                                         ◐ 11m
                                                         ◐ 13m ○ 13m
                                                         ◐ 14m

◐ 14m ◐ 12m ◐ 13m ○ 10m ○ 11m   ◐ 6r ○ 5r   ◐ 11m
○ 12m ○ 15m ○ 13m   ◐ 7r   ◐ 14m ◐ 13m ○ 11m
○ 14m   ◐ 17m   ◐ 6r ◐ 9r   ○ 13m
                                                  ○ 14m ○ 17m ◐ 17m

       ○ 15m ○ 17m ◐ 16m   ◐ 7r
                                    ○ 9r

○ 16m

◐ 14m ◐ 17m   ○ 17m
○ 17m

◐ 8r

○ 8r

10

Key

r	Rat	■	LC50
m	Mouse	◐	LOAEL for less serious effects (animals)
h	Rabbit	○	NOAEL (animals)
g	Guinea pig		

The number next to each point corresponds to entries in Table 2-1.

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Kidney and liver necrosis have also been observed in animals. No data were located regarding chronic inhalation exposure to fluorine. Most of the data that were located regarding systemic effects of chronic inhalation exposure are from occupational exposure to fluoride dusts, sometimes in combination with hydrogen fluoride. In these cases, the predominant systemic effect is skeletal fluorosis. Pre-existing conditions were generally not determined in the occupational or case studies, and levels of exposure and exposure durations were often approximations.

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category of exposure to fluorine are recorded in Table 2-1 and plotted in Figure 2-1. The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category of exposure to hydrogen fluoride are recorded in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. Both fluorine and hydrogen fluoride irritate the respiratory tract and can cause hemorrhaging in a duration-and concentration-dependent manner. Nasal irritation is discussed under dermal exposure (Section 2.2.3) because it is caused by direct contact with the gases.

Fluorine. Limited data are available regarding respiratory effects of fluorine on humans. Five volunteers (gender not specified) (19-50 years of age) were exposed to fluorine through a face mask that covered the eyes and nose but not the mouth (Keplinger and Suissa 1968). A concentration of 16 mg/m^3 was not irritating to the respiratory tract for at least 15 minutes. Intermittent inhalation (not defined further) of 36 mg/m^3 over a 5-minute period did not cause respiratory difficulty. Higher levels were tested only by exposure of the face and eyes. The study is limited by the small number of subjects tested.

An occupational cohort study comparing the incidence of respiratory complaints by 61 exposed workers with over 2,000 "unexposed" workers found no increase in the exposed group (Lyon 1962). The average fluorine level was 1.4 mg/m^3, and the maximum measured value was 38 mg/m^3. The study author concluded that the workers became "hardened" to the irritating effects of fluorine. The study is limited in that both groups were also exposed to uranium hexafluoride and hydrogen fluoride. The method of measuring respiratory complaints (visits to the plant medical department) was also not very sensitive. However, the observation of tolerance caused by repeated low level exposures is supported by the results from animal studies discussed in Section 2.2.1.1 and later in this section (Keplinger 1969).

Dyspnea and diffuse lung congestion were reported for Osborne Mendel rats and Swiss-Webster mice exposed to concentrations greater than or equal to ~25% of the LC$_{50}$ (i.e., 263 mg/m^3 for both species) for 5 minutes (Keplinger and Suissa 1968). Similar effects were seen at levels greater than or equal to ~25% of the LC$_{50}$ for longer exposure durations (15-60 minutes), although rats exhibited dyspnea only at ~50% of the LC$_{50}$ for these durations. The

TABLE 2-2. Levels of Significant Exposure to Hydrogen Fluoride - Inhalation

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (mg F/m^3)[b]	LOAEL (effect) Less serious (mg F/m^3)[b]	LOAEL (effect) Serious (mg F/m^3)[b]	Reference
ACUTE EXPOSURE							
Death							
1	Rat	1 d 60min/d				1084 (LC50 at 60 minutes)	Wohlslagel et al. 1976
2	Rat	1 d 5-60min/d				3862 (5-minute LC50) 2090 (15-minute LC50) 1587 (30-minute LC50) 1016 (60-minute LC50)	Rosenholtz et al. 1963
3	Rat	1 d 5-60min/d				11346 (5-minute LC50) 5144 (15-minute LC50) 2246 (30-minute LC50) 1251 (60-minute LC50)	Haskell Laboratory 1988
4	Gn Pig	1 d 15min/d				3362 (15-minute LC50)	Rosenholtz et al. 1963
5	Mouse	1 d 60min/d				266 (LC50 at 60 minutes)	Wohlslagel et al. 1976
Systemic							
6	Rat	1 d 5min/d	Resp			1890 (temporary respiratory distress and discharge)	Rosenholtz et al. 1963
			Derm/Oc		582 (mild irritation of eyes and nose)		

TABLE 2-2 (Continued)

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (mg F/m^3)[b]	LOAEL (effect)		Reference
					Less serious (mg F/m^3)[b]	Serious (mg F/m^3)[b]	
7	Rat	1 d 15min/d	Resp			1095 (temporary respiratory distress and nasal discharge)	Rosenholtz et al. 1963
			Derm/Oc		238 (slight irritation of eyes and nose)		
8	Rat	1 d 60min/d	Resp			380 (temporary respiratory distress and nasal discharge)	Rosenholtz et al. 1963
Neurological							
9	Rat	1 d 5min/d				1890 (weakness and de- creased activity)	Rosenholtz et al. 1963
10	Rat	1 d 15min/d				1095 (weakness and de- creased activity)	Rosenholtz et al. 1963

TABLE 2-2 (Continued)

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (mg F/m^3)[b]	LOAEL (effect)		Reference
					Less serious (mg F/m^3)[b]	Serious (mg F/m^3)[b]	

INTERMEDIATE EXPOSURE

Death

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (mg F/m^3)[b]	Less serious (mg F/m^3)[b]	Serious (mg F/m^3)[b]	Reference
11	Rat	5 wk 6d/wk 6hr/d				24 (death in 29/29)	Stokinger 1949
12	Mouse	5 wk 6d/wk 6hr/d				24 (death in 18/18)	Stokinger 1949

Systemic

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (mg F/m^3)[b]	Less serious (mg F/m^3)[b]	Serious (mg F/m^3)[b]	Reference
13	Human	15-50 d 6 hr/d	Resp		1.1 (irritation of nasal passages)		Largent 1960
14	Rat	5 wk 6d/wk 6hr/d	Resp	7	24 (pulmonary hemorrhage)		Stokinger 1949
			Renal	7	24 (cortical necrosis)		
15	Rabbit	5 wk 6d/wk 6hr/d	Resp	7	24 (pulmonary hemorrhage)		Stokinger 1949
16	Dog	5 wk 6d/wk 6hr/d	Resp		7 (pulmonary hemorrhage)		Stokinger 1949
			Hemato	24			

TABLE 2-2 (Continued)

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (mg F/m³)[b]	LOAEL (effect)		Reference
					Less serious (mg F/m³)[b]	Serious (mg F/m³)[b]	

Neurological

| 17 | Rat | 5 mo 24hr/d | | .01 | 0.1 (disturbances in conditioned reflexes; lengthened latent period) | | Sadilova et al. 1965 |

[a]The number corresponds to entries in Figure 2-2.

[b]All concentrations expressed as mg fluoride/m³ for consistency with ACGIH guidelines.

d = day(s); Derm/oc = dermal/ocular; Gn pig = guinea pig; hr = hour(s); LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; min = minute(s); mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

FIGURE 2-2. Levels of Significant Exposure to Hydrogen Fluoride - Inhalation

ACUTE
(≤14 Days)

INTERMEDIATE
(15-364 Days)

Systemic

Systemic

Death · Respiratory · Dermal/Ocular · Neurological

Death · Respiratory · Renal · Hematological · Neurological

(mgF/m³)

100,000		
10,000	■3r ■3r ■3r	■3r ■2r ■2r ■1r
1,000	■4g ■3r ■5m	■2r ■2r ●6r ●7r ●8r

Key

r	Rat	■	LC50
m	Mouse	●	LOAEL for serious effects (animals)
h	Rabbit	◑	LOAEL for less serious effects (animals)
g	Guinea pig	○	NOAEL (animals)
d	Dog	▲	LOAEL for less serious effects (humans)

The number next to each point corresponds to entries in Table 2-2.

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severity of the lung congestion was concentration related. Rats and mice exposed for 15-60 minutes, to ~50% of the LC_{50} developed irritation of the nose.

In the single-exposure experiments of Stokinger (1949), rabbits that died from fluorine exposure generally had severe edema of the alveoli, along with necrosis of the bronchial epithelium in some animals. "Infectious processes" were noted in some rabbits that survived exposure to the higher levels, suggesting that bronchial defenses were damaged. Similar effects were noted in rats, except pulmonary hemorrhage was noted in rabbits but rarely in rats. Technical problems with monitoring the fluorine concentration made the concentration data unreliable. Pulmonary irritation was also observed in rabbits that died from the repeated exposures to fluorine and in rats at the high-exposure level. Nasal irritation was observed in dogs and rats subjected to repeated exposures to 25 or 8 mg/m^3.

Swiss-Webster mice that were pre-exposed once to 47 mg/m^3 fluorine for 60 minutes, and were then exposed to 183-637 mg/m^3 fluorine for 15 minutes after an interval of 4-96 hours showed markedly less lung pathology than animals that were not pretreated (Keplinger 1969)., At the highest level (637 mg/m^3)exposure, 4 hours prior to the challenge reduced the lung pathology from the most severe rating to a rating of normal-mild. Pre-exposure also reduced the increased lung weight otherwise seen following fluorine exposure. However, a similar pre-exposure regimen only resulted in slight increases in the LC_{50}, as discussed in Section 2.2.1.1.

Hydrogen Fluoride. Acute inhalation of 100 mg/m^3 hydrogen fluoride by two male volunteers produced marked respiratory irritation within 1 minute (Machle et al. 1934). Pulmonary edema, pulmonary hemorrhagic edema, and tracheobronchitis have been reported in cases of people being splashed in the face with hydrofluoric acid, where concurrent inhalation and dermal exposure are likely (Chan et al. 1987; Chela et al. 1989; Dieffenbacher and Thompson 1962; Kleinfeld 1965; Tepperman 1980). Exposure concentrations were not known in these cases.

Lethality studies in animals have also reported respiratory effects in rats, mice, and guinea pigs from acute inhalation exposure to hydrogen fluoride. True respiratory effects, such as respiratory distress, pulmonary congestion, and intraalveolar edema were generally observed at levels of at least ~50% of the LC_{50} (Haskell Laboratory 1988; Rosenholtz et al. 1963; Wohlslagel et al. 1976). These effects appear to be reversible within a week upon cessation of exposure. Irritation of the conjunctivae and nasal tissues is a result of direct contact with hydrogen fluoride, and is discussed under dermal effects.

Pulmonary hemorrhage was noted in dogs,24 mg/m^3 for 6 hours/day, rabbits and rats exposed to 7 mg/m^3, 6 days/week for 30 days (Stokinger 1949). At no effect was seen in rats or rabbits, and localized hemorrhages were seen in only l/5 dogs.

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Pulmonary hemorrhage, alveolar inflammation, and hyperplasia of the bronchial epithelium were observed in guinea pigs that died due to exposure to 14.4 mg/m^3 for 6-7 hours/day, 5 days/week, for about 35 days (Machle and Kitzmiller 1935). This effect was not readily reversible. The one surviving guinea pig had alveolar exudates, thickening of the alveolar walls, and hemorrhages of the lungs when necropsied 9 months after the conclusion of the full 50-day exposure period. Similarly, all four rabbits exposed under the same conditions had lobular pneumonia and leucocytic infiltration of the alveolar walls, sometimes with edema and thickening of the walls, when necropsied 7-8 months after the last exposure. No clinical signs of toxicity were reported in rabbits and weight gain was generally similar to the controls. This study is limited by the small number of animals used and the incomplete reporting of the data.

Hydrogen Fluoride and Fluoride Dusts. A study of an occupational cohort exposed to hydrogen fluoride and fluoride dusts in the pot rooms of an aluminum smelter reported a significantly lower forced expiratory volume and increased cough and sputum production in the, highest exposure group, compared with controls who worked in the office or casting department and were reported to have no significant occupational exposure to air contaminants. Corrections were made for age, height, and smoking habits. The ambient air fluoride concentration in the high-exposure area was 0.2 mg fluoride/m^3 as vapor (presumably hydrogen fluoride) and 0.28 mg/m^3 "particulate fluoride." It is not clear whether the latter value represented the air concentration of fluoride in particulates or the concentration of the particulates that contain fluoride. Actual exposure was unknown because the workers wore respirators. Although urinary fluoride levels increased over the course of one work shift in the high-exposure group and not in the control group, the decrease in respiratory volume in the same time period was about the same in both groups (Chan-Yeung et al. 1983a). This effect was attributed to the fact that the exposed workers wore respirators; historical use of respirators was not reported. Since actual exposure was not known, no quantitative relationship between clinical symptoms and environmental or urinary fluoride levels could be established. There also may have been concomitant exposure to other respiratory irritants.

No studies were located regarding respiratory effects in animals following inhalation of fluoride dusts.

Cardiovascular Effects

Hydrogen Fluoride. Cardiac arrhythmias have been seen in humans following hydrofluoric acid splashes in the face region, where both dermal and inhalation exposure were involved (Chan et al. 1987; Tepperman 1980). It is not known whether inhalation exposure alone would cause these effects. However, myocardial necrosis and congestion were observed in three rabbits following inhalation exposure of 22.8 mg/m^3 anhydrous hydrogen fluoride for an

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unspecified period (Machle et al. 1934). The study was limited by the small
sample size and undetermined exposure period.

Gastrointestinal Effects

Hydrogen Fluoride. A population exposed to airborne hydrogen fluoride
near a smelter reported nausea (22.6%) and diarrhea (21.7%). The corresponding levels
reported by a control population were 6.9% and 12.1%, respectively. The total level of
gastrointestinal complaints was 70.5% and 36.2% in the subject and control populations,
respectively. The subject population appears to have been derived by self-selection and
random house-to house sampling, while the control population lived in a non industrial
area. Although atmospheric concentrations were not presented, concentrations of fluoride
in animals and plants in the area surrounding the smelter were substantially above
normal. The smelter was also reported to emit metallic oxide fumes (Waldbott 1979).

Hematological Effects

Fluorine. No studies were located on hematological effects of
inhalation exposure of humans to fluorine. No effect on complete blood count
parameters was observed following exposure of Osborne-Mendel rats to
concentrations up to 221 mg/m^3 for 60 minutes, or at concentrations up to
511 mg/m^3 for 15 minutes (Keplinger and Suissa 1968). These concentrations
were higher than the corresponding LC$_{50}$ values. Blood counts were monitored
for 21 days post-exposure. Similarly, Stokinger (1949) saw no effect on
hematological parameters in dogs, rabbits, or rats following repeated
exposures at concentrations up to lethal levels (25 mg/m^3 for 95 exposure
hours over 21 days). This study did not specify which parameters were
measured.

Hydrogen Fluoride. Hemograms of 20 variables (not specified) determined
in the rat (30/group), rabbit (10/group), and dog (4/group) following exposure to 24 mg/m^3
for 6 hours/day, 6 days/week, and dog (4/group) following exposure for 30 days showed no
clear changes (Stokinger 1949).

Five rabbits and two rhesus monkeys were exposed to 14.4 mg/m^3 hydrogen
fluoride via inhalation 6-7 hours a day, for 50 days (Machle and Kitzmiller
1935). Blood counts were done beginning 1 week prior to exposure and ending
3 months after the final exposure. There was a small but significant decrease
in erythrocyte levels in both species, but the study authors considered that
the result may have been due to biological variation. Significant increases
in hemoglobin levels were seen in monkeys. There was no effect on hemoglobin
levels in rabbits or leucocyte levels in either species. These experiments
used only a few animals from each species, and the exposure measurement
technology was not very precise.

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Hydrogen Fluoride and Fluoride Dusts. No signs of hematological effects, as measured by routine blood counts, were seen in a large cohort of aluminum workers exposed to total fluoride levels below 2.5 mg/m^3 for durations of up to at least 10 years (Chan-Yeung et al. 1983b). Similarly, no increase in abnormal findings was seen in 74 workers exposed at a phosphate fertilizer plant (Derryberry et al. 1963). The average urinary fluoride level in the exposed group was 4.6 mg/L. Significantly reduced levels of hemoglobin were reported in Slovak children aged 6-14 years living near an aluminum smelter (Macuch et al. 1963), but no information was provided on any statistical tests used. No information was provided on air fluoride concentrations, but urinary fluoride levels were about 0.8 mg/L for 6-11-year old children, and about 0.4 mg/L for 12-14-year-old children. In an outdated study of 78 workers exposed to cryolite, anemia was present in 11/30 subjects with pathological bone changes (Moller and Gudjonsson 1932). Blood parameters were not analyzed for the workers without bone changes.

Musculoskeletal Effects. Skeletal fluorosis is a clinical syndrome sometimes seen following chronic exposure to fluoride. It is characterized by increased x-ray bone opacity, exostoses, and calcification of ligaments. Symptoms may include bone and joint pain, and limited range of movement. Skeletal fluorosis has been reported following exposure to hydrogen fluoride, cryolite, and sodium fluoride.

Fluorine. No data were located regarding musculoskeletal effects of fluorine inhalation on humans.

Fluoride levels in the teeth of rats exposed to 25 mg/m^3 for approximately 5 hours/day, 5 days/week for 21 days were about 14 times the levels in controls; fluoride levels in the femur were about 6 times that of the controls (Stokinger 1949). The appearance of the teeth was characterized as corresponding to that of very mild to mild dental fluorosis. The fluoride levels in the teeth and bone at lower concentrations decreased in a concentration-related manner. Pigment changes were reported as just perceptible in animals exposed to 3 mg/m^3.

Hydrogen Fluoride. A male exposed for 10 years to hydrogen fluoride at an alkylation unit of an oil company complained of back pains, leg pains, and loss of memory (Waldbott and Lee 1978). Initially, time away from work lessened the symptoms, but as time on the job increased, the symptoms persisted throughout periods away from work. During hospitalization following an accident, advanced osteoarthritis of the spine was diagnosed. Based on bone fluoride measurements of 1,100 ppm 10 years after exposure ceased, the study authors concluded that the worker suffered from chronic intoxication resulting from frequent, variable exposures to airborne hydrogen fluoride. However, concomitant exposure to petroleum products, while not reported, cannot be ruled out as a cause of the pains and memory loss.

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Duration- and concentration-related increases in tooth and bone fluoride levels were reported in the rat following exposure to 7 or 24 mg/m^3 for 6 hours/day, 6 days/week for up to 30 days (Stokinger 1949). The study author did not report whether there were any visible or radiological signs of dental or skeletal fluorosis.

Hydrogen Fluoride and Fluoride Dusts. Marked evidence of skeletal fluorosis was reported in workers exposed to gaseous fluoride (largely hydrogen fluoride) and fluoride dust in the pot rooms of the aluminum industry (Kaltreider et al. 1972). Individual exposure concentrations and durations were not presented. However, the estimated time-weighted average (TWA) 8-hour exposure to total fluorides for one plant ranged from 2.4 to 6.0 mg/m^3. Average urinary fluoride levels were about 9 mg/L. Exposure at a second plant was lower as a result of industrial hygiene measures; no TWA was available, but urinary fluoride levels ranged from 1.4 to 4.6 mg/L. No skeletal changes were observed at the second plant, and detailed physical examinations of the workers at both plants revealed no general health impairment. No data were presented that correlated urinary fluoride levels to the presence or absence of fluorosis.

In a follow-up study of 59 of the potroom workers at the second plant, the average preshift (after 48 hours away from work) urinary fluoride level was 2.24 mg/L (range, 1.4-3.1). The average level after 3-5 working days (postshift) was 5.68 mg/L (range, 2.7-10.4). In spite of this evidence of fluoride exposure, there was no radiological evidence of any fluoride-related bone abnormalities (Dinman et al. 1976c). Total occupational exposure ranged from 10 to 43 years. This study may provide urinary fluoride levels that are not associated with any bone effects in healthy adults. However, since only workers who remained at the high-exposure tasks for the duration of the study were examined, any sensitive population that may have found work elsewhere because of adverse health effects might have been missed.

Clinical and radiological investigations were performed for 2,258 aluminum workers exposed to fluoride for an average of 17.6 years (Czerwinski et al. 1988). The form of fluoride was not reported, but it was probably hydrogen fluoride and fluoride dust. Possible fluorosis (multiple joint pains, limited motion in at least two joints or in the spine, and initial ossifications visible on x-ray films) was found in 14% of the workers. The prevalence of definite fluorosis, with advanced limitation of movement in at least two joints or the spine, marked ossifications, and osteosclerosis, or more severe symptoms, was 6.2%. The study authors reported finding a close positive correlation between the occurrence of fluorosis and the time and level of fluoride exposure. Another health study of 2,066 workers in an aluminum smelter reported early signs of skeletal fluorosis in pot room workers employed for more than 10 years. No effects, however, were seen in workers exposed for less than 10 years. Actual airborne fluoride levels measured at the time of the health assessment were 0.2 mg/m^3 hydrogen fluoride and 0.28 mg/m^3 fluoride dusts. Historical fluoride levels were not reported,

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although the study authors implied that exposure levels had been below
2.5 mg/m^3 for some period (Chan-Yeung et al. 1983b).

While the above studies generally found radiologically-apparent skeletal
fluorosis appearing prior to or concurrent with musculoskeletal symptoms,
Carnow and Conibear (1981) found musculoskeletal symptoms in aluminum workers
in the absence of radiological findings. Questionnaire answers suggested a
significant increase in incidence and severity of musculoskeletal disease and
fracture frequency with fluoride exposure. By contrast, there was no
exposure-related increase in evidence of skeletal fluorosis on chest and
spinal X-ray films that were analyzed blind. Neither radiologic data nor
actual exposure levels or durations were reported. As the authors recognized,
the exposure group was heterogeneous and were exposed to other chemicals, and
some of the musculoskeletal symptoms may have actually been due to heavy
physical labor.

Fluoride. A 58-year-old man was exposed to various fluoride compounds
(chiefly sodium fluoride) for 30 years while employed in a chemical plant.
The route of exposure was presumed to be inhalation with some concomitant
dermal exposure. He had fluoride deposits in almost all of his bones, but the
main accumulation was in the vertebrae, ribs, and pelvic bones (McGarvey and
Ernstene 1947). No other effects were observed that could be attributed to
the fluoride exposure. Another man exposed almost daily for 18 years to a
finely ground rock phosphate dust containing 3.88% fluoride had "thicker and
heavier" bones with a white, chalky material covering the surface as observed
by x-ray (Wolff and Kerr 1938). His bones also appeared more opaque when
compared by x-ray to normal bones.

No studies were located regarding musculoskeletal effects in animals
after inhalation exposure to fluoride.

Hepatic Effects

Fluorine. No studies were located regarding hepatic effects of fluorine
inhalation in humans. Mice exposed to fluorine exhibited coagulation necrosis
of the liver, periportal hemorrhages, and diffuse cloudy swelling (Keplinger
and Suissa 1968). These effects were generally observed after exposure to
concentrations near 50% of the LC$_{50}$, i.e., at 303, 180, or 124 mg/m^3 for 5,
30, or 60 minutes, respectively. Pathology occurred at a somewhat lower level
following a 15 minute exposure, i.e., 224 mg/m^3, or about 40% of the LC$_{50}$
Damage became apparent 7-14 days after exposure. Liver congestion was
reported in dogs, but not in other species subjected to repeated exposures to
fluorine (about 5 hours/day, 6 days/week) at a concentration that killed all 5
dogs by the 60th hour of exposure (Stokinger 1949).

Hydrogen Fluoride. Ten animals (five rabbits, three guinea pigs, and
two rhesus monkeys) were exposed via inhalation to 14.4 mg fluoride/m^3 as
hydrogen fluoride 6-7 hours a day, for 50 days (Machle and Kitzmiller 1935).

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Fatty degeneration of the liver parenchyma, scattered focal necroses, and fibroblastic encroachment of periportal spaces *were* observed in the guinea pigs. Two of the three guinea pigs began losing weight after about 145 hours of exposure, were withdrawn from the exposure regimen, and died about 2 weeks later. Generalized fatty changes were also seen in two of four rabbits sacrificed 7 months after exposure termination. These experiments used only a few animals from each species, and the exposure measurement technology was not very precise.

Hydrogen Fluoride and Fluoride Dusts. The occupational health study by Chan-Yeung et al. (1983b) discussed above revealed no adverse effects on liver function, as measured by levels of total bilirubin, serum glutamic oxaloacetic transaminase (SGOT), and alkaline phosphatase.

Renal Effects

Fluorine. No studies were located regarding renal effects of fluorine inhalation in humans. Mice exposed to fluorine exhibited focal areas of coagulation necrosis in the renal cortex and focal areas of lymphocyte infiltration in the cortex and medulla (Keplinger and Suissa 1968). The percentage of the LC_{50} at which effects were observed increased with exposure duration and ranged from -19% of the LC_{50}, following a 5-minute exposure to ~36% of the LC_{50}, following 30- or 60-minute exposures. Damage became apparent 7-14 days postexposure.

Hydrogen Fluoride. Pathologically elevated serum creatinine and urea levels were seen 24 hours after accidental dermal and inhalation exposure to a mixture of 70%-80% sulfuric acid and 10% hydrofluoric acid at 150°C (Braun et al. 1984). Neither the effect of the sulfuric acid nor the exposure levels were known.

Degeneration and necrosis of the renal cortex was reported in 27/30 rats exposed to 24 mg fluoride/m^3 as hydrogen fluoride for 6 hours/day, 6 days/ week, for up to 30 days, but not in rats exposed to 7 mg/m^3 (Stokinger 1949). Pathological examination of rabbits and guinea pigs (n=3/species/exposure level) exposed to hydrogen fluoride revealed tubular necrosis, congestion, and edema (Machle et al. 1934). A variety of different exposure levels and duration's were tested, but the levels at which exposure-related effects were seen were not reported. Rabbits (n=4) exposed via inhalation to 14.4 mg fluoride/m^3 as hydrogen fluoride 6-7 hours a day, for 50 days, developed degeneration and necrosis of convoluted tubules, accompanied by fibrous tissue replacement of cortical tissues (Machle and Kitzmiller 1935). Degenerative and inflammatory changes were also seen in the single exposed monkey at necropsy. The experiments described in both of these papers used a small number of animals, and no control data were presented.

Hydrogen Fluoride and Fluoride Dusts. Increased incidence of albuminuria (p<0.1) was observed in phosphate fertilizer plant workers with an average urinary fluoride level of 4.6 mg/L (Derryberry et al. 1963). However,

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the testing method used in this study is considered hypersensitive (Dinman et al. 1976a), and several other studies have found no effects. No signs of renal effects, as measured by standard renal function tests, were seen in a large cohort of aluminum workers exposed to total fluoride levels estimated to be below 2.5 mg/m^3 (Chan-Yeung et al. 1983b). Two other studies of aluminum workers failed to find an increase in the incidence of albuminuria (Dinman et al. 1976c; Kaltreider et al. 1972). Average postshift urinary fluoride levels were ≤5.68mg/L (Dinman et al. 1976c) and ≤9.6mg/L (Kaltreider et al. 1972). The exposed population included workers exposed to estimated air fluoride levels of 4-6 mg/m^3 (time-weighted average), of which 50% was gaseous fluoride (presumably hydrogen fluoride) (Kaltreider et al. 1972).

The weight of evidence indicates that typical inhalational occupational exposure to hydrogen fluoride and fluoride dust is not nephrotoxic. The overall animal data indicate that inhalation exposure to sufficiently high levels of hydrogen fluoride or fluorine can cause kidney damage, but the relavance to human health and the potential nephrotoxic level cannot be determined because of generally incomplete human and animal data. In addition, only one animal experiment was located that conducted a histopathic exam following fluorine exposure.

Dermal/Ocular Effects. Dermal/ocular effects have been seen following whole body inhalation exposure of humans and animals to fluorine and hydrogen fluoride. The effects are believed to be due to irritation caused by direct dermal contact with these gases, so they are discussed in the dermal exposure section (see Section 2.2.3).

Other Systemic Effects

Fluorine. Decreased weight gain was observed in rats, guinea pigs, and rabbits exposed to 25 mg/m^3 fluorine (and somewhat lower levels) for about 5 hours/day, 5 days/week for 35 days. While a decrease compared to the low exposure level group is clear, no control animals were used, so the lowest level with a significant change is unclear.

Hydrogen Fluoride. Pronounced weight loss shortly before death was observed in rats exposed to a lethal level of hydrogen fluoride (24 mg/m^3 for 6 hours/day, 6 days/week for 30 days). Guinea pigs exposed under the same conditions lost weight following the third exposure week, even though there were no deaths (Stokinger 1949). While a decrease compared to the low exposure level group is clear, no control animals were used, so the lowest level with a significant change is unclear. Animals surviving a lethal exposure exhibited a body weight loss of 10-15% for up to a week after exposure (Rosenholtz et al. 1963).

2.2.1.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after inhalation exposure to fluorine, hydrogen fluoride, or fluoride.

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2.2.1.4 Neurological Effects

Fluorine. No studies were located regarding neurological effects in humans of fluorine following inhalation exposure. Dogs exposed to 8 or 25 mg/m^3 for 5-6 hours/day, 5-6 days/week for up to 35 days had seizures for prior to death (Stokinger 1949). Because no further details were available, the neurotoxic potential of fluorine cannot be evaluated.

Hydrogen Fluoride. The threshold of the light adaptive reflex was measured as a marker for neurological effects in three subjects following exposure to hydrogen fluoride at concentrations of 0.02, 0.03, or 0.06 mg/m^3 fluoride (Sadilova et al. 1965). While the threshold level was determined to be 0.03 mg/m^3, it is not clear whether this response is due to irritation of mucous membranes or is the result of an effect on cerebral cortical function. Details of atmosphere generation were not provided.

Exposure to concentrations at about 50% of the LC$_{50}$ values was reported to cause general weakness and decreased activity in rats of a Wistar-derived (Rosenholtz et al. 1963). Albino rats given 24-hour exposures to either 0.1 or 0.03 mg/m^3 hydrogen fluoride for 5 months developed central nervous system dysfunctions, as evidenced by diminished conditioned responses and increased time before motor nerve response. Histological studies showed changes in the nerve cell synapses of only those animals exposed to 0.1 mg/m^3. A concentration of 0.01 mg/m^3 was found to be without effect on conditioned responses, latency in motor nerve response, or neurohistological parameters. When additional stresses were added (alcohol, 24-hour starvation), the conditioned responses were extinguished more frequently (Sadilova et al. 1965). Some recovery in conditioned responses was seen following a l-month recovery period in the animals exposed to 0.1 mg/m^3. Animals exposed to 0.03 mg/m^3 recovered completely.

All reliable LOAEL values for neurological effects of exposure to hydrogen fluoride in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.1.5 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to fluorine, hydrogen fluoride, or fluoride.
2.2.1.6 Reproductive Effects

2.2.1.6.Reproductive Effects

Fluorine. Rats exposed to 25 mg/m^3 fluorine for 95 hours over the course of 21 days showed testicular degeneration (Stokinger 1949). No further details were available. It is not clear whether this effect was seen both in animals that died and in those that survived. Furthermore, it is not clear whether this is a systemic effect or a result of irritation from dermal contact with the gas.

Hydrogen Fluoride. All four dogs exposed to 24 mg/m^3 for 6 hours/day, 6 days/week for 30 days developed degenerative testicular changes and ulceration of the scrotum (Stokinger 1949). This effect was not seen at 7 mg/m^3, or in rabbits or rats at either exposure level. No further details were available. Furthermore, it is not clear whether this is a systemic effect or a result of irritation from dermal contact with the gas.

No studies were located regarding reproductive effects in humans after inhalation exposure to fluorine, hydrogen fluoride, or fluoride, and no studies were located regarding reproductive effects in animals after inhalation exposure to fluoride.

2.2.1.7 Genotoxic Effects

No human in vivo data were located regarding the genotoxicity of fluorine, hydrogen fluoride, or fluoride.

Hydrogen Fluoride. Data on the genotoxic effects, if any, following inhalation exposure to hydrogen fluoride are very limited. Cell damage was reported in bone marrow cells of unpedigreed female white rats exposed by inhalation to hydrogen fluoride for 6 hours, 6 days a week, for 1 month, at 1.0 mg/m^3 (Voroshilin et al. 1975). This was the only concentration tested. The increased rate of damaged cells was due largely to an increase in hyperploidy, an effect for which the biological relevance is unknown. These investigators also tested for dominant lethal mutations in C57Bl mice and found that the number of resorbed and developing embryos did not differ significantly from those of the controls at the concentration tested. Drosophila melanogaster eggs were collected from adults of two different strains that were exposed for 3 or 6 weeks to 1.0 or 2.2 mg fluoride/m^3 as hydrogen fluoride, and reproductive parameters were measured as an indicator of genotoxicity (Gerdes et al. 1971b). Both the number of eggs per female and male fertility were significantly reduced, but the analysis did not indicate the exposure level(s) or duration(s) at which the reduction was significant. The maximum lethality to adults of one strain was 60%; under most of the test conditions the lethality was ≤40%.

Other genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

Hydrogen Fluoride and Fluoride Dusts. Most occupational exposure to fluoride occurs as a result of inhalation of hydrofluoric acid fumes or dust from cryolite or fluorspar. A cohort of cryolite workers in Denmark was reported to have an increase in mortality and morbidity from respiratory cancer compared with the national average (Standardized Mortality Ratio of 2.52 [95% confidence limit between 1.40 and 4.12], Standardized Incidence Ratio of 2.5 [95% confidence limit between 1.6 and 3.51) (Grandjean et al.

1985). The study authors stated that the increase can be explained by the fact that the respiratory cancer death rate for the Copenhagen area is about twice the national average for the birth cohorts from 1890 to 1929, so that comparison with national rates may not be appropriate. Respiratory cancer rates for the workers were slightly higher than those of the general population of Copenhagen, but the difference was not significant. No explanation for the high Copenhagen rates was offered.

Increased lung cancer rates have reported in several studies of aluminum industry workers (Andersen et al. 1982; Gibbs and Horowitz 1979; Milham 1979), but no correction was made for smoking and the workers were also exposed to tars and polycyclic aromatic hydrocarbons. Similarly, fluorspar miners had increased lung cancer rates, but they were exposed to elevated radon levels (devilliers and Windish 1964). A cohort study of 21,829 workers in aluminum reduction plants for ≥5 years did not find an increase in lung cancer, but did report an increase in mortality due to pancreatic cancer, lymphohematopoietic cancers, genitourinary cancer, and nonmalignant respiratory disease (Rockette and Arena 1983). Only the effect on pancreatic cancer was statistically significant. Increases in hematopoietic cancers and respiratory disease were also reported by Milham (1979). Because of the confounding factors mentioned above, and since no breakdown was done by fluoride exposure, these studies are of questionable relevance to the issue of possible carcinogenicity of inhalation exposure to hydrogen fluoride and/or fluorides.

A study was published describing a positive relationship between increased lung cancer and residing near, or working in, the steel industry (Cecilioni 1972). Possible occupational exposures to other carcinogenic substances from steel and other industries were not considered. Carcinogenicity via inhalation of fluoride is not considered to be likely by most investigators reporting in the existing literature.

No studies were located regarding cancer in animals after inhalation exposure to fluorine, hydrogen fluoride, or fluoride.

2.2.2 Oral Exposure

Because fluorine and hydrogen fluoride are gases, oral exposure to these substances occurs only concomitant with inhalation exposure. Oral exposure to hydrofluoric acid has been reported very rarely. Except where otherwise indicated, the following sections regarding oral exposure discuss oral exposure to fluoride.

Much of the research on fluoride exposure in humans has focused on the ingestion of fluoride through supplemented public drinking water supplies. Additional information comes from studies of areas with high natural fluoride levels. Drinking water levels of other minerals may differ between artificially fluoridated areas and areas with naturally high fluoride levels. Chronic fluoride ingestion can affect bone structure and possibly nerve and

muscle function. High skeletal fluoride levels can lead to skeletal fluorosis, a disease characterized by increased bone density. The most severe form of fluorosis can result in crippling deformities, but this is extremely rare in the United States. Teeth mottling is another chronic effect that can occur in children exposed to fluoride during tooth formation. A review of studies concerning dental fluorosis found that in the surveyed cities with water containing 0.7-1.2 ppm (the level to which water is fluoridated), an average of 10%-20% of the children had barely noticeable changes in their teeth, while up to 1% had brown spots due to fluoride (DHHS 1991). Based on this result, the study concluded that total fluoride intake from multiple sources has risen since the optimal water fluoridation levels were set.

Much of the data regarding toxic effects of oral exposure to fluoride were obtained from studies using sodium fluoride. Fluoride is often added to water in the form of hydrofluosilicic acid, so exposure to this chemical is included in some epidemiological studies. Other studies investigate oral exposure to calcium fluoride, hydrofluoric acid, cryolite, and fluoride in rock phosphate. For all forms of fluoride discussed, doses are reported as amount of the fluoride ion.

Conflicting results have been obtained from experiments addressing whether fluorine is an essential element. Much of this conflict appears to result from the great difficulty in preparing an animal diet that has negligible amounts of fluoride, but otherwise allows normal animal growth and development. Different conclusions have been reached by different official organizations. The National Research Council (NRC) concluded that the results do not justify a classification of fluorine as an essential element (NRC 1989), while the World Health Organization (WHO) lists fluorine as essential for animal life, without providing supporting data (WHO 1973).

As discussed in Section 2.2.2.6, there have been suggestions that fluoride can aid fertility by improving intestinal absorption of iron and other trace elements (Messer et al. 1973; Tao and Suttie 1976). In a study where fluoride was rigorously removed from dietary components, a total of 110 Wistar rats were observed over the course of four generations (Maurer and Day 1957). There were no adverse effects compared to controls that received the same diet and 0.28 mg fluoride/kg/day in drinking water. Animals fed the low-fluoride diet were healthy, had sleek coats and healthy teeth, and had similar weight gains to those of the controls. Low success in bringing pups to weaning (50%) was reported for both the low-fluoride and control groups. No fluoride was detectable in the diet (detection limit not reported), and fluoride levels in femurs were ≤8.8ppm fluoride in bone ash. In a more recent study, dose-dependent increases in daily weight gain of F344 rats were observed when a low-fluoride diet was supplemented with fluoride (Schwarz and Milne 1972). The fluoride provided by the basal diet varied but was sometimes 0.023 mg/kg/day and occasionally dropped below 0.002 mg/kg/day. However, the results are likely to be due to other nutritional deficiencies that were partially compensated by fluoride. Rats in both the control and low-fluoride

groups had shaggy fur, loss of hair, and seborrhea. Fluoride was only partially effective in correcting the bleached incisors found in the low fluoride group. Bleached incisors have been related to deficiencies of calcium, phosphorus, magnesium, iron, and vitamins E, D, and A. None of these studies provide strong evidence that fluoride is an essential element.

2.2.2.1 Death

Fluoride. Based on numerous incidents of fatal fluoride poisoning, Hodge and Smith (1965) estimated the certainly lethal dose (CLD) (without treatment) for a 70-kg man at 5-10 g sodium fluoride, or 32-64 mg fluoride/kg body weight. The faster uptake of fluoride to the bone in children helps to clear fluoride from the bloodstream, so Heifetz and Horowitz (1986) did not believe the CLD for children would be lower than that for adults. The safely tolerated dose has been reported as 8-16 mg fluoride/kg, but no support was provided for this conclusion (Heifetz and Horowitz 1986). As indicated below, this dose may not be tolerated by very small children.

Fatal ingestion of sodium fluoride has been reported as early as 1899 (Sharkey and Simpson 1933). A summary of early fatalities indicates that the primary symptoms were the sudden onset of nausea and vomiting, accompanied by burning, cramp-like abdominal pains and diarrhea. Clonic convulsions and pulmonary edema were reported in some cases; the pulmonary edema may have been due to aspiration of vomitus. While a few of these deaths were suicides, most of them resulted from accidental exposure to sodium fluoride when containers of insecticide were mistaken for baking powder or epsom salts.

More recent information includes the case report of a 3-year-old boy who swallowed 200 sodium fluoride tablets (1 mg fluoride each) for a dose of 16 mg fluoride/kg body weight (Eichler et al. 1982). Immediately after ingestion, he vomited and appeared to recover, but he collapsed 4 hours later. The boy died 7 hours after fluoride ingestion. Upon autopsy, hemorrhagic edema of the lungs, hemorrhagic gastritis, and massive cerebral edema were observed. The hemorrhagic edema observed in the lungs was probably due to aspiration of the gastric contents. Cloudy swelling was observed in the cells of the liver, heart, and kidney. In another case, a 27-month-old child died 5 days after ingesting about 100 fluoride tablets, for a dose of about 8 mg fluoride/kg body weight (Whitford 1990). Based on this case and weight tables for 3-year-old boys, Whitford (1990) calculated a probably toxic dose of about 5 mg fluoride/kg body weight.

A comparison of death rates between U.S. cities with fluoridated water and those with nonfluoridated water found no association between fluoride and increased death rate (Erickson 1978). It is difficult to draw definitive conclusions from this study because it is limited by dissimilarities between the populations, which led to a need for multiple adjustments.

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In rats; LD_{50} values for sodium fluoride administered by oral gavage range from 31 to 101 mg fluoride/kg (DeLopez et al. 1976; Lim et al, 1978; Skare et al. 1986). These LD_{50} values for rats are for different strains with variations in weight. Gender differences may also account for the reported differences in LD_{50} values; an LD_{50} of 101 mg fluoride/kg was reported for male Sprague-Dawley rats weighing 150-290 g, while LD_{50} values for female Sprague-Dawley rats weighing 112-184 g and 200-359 g were 52 mg/kg and 31 mg/kg, respectively. An LD_{50} of 44.3 mg fluoride/kg was reported for mice (Lim et al. 1978).

Hydrofluoric Acid. Six deaths were reported to have occurred between 1 and 6 hours following accidental or intentional ingestion of a rust remover containing hydrofluoric acid (Menchel and Dunn 1984). No dose levels of fluoride were reported. At autopsy, severe hemorrhagic gastritis was noted in all cases. In one case, hemorrhage and necrosis of the pancreas were also noted. A fatal case of hydrofluoric acid ingestion occurred when a 29-yearold man drank a mouthful, thinking it was water (Manoguerra and Neuman 1986). In spite of immediate vomiting, respirations were shallow within an hour, and the patient died within 2 hours of exposure. Serum calcium and SGOT levels were markedly depressed. Serum fluoride level was 35 ppm. Another study reported six deaths due to hydrofluoric acid ingestion (Menchel and Dunn 1984). The major symptoms reported were nausea, thirst, and ulcerations of the buccal mucosa, followed by the rapid onset of tetany and coma.

All reliable LD_{50} and LOAEL values for death in each species and duration category are recorded in Table 2-3 and plotted in Figure 2-3.

2.2.2.2 Systemic Effects

The predominant systemic effects that have been observed following acute oral exposures to sodium fluoride are hypocalcemia (resulting in tetany and ventricular fibrillation, among other effects), hyperkalemia, and gastrointestinal pain; fluorosis is the major effect of chronic exposure.

No studies were located regarding respiratory or dermal/ocular effects in humans or animals after oral exposure to fluorine, hydrogen fluoride or fluoride.

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-3 and plotted in Figure 2-3.

Cardiovascular Effects. The cardiovascular effects of fluoride have been attributed to hypocalcemia and hyperkalemia caused by high fluoride levels. Fluoride can bind with serum calcium if the dose is sufficient and cause hypocalcemia. Calcium is necessary for the functional integrity of the voluntary and autonomic nervous systems. Hypocalcemia can cause tetany,

TABLE 2-3. Levels of Significant Exposure to Fluoride - Oral

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg F/kg/day)	LOAEL (effect)		Reference	
						Less serious (mg F/kg/day)	Serious (mg F/kg/day)		
ACUTE EXPOSURE									
Death									
1	Human	(C)	1 d 1x/d				16 (1 child)	Eichler et al. 1982	NaF
2	Rat	(GW)	1 d 1x/d				101.3 (LD50)	Skare et al. 1986	NaF
3	Rat	(GW)	1 d 1x/d				54 (LD50 for 80g rats) 52 (LD50 for 150g rats) 31 (LD50 for 250g rats)	DeLopez et al. 1976	NaF
4	Rat	(GW)	1 d 1x/d				51.6 (LD50)	Lim et al. 1978	NaF
5	Mouse	(GW)	1 d 1x/d				44.3 (LD50)	Lim et al. 1978	NaF
Systemic									
6	Rat	(W)	2 wk	Musc/skel		9.5 (decreased modulus of elasticity)		Guggenheim et al. 1976	NaF
Reproductive									
7	Mouse	(G)	5 d 1x/d		32			Li et al. 1987a	NaF
INTERMEDIATE EXPOSURE									
Death									
8	Mouse	(W)	6 mo ad lib				300 (mortality [M]) 600 (mortality [F])	NTP 1990	NaF

TABLE 2-3 (Continued)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg F/kg/day)	LOAEL (effect)		Reference
						Less serious (mg F/kg/day)	Serious (mg F/kg/day)	

Systemic

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg F/kg/day)	Less serious (mg F/kg/day)	Serious (mg F/kg/day)	Reference	
9	Rat	(W)	30 d	Musc/skel		14 (delayed healing of broken bones)		Uslu 1983	
10	Rat	(W)	6 mo ad lib	Gastro	1.9	6.3 (hyperplasia of the glandular stomach		NTP 1990	NaF
				Hepatic	19				
11	Rat	(W)	2 mo 7d/wk 24hr/d	Other		0.5 (decreased thyroxine levels; increased T3- resin uptake ratio)		Bobek et al. 1976	NaF
12	Rat	(W)	5 wk 7d/wk 24hr/d	Musc/skel		10.5 (decreased mineral content and increased proline in tooth enamel matrix)		DenBesten and Crenshaw 1984	NaF
13	Rat	(W)	5 wk	Musc/skel	13	19 (histological fluorosis; de- creased bone growth)		Harrison et al. 1984	
14	Mouse	(GW)	35 d 1x/d	Hemato		5.2 (decreased RBC, decreased hemo- globin, increased WBC)		Pillai et al. 1988	NaF
				Other		5.2 (decreased body weight)			
15	Mouse	(W)	4 wk 7d/wk 24hr/d	Musc/skel		0.80 (increase in bone formation rate; slight de- crease in bone calcium)		Marie and Hott 1986	NaF

TABLE 2-3 (Continued)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg F/kg/day)	LOAEL (effect) Less serious (mg F/kg/day)	LOAEL (effect) Serious (mg F/kg/day)	Reference	
16	Mouse	(W)	6 mo ad lib	Cardio			52 (myocardial degeneration and mineralization)	NTP 1990	NaF
				Hepatic		26 (enlarged cells)			
				Renal			26 (necrosis and tubule degeneration)		
				Other		17 (body weight decreased 20%)			
17	Mouse	(W)	280 d	Renal		1.9 (nephron degeneration)		Greenberg 1986	NaF
18	Mouse	(W)	280 d 24hr/d	Hepatic		0.95 (pale, granular hepatocytes with fatty vacuoles)		Greenberg 1982a	NaF

Developmental

Key to figure	Species	Route	Exposure duration/ frequency	System	NOAEL	Less serious	Serious	Reference	
19	Rat	(W)	28 wk 7d/wk 24hr/d		21			Ream et al. 1983	NaF

Reproductive

Key to figure	Species	Route	Exposure duration/ frequency	System	NOAEL	Less serious	Serious	Reference	
20	Rat	(F)	60 d 7d/wk 24hr/d			5.0 (decreased diameter of seminiferous tubules)		Araibi et al. 1989	NaF
21	Rat	(F)	3 mo 7d/wk 24hr/d		23			Marks et al. 1984	NaF
22	Mouse	(GW)	35 d 1x/d		5.2			Pillai et al. 1988	NaF
23	Mouse	(W)	25 wk		9.5		19 (nearly complete infertility)	Messer et al. 1973	NaF

TABLE 2-3 (Continued)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg F/kg/day)	LOAEL (effect)		Reference
						Less serious (mg F/kg/day)	Serious (mg F/kg/day)	

CHRONIC EXPOSURE

Systemic

24	Human	(C)	4 yr	Musc/skel		0.48[b](increased fracture rate)		Riggs et al. 1990	NaF
25	Rat	(W)	<103 wk	Gastro Hemato Hepatic Renal	4.5 4.5 4.5 4.5			NTP 1990	NaF
26	Rabbit	(GW)	24 mo 1x/d	Gastro		5 (roughened duodena mucosa)		Susheela and Das 1988	NaF
27	Rabbit	(G)	6-12 mo 1x/d	Hemato		4.52 (decreased white blood cells and hemoglobin)		Susheela and Jain 1983	NaF
28	Mouse	(W)	<104 wk	Gastro Hemato Hepatic Renal	4.9 4.9 4.9 4.9			NTP 1990	NaF
29	Mink	(F)	382 d 24hr/d	Musc/skel		5 (mottled and brittle kit teeth)	9.1 (sagittal crests deformed; 3/6 adults)	Aulerich et al. 1987	NaF

Immunological

| 30 | Rabbit | (G) | 18 mo 1x/d | | | 4.5 (decreased primary and secondary antibody titters) | | Jain and Susheela 1987 | NaF |

TABLE 2-3 (Continued)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg F/kg/day)	LOAEL (effect) Less serious (mg F/kg/day)	LOAEL (effect) Serious (mg F/kg/day)	Reference	
Reproductive									
31	Mouse	(F)	3 gen		13			Tao and Suttie 1976	NaF
32	Mink	(F)	382 d 24hr/d		9.1			Aulerich et al. 1987	NaF
Cancer									
33	Rat	(W)	<103 wk				2.5 (osteosarcoma in males)	NTP 1990	NaF

[a]The number corresponds to entries in Figure 2-3.

[b]Used to derive a chronic oral Minimal Risk Level (MRL) of 0.05 mg/kg/day; dose divided by an uncertainty factor of 10 (for use of a LOAEL).

ad lib = ad libitum; (C) = capsule; Cardio = cardiovascular; d = day(s); (F) = feed; F = female(s); (G) = gavage, not specified; Gastro = gastrointestinal; gen = generation(s); (GW) = gavage in water; Hemato = hematological; hr = hour(s); LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male(s); mo = month(s); Musc/sk = musculoskeletal; NaF = sodium fluoride; NOAEL = no-observed-adverse-effect level; RBC = red blood cell(s); T3 = triiodothyronine; (W) = drinking water; WBC = white blood cell(s); wk = week(s); x = time(s); y = year(s)

FIGURE 2-3. Levels of Significant Exposure to Fluoride - Oral

ACUTE
(≤14 Days)

Systemic

(mgF/kg/day)

			Key	
r	Rat	■	LD50	
m	Mouse	◑	LOAEL for less serious effects (animals)	
		○	NOAEL (animals)	
		▲	LOAEL for serious effects (humans)	

The number next to each point corresponds to entries in Table 2-3.
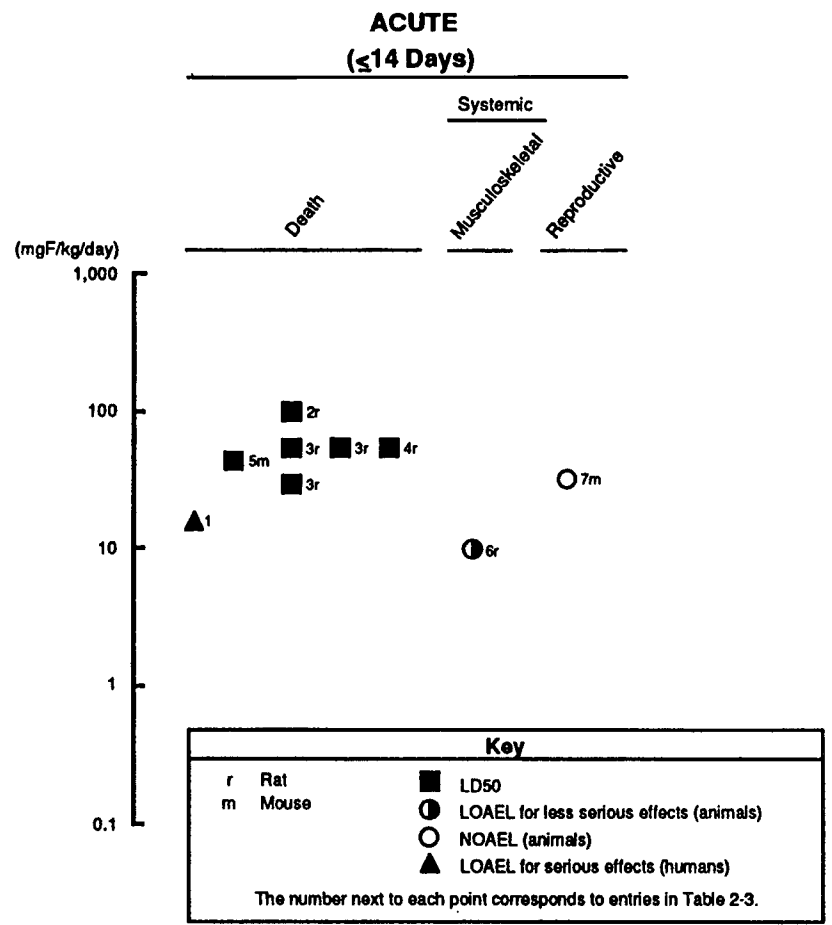
FIGURE 2-3 (Continued)

INTERMEDIATE
(15-364 Days)

FIGURE 2-3 (Continued)

CHRONIC
(≥ 365 Days)

Key

r	Rat
m	Mouse
h	Rabbit
n	Mink

● LOAEL for serious effects (animals)

◐ LOAEL for less serious effects (animals)

○ NOAEL (animals)

◆ CEL - Cancer Effect Level (animals)

▲ LOAEL for less serious effects (humans)

┊ Minimal risk level for
┊ effects other than cancer

The number next to each point corresponds to entries in Table 2-3.

* Doses represent the lowest dose tested per study that produced a tumorigenic
response and do not imply the existence of a threshold for the cancer end point.
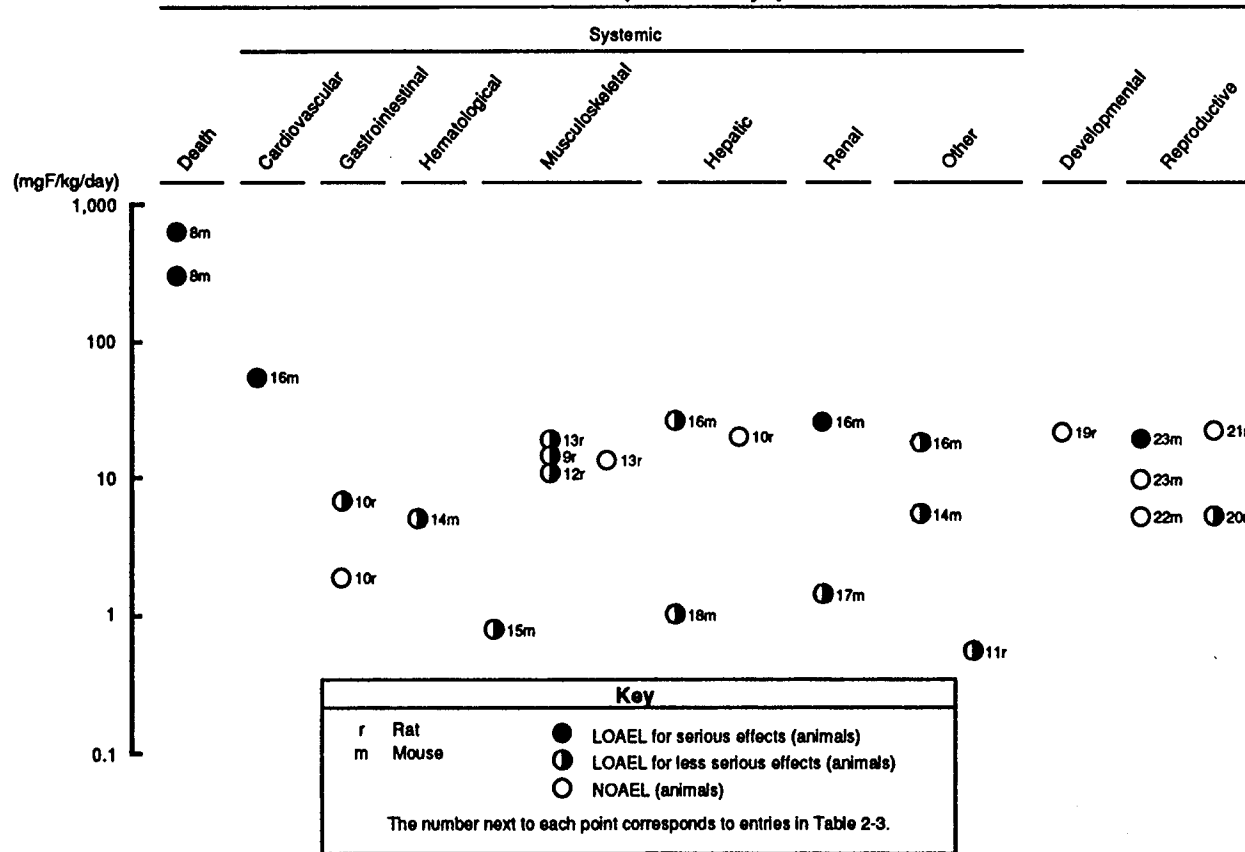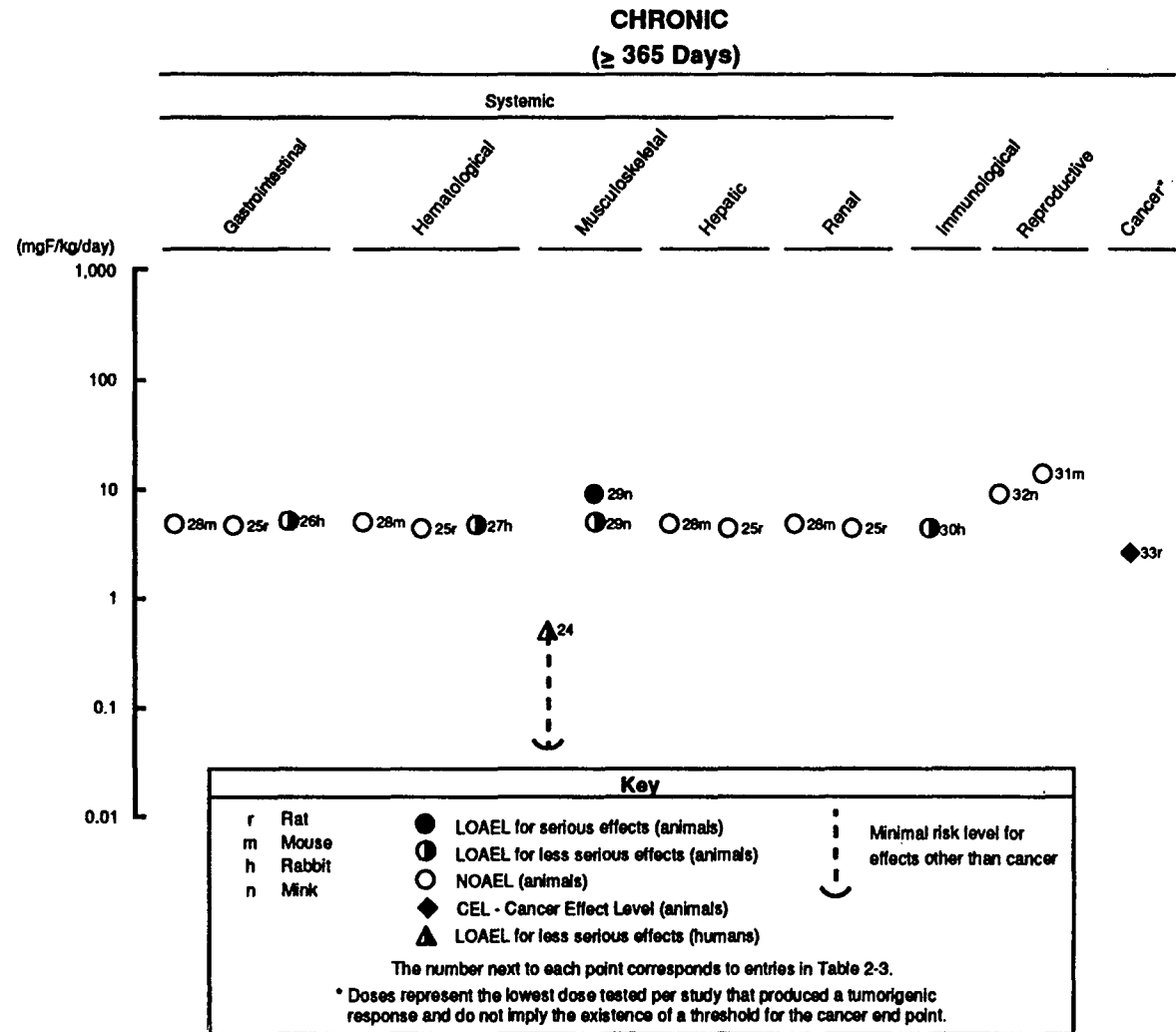
2. HEALTH EFFECTS

decreased myocardial contractility, and possibly cardiovascular collapse (Bayless and Tinanoff 1985). Hyperkalemia has been suggested as the cause of the repeated episodes of ventricular fibrillation and eventual death that are often encountered in cases of fluoride poisoning (Baltazar et al. 1980).

Approximately 2 hours after ingestion of 120 g of roach powder (97% sodium fluoride) in an unsuccessful suicide attempt, a 25-year-old male had severe toxic reactions that included tetany, multiple episodes of ventricular fibrillation, and esophageal stricture (Abukurah et al. 1972). Within 14 hours following exposure, the patient experienced 63 episodes of ventricular fibrillation.

In two epidemiological studies, fluoride in the drinking water did not increase the mortality rates from cardiovascular effects. One of these studies was a report of 428,960 people in 18 areas of "high" natural fluoride (0.4->3.5 ppm) in England and Wales and 368,580 people in control areas (<0.2 ppm fluoride). The water supply for 52% of the "high" fluoride population had average fluoride levels of ≥1ppm (Heasman and Martin 1962). Results indicated that there were no significant differences between areas with different fluoride levels in mortality due to coronary disease, angina, and other heart disease, as evidenced by Standard Mortality Ratios (SMRs). The second study (Hagan et al. 1954) examined 32 pairs of cities in the United States that contained 892,625 people in the high fluoride areas and 1,297,500 people in the control cities. A positive relationship between heart disease and water fluoridation was reported, but these authors did not adjust for a doubling of the members of this population over 75 years old during the period of fluoridation under study (Jansen and Thomson 1974). In addition, this study lacked statistical analysis and drew conclusions regarding trends that were not obvious from the data presented. The large variation in the presented data was not discussed. Doses of fluoride are difficult to estimate for large populations, however, because most people are potentially exposed to fluoride through a variety of sources, such as food, beverages, medicine, and dental products.

By contrast, a comparison of Bartlett and Cameron, two Texas towns with water supplies containing 8 ppm and 0.4 ppm fluoride, respectively, found a significantly higher rate of cardiovascular system abnormalities in the town with the lower fluoride level (Leone et al. 1954). The authors attributed the finding of a significant result to the number of statistical tests that were conducted in the study. However, it is interesting to note that a study of 300 North Dakota residents who drank water containing 4-5.8 ppm and 715 people who drank water containing 0.15-0.3 ppm found a lower incidence of calcification of the aorta in the high-fluoride group (Bernstein et al. 1966). Significant differences were found in 45-54-year-old males (p<0.05), as well as in males aged 55-64 years and 65+ years (p<0.01). This effect was not due solely to differences in age distribution, because the incidence in the 55-64-year-old, high-fluoride group was lower than the incidence in the 45-54-year-

old, low-fluoride group. A crude analysis also found no association with milk and cheese consumption.

About half of the male and female B6C3F$_1$ mice that died as a result of exposure to 52 mg fluoride/kg/day for 6 months as sodium fluoride in drinking water had mineralization of the myocardium (NTP 1990); some female mice also had myocardial degeneration.

Gastrointestinal Effects. The primary gastrointestinal effects following both acute and chronic oral exposure to fluoride consist of nausea, vomiting, and gastric pain. The irritation of the gastric mucosa is attributed to fluoride (as sodium fluoride) forming hydrofluoric acid in the acidic environment of the stomach (Hoffman et al. 1980; Waldbott 1981). The uncharged hydrogen fluoride molecule can then penetrate cell membranes and enter the neutral environment of the cytoplasm.

Thirty-four students (kindergarten through third grade) exhibited acute gastrointestinal effects after drinking water from school water fountains that provided a fluoride supplement designed to raise the water level to a range of l-5 ppm (Hoffman et al. 1980). An accident with the delivery system resulted in the water levels reaching 375 ppm; specific doses could not be calculated but were estimated to range from 1.4 to 90 mg per child. In another case, a 16-year-old girl vomited and had abdominal pain immediately after accidentally consuming 1 tablespoon of sodium fluoride (used as a dusting powder for poultry) (Rao et al. 1969).

Of the 150 cases involving fluoride intake reported to a poison control center from 1978 to 1979, most of the cases involved ingestion of less than 1 mg/kg fluoride, although exact doses could not be determined (Spoerke et al. 1980). Effects included nausea (13.9%), vomiting (77.8%), and diarrhea (8.3%). These effects usually subsided within 24 hours. Symptoms of a more serious nature were not reported.

Endoscopies were performed and biopsy samples taken from 12 healthy volunteers either after no treatment (control) or 2 hours after drinking 20 mL of a solution containing 20 mg fluoride as sodium fluoride (Spak et al. 1989). Both treatment and control tests were preceded by overnight fasts, and at least 2 weeks were allowed between endoscopies to allow for healing of any iatrogenic injuries from the gastroscope. All subjects had six or more petechiae (minute hemorrhages) or erosions after fluoride treatment, while only one petechia or erosion was found in one control subject. Upon microscopic evaluation of biopsies, irritation of the stomach was found in all subjects after fluoride treatment, but none of the subjects showed stomach irritation after fasting only. Nausea was present in only one-third of the subjects, suggesting that nausea may not be the first sign of fluoride irritation of the gastric mucosa. The study suffers from several limitations. Only one dose was tested, the subjects were aware of whether or not they had

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received fluoride, it is unclear whether endoscopy videotapes were coded prior to evaluation, and the order of test and control endoscopies does not appear to have been randomized. For these reasons, this study has not been included in Table 2-3 or plotted in Figure 2-3.

While high levels of fluoride clearly can cause gastrointestinal irritation, it is unclear whether there are any gastrointestinal effects of chronic exposure to fluoride in drinking water. Gastrointestinal tract disorders were not evaluated in the Bartlett-Cameron study of the effect of water containing 8 ppm fluoride (Leone et al. 1954). The sole evidence of an effect comes from a study of twenty non-ulcer dyspepsia patients at an outpatient clinic in India and 10 volunteers without gastrointestinal problems from the surgical clinic (Susheela et al. 1992). While the drinking water supplies of none of the controls had fluoride levels >l ppm, the water supplies of 55% of the dyspepsia patients were at this level. In addition, all of the dyspepsia patients and 30% of the controls had serum fluoride levels >0.02 ppm (mean of the dyspepsia group, 0.1 ppm); all of the dyspepsia patients and none of the controls had urine fluoride levels >0.l ppm (mean, 1.34 ppm). The study was compromised by small treatment size, undetermined total fluoride doses, undetermined nutritional status of the subjects, and lack of statistical comparisons. In addition, the appropriateness of the control population was not clear.

Seventy-eight workers engaged in the crushing and refining of cryolite, a mineral compound composed of sodium, aluminum, and fluoride, were examined (Moller and Gudjonsson 1932). Although an average exposure period was not presented, no workers with less than 2 years of exposure were included; 18 workers had been exposed for more than 10 years. Forty-two workers reported evidence of gastrointestinal effects. The primary effect was nausea, followed by loss of appetite and vomiting. Chronic indigestion was also reported in these workers. The study authors stated the effects were due only to cryolite dust being swallowed (either due to dust being deposited in the mouth during mouth breathing, or due to deposition on the bronchial tree followed by mucociliary action bringing the material to the epiglottis) and absorbed through the gastrointestinal tract. They based this conclusion on the fact that 21 enamel-, glass-, and sulphuric acid-industry workers exposed by inhalation to fluorine gas (some for up to 40 years) revealed no evidence of any effect on the stomach. In light of what is now known about the absorption of fluorides through the lung, the cryolite workers probably were exposed by both the oral and inhalation routes.

Decreased appetite, congestion of the duodenum, and mild diarrhea were reported in sheep given a single intragastric dose of sodium fluoride as low as 28.5 mg fluoride/kg via nasoesophageal catheter (Kessabi et al. 1985). It is difficult to extrapolate possible human effects from this study because the gastrointestinal system of ruminants (sheep, cows, goats) is quite different from that of humans.

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Thickening of the mucosa of the glandular stomach and punctate hemorrhages were seen in F344/N rats given 19 mg fluoride/kg/day in drinking water for 26 weeks as sodium fluoride (NTP 1990). Similar but less severe alterations were seen in some rats that received 6.3 mg/kg/day. Stomach ulcers were also seen in some high-dose males and females. Histologically identified stomach lesions included necrosis and hyperplasia. No gastrointestinal effects were reported in B6C3F$_1$, mice in this study at doses up to 52 mg/kg/day. No gastrointestinal effects were reported in the chronic portion of this study at doses up to 9.1 mg/kg/day (mice) or 4.5 mg/kg/day (rats). Roughened duodenal mucosa and a "cracked-clay" appearance of the absorptive cells was observed following daily dosage of nine rabbits with 5 mg/kg fluoride via oral gavage for 24 months (Susheela and Das 1988). The rabbit gastrointestinal system also differs from that of humans, and the study is limited by the small number of rabbits per group and the use of only one dose.

Hematological Effects. The incidence of abnormal white blood cell counts was significantly higher in Bartlett, Texas (8 ppm natural fluoride), than in Cameron, Texas (0.4 ppm fluoride). However, the study authors did not consider this finding as necessarily an effect of fluoride (Leone et al. 1954). No other significant hematological effects were observed.

As part of the 2-year NTP study of fluoride (NTP 1990) hematological analyses were conducted at 27 and 66 weeks. No treatment-related effects were observed at doses up to 4.5 mg/kg/day and 9.1 mg/kg/day in F344/N rats and B6C3F$_1$ mice, respectively.

Lactating Holstein cows were fed a mineral supplement containing soft rock phosphate (6000 ppm fluoride) and a protein supplement containing 1,088 ppm fluoride (Hillman et al. 1979). Because consumption of minerals fed ad libitum could not be determined accurately under farm conditions, no dose estimates could be made. After 9 months, red blood cells per unit volume, blood hemoglobin, hematocrit, and mean corpuscular volume were significantly lower (p<0.05) in herds exhibiting evidence of high fluoride exposure. The number of eosinophils increased with increasing urinary fluoride. Rabbits administered 4.52 mg fluoride/kg/day by gavage for 6-12 months had significantly decreased numbers of blood cells (e.g., erythrocytes, leukocytes, thrombocytes, monocytes, neutrophils) and hemoglobin (Susheela and Jain 1983). Similar, although not identical, results were seen in mice fed 5.2 mg fluoride/kg body weight (Pillai et al. 1988). These animals showed a significant decrease in red blood cell count but a significant increase in white cells. Although a dose-effect relationship cannot be determined from single-dose studies, these studies suggest that the hematopoietic system may be affected by oral exposure to fluoride.

Musculoskeletal Effects. Fluoride mottles teeth (dental fluorosis) and results in thickened bones and exostoses (skeletal fluorosis) when ingested in

large doses for an extended period of time. During development of the deciduous and permanent teeth, excessive fluoride intake produces a malformation of the enamel surface, which then becomes stained (Hodge and Smith 1972). Fluoride causes mottled enamel by interfering with osteocytes and impairing the work of ameloblast cells (Hodge and Smith 1972).

Several different methods have been developed for quantifying dental fluorosis. Dean's index (Dean 1934) rates teeth as having class 0, no fluorosis; class 1, very mild (opaque white areas irregularly covering ≤25%of the tooth surface); class 2, mild (white areas covering 25%-50% of the tooth surface); class 3, moderate (all surfaces affected, with some brown spots and marked wear on surfaces subject to attrition); and class 4, severe (widespread brown stains and pitting). People are classified according to the two most severely affected teeth; the mean fluorosis index is the mean of the score class. Other methods score tooth surfaces or relate fluorosis to the period during which the developing dentitioncould be exposed to fluoride. Drying teeth prior to scoring increases the frequency of observing opaque areas (DHHS 1991).

There is some evidence that levels of fluorosis have increased due to the multiple, widespread sources of fluoride in food processed with fluoridated water and dentifrices containing fluoride, in addition to the water of fluoridated communities. Comparison of fluorosis levels in the 21 cities with fluoride levels ranging from <0.4 to 2.7 ppm that were surveyed by Dean in the 1940s, and studies of dental fluorosis in 21 cities that were conducted in the 1980s found that the prevalence and severity of dental fluorosis correlated with the level of fluoride in the drinking water (DHHS 1991). During this 40-year period, the prevalence of fluorosis in areas with <0.4 ppm fluoride increased from <l% to about 6%; nearly all of the increase was in the very mild and mild categories. Both the prevalence and severity of fluorosis increased in communities with 0.7-1.2 ppm fluoride, with prevalence increasing from about 13% to about 22%. Most of the increase was in the very mild and mild categories, which increased from 12.3% to 17.7%, and from 1.4% to 4.4% of the population, respectively. The combined prevalence of the severe and moderate categories went from 0.0% to 0.9%. While there were some differences between the studies in the 1940s and those in the 198Os, such as the subject population and examination conditions, they do not affect the overall trends. Although total fluoride intake was not measured, these studies indicate that intake has increased since the 1940s, because fluorosis levels increased for all water fluoride levels.

Fluorosis levels in 1985 in communities with fluoride levels at about 1, 2, 3, and 4 ppm were compared with levels of fluorosis in the same communities in 1980 (Heifetz et al. 1988). Both examinations included 8-10-year-old and 13-15-year-old children. The 13-15-year-old children in the follow-up study had also participated in the initial study. While there were no marked changes in fluorosis levels in 8-10-year-old children, both the prevalence and severity increased in the 13-15-year-old children. Increases in the 1-ppm

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communities were mostly in the category of barely visible white spots. However, the percentage of labial surfaces of incisors and canines from children in the 2-ppm group that had brown mottling went from 0% to 7.6%. Less marked increases in mottled and pitted teeth were seen in the higher dose groups. The increased levels of fluorosis were attributed to increased fluoride exposure from multiple sources.

While drinking water fluoride levels ranging from 0.7 to 3 ppm can reduce the incidence of dental caries, susceptibility to caries can increase at higher fluoride levels. Adolescents consuming water containing 5 ppm fluoride since birth were evaluated for fluorosis and prevalence of caries. The prevalence of dental fluorosis was 100%, with the 182 subjects showing effects ranging from mild to severe. The incidence of dental caries increased with increasing severity of fluorosis symptoms. The increase in caries was apparently caused by a degenerative effect of high levels of fluoride on ameloblast cells, resulting in porosity and hypoplasia of the tooth (Mann et al. 1987).

In an early study, 78 workers engaged in the crushing and refining of cryolite were examined. Thirty-nine workers showed evidence of skeletal fluorosis in the form of dense calcification in the long bones, cartilage, and in extreme cases, of the skull as well (Moller and Gudjonsson 1932). Although an average exposure period was not presented, no workers with less than 2 years of exposure were included; some workers had been exposed for as long as 40 years. The authors stated that the effects were due only to cryolite dust being swallowed and absorbed through the gastrointestinal tract. They based this conclusion on the fact that their examination of 21 workers exposed to fluorine gas (some for up to 40 years) revealed no skeletal effects. In light of what is now known about the absorption of fluorides through the lung, the cryolite workers probably incurred both oral and inhalation exposures.

Signs of skeletal fluorosis range from increased bone density to severe deformity, known as crippling skeletal fluorosis. Crippling fluorosis is characterized by complete rigidity of the spine, often accompanied by kyphosis (humpbacked) or lordosis (arched back). Reported cases are found almost exclusively in developing countries, particularly India, and are associated with malnutrition (Pandit et al. 1940). Tea consumption and high water intake due to the tropical climate are probably also contributing factors. As discussed in Chapter 5, tea is high in fluoride. High water intake would increase the intake of fluoride from water. It is generally stated that a dose of 20-80 mg/day (equivalent to 10 ppm in the water) is necessary for the development of crippling skeletal fluorosis (NAS 1971a), but individual variation, variation in nutritional status, and the difficulty of determining water fluoride levels in such situations make it difficult to determine the critical dose. Pandit et al. (1940) found severe skeletal fluorosis in people who had consumed 13-24 mg/day for >15 years. Cases of kyphosis, fused vertebrae, and marked exostoses (ossification of muscle attachments to bone) were reported in an area of India with water supplies containing 1.2-16.2 ppm

fluoride (Singh et al. 1963), but fluoride levels were not reported for the water supplies used by the people with the most severe symptoms. Soil fluoride levels were not reported. Kyphosis, lordosis, and wedging of dorsal vertebra was reported in poorly nourished English children in 1932 (Kemp et al. 1942). Water supplies ranged from 0.3-1.2 ppm. The study was marked by small sample size and the absence of controls.

The incidence of early skeletal fluorosis in the United States is unknown, since it appears that the early signs can only be identified radiologically. A study of 116 people who had lived in an area with an average of 8 ppm fluoride in the drinking water for at least 15 years found a 10%-15% incidence of fluoride-related bone changes (Leone et al. 1955). Coarsened trabeculation and thickened bone were observed, but no exostoses.

A limited number of cases of crippling skeletal fluorosis due to oral exposure have been reported in the United States. Where the doses are known, they are generally 15-20 mg fluoride/day for over 20 years; two of the cases were associated with renal disease, which would reduce fluoride excretion. Two of the cases were associated with drinking large quantities of water with >3.5 ppm fluoride. In the most severe case, a man who consumed at least 15 mg fluoride/day by drinking over 4 liters of water with 3.5 ppm fluoride for 43 years developed kyphosis and severe joint stiffness. The diagnosis was confirmed by radiological analysis; bone fluoride content at autopsy was 6,100 ppm of dried bone (Sauerbrunn et al. 1965). Complete neck and spine rigidity was reported in a man who had ingested unspecified large volumes of water containing 4-7.8 ppm fluoride and large volumes of tea for 55 years (Goldman et al. 1971). A recent immigrant from Mexico developed symptoms consistent with spinal cord compression (Fisher et al. 1989). Her tap water in Mexico contained 3.9 ppm fluoride; fluoride levels in neighboring areas ranged from 0.1 to 5.5 ppm. A 40-year-old woman with renal failure developed progressive muscle weakness and severe pain in her ribs, back, and hip (Fisher et al. 1981). Fluoride content of an ashed iliac crest bone was 10,000 ppm. Questioning to determine her sources and intake of fluoride elicited the information that she practiced geophagia, the custom of eating earth, which is often a symptom of iron deficiency. The patient ingested about 15 mg fluoride/day, of which 10 mg/day were from eating soil, 4.2 mg/day were from tea, and 1.4 mg/day was from her drinking water, which had a fluoride content of 0.7 ppm. A 65-year-old woman who drank well water containing an undetermined fluoride concentration for most of her life developed paresthesias of both legs and pain in the back and chest (Bruns and Tytle 1988). The paresthesias were considered secondary to bone deformities. The fluoride level in the iliac crest bone was reported as 1,900 ng/L (sic) (normal is <140 ng/L); urinary fluoride was 3.39 mg/L (normal, 0.2-1.0 mg/L). Two of the cases were initially diagnosed as bone malignancies but recognized as fluorosis upon further investigation (Bruns and Tytle 1988; Fisher et al. 1981).

Fluoride is found in all bone, with the concentration depending on total fluoride exposure. The amount varies among different bones. Levels of

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fluoride in human bone are generally determined by biopsy of the iliac crest bone, and are generally reported as ppm of bone ash. Normal bone contains 500-1,000 ppm fluoride (Boivin et al. 1988; Franke et al. 1975). Bone from people with preclinical skeletal fluorosis, which is generally asymptomatic and characterized by slight radiologically detectable increases in bone mass, contains 3,500-5,500 ppm fluoride. Sporadic pain, joint stiffness, and osteosclerosis of the pelvis are observed at 6,000-7,000 ppm, while chronic joint pain, increased osteosclerosis, and slight calcification of ligaments occur at 7,500-9,000 ppm. Crippling fluorosis is observed at fluoride bone concentrations >10,000 ppm (Franke et al. 1975). The fluoride concentration in bone increases with age (Zipkin et al. 1958). In a group of five people ages 64-85 who had lived for at least 10 years in an area with water containing 1 ppm fluoride, the average fluoride concentration of the iliac crest bone was 2,250 ppm of bone ash.

Since fluoride increases bone density, it has been hypothesized that fluoride could be used to treat osteoporosis. Additional support for this hypothesis came from a study that found that women in a high-fluoride area (4-5.8 ppm fluoride in the water) had lower incidences of decreased bone density and collapsed vertebrae than did women in a low-fluoride area (0.15-0.3 ppm) (Bernstein et al. 1966). There have been reports of successful treatment of osteoporosis with fluoride. For example, one study reported that intermittent dosing with sodium fluoride and calcium supplements reduced vertebral and total fractures (Pak et al. 1989).

However, there is evidence that the newly formed bone following fluoride treatment may be more brittle and more fracture-prone. The bones of a man with severe skeletal fluorosis had increased compressive strength, but decreased tensile strength and modulus of elasticity (a measure of stiffness, or resistance to being strained by a load) compared to normal controls (Evans and Wood 1976). However, only one subject was tested, and the fact that he had been bedridden for the previous five years may have been a confounding factor. A prospective, randomized, double-blind, placebo-controlled study of 202 women with postmenopausal osteoporosis ascertained the effect of administering 34 mg fluoride/day as sodium fluoride (Riggs et al. 1990). Both groups received 1500 mg calcium/day. Rigorous criteria excluded patients with metabolic diseases. A total of 135 patients (66 in the treatment group and 69 in the control group) completed the full four years of treatment. Although bone mineral density in the lumbar spine, femoral neck, and femoral trochanter increased markedly in the treatment group, bone mineral density in the shaft of the radius decreased 4%. There was no significant difference in the number of new vertebral fractures between the treatment and control groups, although the number of vertebral fractures in the fluoride group was slightly elevated in the first year. In contrast, the level of nonvertebral fractures in the fluoride group was 3.2 times that of the control group, with significant increases in both the frequency and rate of fractures. Most of the increase was due to increased incidences of incomplete ("stress") fractures, which occurred 16.8 times more often in the treatment group. A parallel study was

carried out with identical protocols, except that all of the women participated in a supervised exercise program (Kleerekoper et al. 1989). There was no significant difference between the treatment and control groups in vertebral fracture rate or annual height loss. This study was only reported as an abstract and has not been followed up in the literature, but it is included here because of its importance in confirming the results of the Riggs et al. (1990) study. Although the fluoride levels used in these two studies were higher than used in some treatments of osteoporosis, there is no evidence that lower fluoride doses would be more efficacious in reducing vertebral fracture rates. In a smaller version of the Riggs et al. (1990) study, osteoporotic women who received 22.6 mg fluoride/day as sodium fluoride with either calcitriol or calcium had an increased incidence of hip fractures compared to osteoporotic women who received placebo or calcitriol only (Hedlund and Gallagher 1989). The study was limited by the small sample size (17-22/group). An MRL of 0.05 mg/kg/day was calculated based on a LOAEL of 0.48 mg/kg/day for increased fracture rate in the Riggs et al. (1990) study, as decribed in the footnote to Table 2-3.

Prompted by the above results, researchers have examined the effect on bone fracture rate of lower fluoride levels in drinking water. The most thorough study to date compared three demographically similar communities in rural Iowa. In the control community drinking water contained 1 ppm fluoride and 67 ppm calcium, in the high fluoride community it had 4 ppm fluoride and 15 ppm calcium, and the high calcium community water had 375 ppm calcium and 1 ppm fluoride (Sowers et al. 1991). Women aged 55-80 years in the high fluoride community had significantly faster loss of radial bone mass and a two-fold increase in the rate of all fractures. The effects remained after adjusting for age, body size and weight, total calcium intake, and hormone use. Although the effect does not appear to be due to total calcium intake, it is not clear whether the low calcium level in the high fluoride water affected fluoride uptake. The high-fluoride water was naturally fluoridated, while the water in the other two communities was artificially fluoridated. Individual fluoride intake from beverages, but not other sources, was calculated and found to correlate with fracture risk. A geographical correlational study of 541,985 white women hospitalized for hip fractures found a weak association (regression coefficient=0.0001, p=0.1) between hip fracture incidence and fluoridation of water (Jacobsen et al. 1990). The association was strengthened (regression coefficient=0.003, p=0.0009) after correcting by county for other factors found to correlate with hip fracture incidence (latitude, hours of sunlight, water hardness, income level, and percentage of land in farms).

A recent ecologic cohort study compared the hip fracture rate for men and women in a Utah community that had water fluoridated to 1 ppm with the rate in two communities with water containing <0.3 ppm fluoride (Danielson et al. 1992). Fluoridation began in the fluoridated community in 1966. The ageadjusted rate was significantly elevated in both women (relative risk 1.27, 95% confidence interval 1.08-1.46) and men (relative risk 1.41, 95% confidence

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interval 1.00-1.81). In men, the rates in the fluoridated and nonfluoridated communities were similar until age 70. From age 75 on, the difference between the rates in the fluoridated and nonfluoridated areas increased with age. The difference between the hip fracture rates in the fluoridated and nonfluoridated areas increased for women in the 70- and 75-year age groups. However, the fracture rates in women at ages ≥80years old were similar in the fluoridated and nonfluoridated towns. The study authors attributed this to the fact that women older than 80 years would have already gone through menopause by the beginning of fluoridation, and so would have had less bone remodeling and less incorporation of fluoride into the bone. The study authors also suggested that the reason that they found an effect when other investigators have not was the low levels of exposure to risk factors for osteoporosis (smoking and alcohol) in the Utah populations. This was a well conducted study that suggests that communities with fluoridated water have an elevated risk of hip fracture. However, several possible confounding factors were not examined. Calcium levels in the water, total calcium and vitamin D intake, and individual fluoride intake were not determined. Estrogen use was not evaluated, but was assumed to be similar since the communities were similar distances from larger medical centers. In addition, estrogen levels would not cause the effect in men.

A study in England and Wales also found increased rates of hip fractures in men and women over age 45 as water fluoride levels increased up to 0.93 ppm (Cooper et al. 1991). Hip fracture rates in 39 counties (standardized by age and sex) were compared with water fluoride levels in those counties. In the original analysis (Cooper et al. 1990), no significant correlation was found. However, when the authors reanalyzed the data using a weighted least-squares technique (weighting by the size of the population aged ≥ 45years) to account for differences in the precision of the county-specific rates, a significant positive correlation between water fluoride levels and hip fracture rates was found (r=0.41, p=O.009). The correlation existed for both women (r=0.39, p=0.014) and men (r=0.42, p=0.007) (Cooper et al. 1991). No effect of fluoridation was found when the age-specific rates of femoral fractures were compared for the 5 years prior to fluoridation and the 5 years after fluoridation in a New York town (Goggin et al. 1965). The period of exposure to fluoridated water may have been too short to observe an effect in this study. In addition, as in the ≥80 age group of the Danielson et al. (1992) study, most of the women in this study would have gone through menopause prior to fluoridation of the water. Finally, fractures throughout the length of the femur, rather than just hip fractures, were included in this study. A Finnish study found decreased hip fracture rates in men of all age groups >50 years, and in women age 70 and over (Simonen and Laitinen 1985). It is not clear why this study differs from the other ones, but readmissions were included in the study.

The weight of evidence from these experiments suggests that fluoride added to water can increase the risk of hip fracture in both elderly women and men. However, questions remain due to issues such as the lack of information

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on trends in hip fracture incidence and total individual fluoride consumption. If this effect is confirmed, it would mean that hip fracture in the elderly replaces dental fluorosis in children as the most sensitive endpoint of fluoride exposure.

Evidence from animal experiments may provide insight into the mechanism of the effects of fluoride on bones. The femurs of weanling male rats of a Wistar-derived strain that were given ≥9.5mg fluoride/kg/day as sodium fluoride for 2 weeks exhibited a marked decrease in the modulus of elasticity. It is not clear if the change was analyzed statistically. No lower doses were tested (Guggenheim et al. 1976). Musculoskeletal effects in albino rats (strain not identified) following oral exposure of intermediate duration have been investigated. After 30 days of exposure to 100 ppm of fluoride in water (14 mg/kg), tibia bones were broken and allowed to heal (Uslu 1983). Collagen synthesis was determined to be defective, and fracture healing was delayed, when compared to the controls. Decreased bone growth and signs of fluorosis were observed in rats given 19 mg/kg in their drinking water and adequate calcium for 5 weeks; with elevated calcium levels, fluorosis was not observed until the fluoride level reached 35 mg/kg (Harrison et al. 1984). Rats administered 10.5 mg fluoride/kg/day for 5 weeks had significantly decreased mineral content and increased proline content of tooth enamel (DenBesten and Crenshaw 1984). According to the authors, chronic high levels of fluoride interfere with the progressive deposition of mineral and withdrawal of organic matrix and water that characterizes normal pre-eruptive enamel development. Male mice administered 0.80 mg fluoride/kg/day for 4 weeks exhibited a statistically significant increase in the bone formation rate and a slight but statistically significant decrease in bone calcium levels (Marie and Hott 1986). The authors concluded that 0.80 mg fluoride/kg increased the population of osteoblasts under the conditions of this experiment.

It is possible that the decreased level of bone resorption in the presence of fluoride, and the associated lowered serum calcium levels, would lead to secondary hyperparathyroidism in an attempt to maintain normocalcemia. To address this issue, rats were dosed with 3.3 mg fluoride/kg in drinking water for 46 weeks (Rosenquist et al. 1983). There were no changes in serum calcium or parathyroid hormone levels, and no increase in parathyroid activity.

The sagittal crests were enlarged and/or deformed in three of six adult female mink fed 9.1 mg fluoride/kg/day as sodium fluoride for 382 days (Aulerich et al. 1987). The authors attributed the abnormalities of the sagittal crests to increased osteoblastic activity. After about 210 days of exposure, the females were mated. The mink kits were exposed during gestation and during the suckling period, and were fed the same diets as their mothers. Kits in the 5.0 mg fluoride/kg/day and over groups had dark mottling of their teeth. Several of the kits had broken canines.

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Hepatic Effects. No studies were located regarding hepatic effects in humans after oral exposure to fluorine, hydrogen fluoride, or fluoride.

Pale, granular hepatocytes, compatible with parenchymal degeneration, were observed in mice administered 0.95 mg fluoride/kg/day in drinking water for 7-280 days (Greenberg 1982a). Fatty granules were observed after 3 weeks. Liver congestion was observed in sheep given a single intragastric dose of fluoride as low as 9.5 mg fluoride/kg. Mild serum increases of liver enzymes (glutamate dehydrogenase [GDH] and gamma-glutamyl transferase [GGT]) also occurred in sheep administered 38 mg fluoride/kg (Kessabi et al. 1985). It is difficult to use this result to predict to possible human effects because ruminants (sheep, cows, goats) have gastrointestinal systems quite different from that of humans.

Enlarged liver cells with multiple foci were seen in about half of the male $B6C3F_1$ mice that died after receiving 26 or 52 mg fluoride/kg/day for up to 6 months as sodium fluoride in drinking water (NTP 1990). This change was seen in all of the female mice that died at the 52 mg/kg/day dose level. No liver effects were seen in a parallel experiment with F344/N rats at doses up to 19 mg/kg/day. Similarly, no liver histopathology was seen in the chronic portion of this study (NTP 1990), in which rats received total fluoride doses (amount added to water plus endogenous fluoride in food) of about 4.5 mg/kg/day (rats) or up to 9.1 mg/kg/day (mice). Alkaline phosphatase levels were significantly increased in male and female mice at the 66 week interim sacrifice of the chronic study.

Renal Effects. One study was located in which ingestion of fluoride appeared to be linked with renal insufficiency (Lantz et al. 1987). A 32-year-old man ingested 2-4 L of Vichy water (a highly gaseous mineral water containing sodium bicarbonate and approximately 8.5 mg/L of fluoride) every day for about 21 years. This exposure ended 4 years before his hospital admission. The patient also had osteosclerosis and a moderate increase in blood and urinary levels of fluoride. No teeth mottling was observed. The authors could not find factors, other than fluoride, related to his interstitial nephritis. No effect on the incidence of urinary tract calculi or the incidence of albuminuria was found in the Bartlett-Cameron study of people drinking water containing 8 ppm fluoride (Leone et al. 1954).

Congestion of the kidney was observed in sheep given a single intragastric dose of fluoride as low as 9.5 mg fluoride/kg (Kessabi et al. 1985). An intermediate exposure study tested the effect of administering up to 52 mg fluoride/kg/day to $B6C3F_1$ mice (8-9/group) as sodium fluoride in drinking water for 26 weeks (NTP 1990). Acute nephrosis characterized by extensive multifocal degeneration and necrosis of the tubular epithelium was believed to be the main cause of death in two of the four males exposed to 52 mg/kg/day that died, the single male that died after exposure to 26 mg/kg/day, and two of the four females in the high dose group that died.

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No kidney histopathology was observed at doses ≤17mg/kg/day in males or 126 mg/kg/day in females, or at doses up to 19 mg/kg/day in F344/N rats.

Changes in kidney histology were seen in mature Swiss mice given a dose of sodium fluoride in drinking water for up to 280 days that was described as the maximum dose that could be chronically tolerated, i.e., 1.9 mg/kg/day (Greenberg 1986). Using a sensitive staining technique, increased collagen levels were seen after about 45 days. Thickening of the Bowman's capsule, edematous swelling of the tubules, and infiltrations of mononuclear cells were also noticed. No kidney pathology was seen in a 2-year study in B6C3F1 mice at doses up to 8.1 mg/kg/day (males) or 9.1 mg/kg/day (females), or in F344/N rats at doses up to 4.1 mg/kg/day (males) or 4.5 mg/kg/day (females) (NTP 1990).

Other Systemic Effects. Fluoride has been shown to affect the endocrine system in rats given 0.5 mg fluoride/kg/day as sodium fluoride in drinking water every day for 2 months (Bobek et al. 1976). These animals showed decreased thyroxine levels and an increased T_3-resin uptake ratio.

It is possible that the decreased level of bone resorption in the presence of fluoride, and the associated lowered serum calcium levels, would lead to secondary hyperparathyroidism in an attempt to maintain normocalcemia. To address this issue, rats were dosed with 3.3 mg fluoride/kg in drinking water for 46 weeks (Rosenquist et al. 1983). There were no changes in serum calcium or parathyroid hormone levels, and no increase in parathyroid activity.

Final body weight was reduced by >40% relative to the controls in female F344/N rats administered 25 mg fluoride/kg/day as sodium fluoride in drinking water for 14 days; body weight in males was reduced by >10% at doses ≥6.3 mg/kg/day (NTP 1990). A clear and consistent effect on body weight of B6C3F1 mice was seen only at the high dose (69 mg/kg/day), which was lethal to males (3/5), but not to females. In the intermediate-duration (6 month) phase of the study, the body weight of mice administered 17 mg fluoride/kg/day was reduced by 20%; it was reduced by 10% at 19 mg/kg/day in male and female rats.

F344/N rats and B6C3F1 mice given large doses of sodium fluoride in drinking water for 14 days had reduced water intake (NTP 1990). Male and female rats given 25 mg fluoride/kg/day drank about 30% less water than the controls. Water consumption by male rats given 51 mg fluoride/kg/day was 50% of controls, while it was 25% of controls for females. Similarly, mice given 69 mg fluoride/kg/day drank ≤60%the volume of water consumed by the controls. This means that actual fluoride doses are lower than the estimates given here, since these values were calculated assuming normal water intake. However, the reduced water intake may have been due to the disagreeable taste of fluoride at high concentrations in the water.

2.2.2.3 Immunological Effects

A request to the American Academy of Allergy was made by the U.S. Public Health Service for an evaluation of suspected allergic reactions to fluoride as used in the fluoridation of community water supplies (Austen et al. 1971). The response to this request included a review of clinical reports and an opinion as to whether these reports constituted valid evidence of a hypersensitivity reaction to fluoride exposure of types I, II, III, or IV (Austen et al. 1971), which are, respectively, anaphylactic or reaginic, cytotoxic, toxic complex, and delayed-type reactivity. The Academy reviewed the wide variety of symptoms presented (vomiting, abdominal pain, headaches, scotomata [blind, or partially blind areas in the visual field], personality change, muscular weakness, painful numbness in extremities, joint pain, migraine headaches, dryness in the mouth, oral ulcers, convulsions, mental deterioration, colitis, pelvic hemorrhages, urticaria, nasal congestion, skin rashes, epigastric distress, and hematemesis) and concluded that none of these symptoms were likely to be immunologically mediated reactions of types I-IV. No studies were located that investigated alterations in immune response following fluoride exposure in humans.

In a study with rabbits administered 4.5 mg fluoride/kg/day as sodium fluoride for 18 months, decreased antibody titers were observed (Jain and Susheela 1987). These results were observed after 6 months of treatment; the authors hypothesized that a threshold level is reached at which time the immune system is impaired. However, as only one dose level (4.5 mg fluoride/kg/day) was tested, no dose-effect relationships can be established.

2.2.2.4 Neurological Effects

Fluoride has been shown to interfere with glycolysis. (See Section 2.4 for a discussion of the effect of fluoride on various glycolytic enzymes.) Because the central nervous system relies heavily on this energy source, hypotheses have been advanced as to a mechanism for fluoride effects on the central nervous system. Although effects on glycolytic enzymes could explain the neuromuscular symptoms seen frequently in cases of fluoride poisoning (e.g., tetany, paresthesia, paresis, convulsions), studies tend to indicate that hypocalcemia caused by fluoride binding of calcium causes these symptoms (Eichler et al. 1982).

No studies were located regarding neurological effects in animals after oral exposure to fluorine, hydrogen fluoride, or fluoride.

2.2.2.5 Developmental Effects

Fluoride crosses the placenta in limited amounts and is found in fetal and placental tissue (Gedalia et al. 1961; Theuer et al. 1971). No recent developmental studies of conventional design in animals were located, and results from existing animal studies are mixed.

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Analysis of birth certificates and hospital records for over 200,000 babies born in an area.with fluoridated water and over l,000,000 babies born in a low fluoride area found no difference in the incidence of birth defects attributable to fluoride (Erickson et al. 1976).

Bone morphology of weanling Sprague-Dawley rats from dams who received 21 mg fluoride/kg day for 10 weeks prior to breeding and during gestation was examined with both light and electron microscopy. No pathological changes were seen, suggesting that although fluoride is transported across the placenta, the amount transported was not sufficient to affect fetal bone development (Ream et al. 1983). There were no developmental effects of fluoride in the first litter of an extended two-litter reproduction study in UPj:TUC(SD)spf rats that were fed diets containing 23 mg fluoride/kg/day or 2.8 mg fluoride/kg/day (two litters from each dam) (Marks et al. 1984). However, the second litters born to mothers in the high-fluoride group had a higher number of abnormal newborns and affected litters than were found in the low-fluoride group. The significance of this finding is unclear because the effect was not analyzed statistically.

Wild and domestic animals may be more sensitive than are laboratory animals to developmental effects of fluoride. Stunted growth (Krook and Maylin 1979) and lameness (Maylin and Krook 1982) have been reported in calves that foraged on land downwind of an aluminum plant. Severe dental fluorosis confirmed high levels of fluoride ingestion. Mink kits that were born to mothers fed 9.1 mg fluoride/kg/day and fed the same feed after weaning exhibited a marked decrease in survivability (14% at 3 weeks, compared with 86% for the control) (Aulerich et al. 1987). There was no effect at the next lower dose. No further clinical details were provided for these pups. However, survival of the females exposed to that level was also decreased (17% at the end of the trial [382 days], compared with 100% for the control), so it is not clear if the kit effects were secondary to maternal toxicity. The only clinical signs in the adult mink were general unhealthiness, hyperexcitabilitY, and lethargy a few days before they died. No lameness was observed.

2.2.2.6 Reproductive Effects

Studies that reported an increased incidence of Down's syndrome in areas of high fluoridation have not been replicated by several other investigations (Berry 1958; Erickson et al. 1976; Needleman et al. 1974). No correlation was found between fluoridation and Down's syndrome incidence (corrected for maternal age) in a study of over 234,000 children in fluoridated areas and over l,000,000 children in low-fluoride areas (Erickson et al. 1976). Ascertainment was based on birth certificates and hospital records, but was probably incomplete. Ascertainment was nearly complete in a study of over 80,000 children in fluoride areas and over 1,700,000 in low-fluoride areas, but no age-specific rates were reported (Needleman et al. 1974). Similarly, a study of the incidence of Down's syndrome in England did not find an

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association with the level of fluoride in water, but age-specific rates were not determined and tea was not taken into account as a source of fluoride (Berry 1958).

Animal studies provide conflicting results on any reproductive effect of fluoride. Some authors have seen no effect on sperm abnormalities and no accumulation of fluoride in the testes (Dunipace et al. 1989; Li et al. 1987a; Skare et al. 1986), while others have seen reduced male fertility (Araibi et al. 1989). Decreased female fertility has been observed at toxic levels in Swiss-Webster mice (Messer et al. 1973), but there have also been suggestions that fluoride can aid fertility by improving intestinal absorption of iron and other trace elements (Messer et al. 1973; Tao and Suttie 1976).

Nearly complete infertility was observed in female Swiss-Webster mice that were fed a low-fluoride diet (0.026 mg fluoride/kg/day) supplemented with sodium fluoride in drinking water at a dose that resulted in a ≈20% decrease in maternal weight gain (19 mg fluoride/kg/day). A higher dose (39 mg fluoride/kg/day) resulted in 100% maternal lethality by the end of the experiment; no litters were produced by this group. No effect was seen in two generations receiving 9.5 mg fluoride/kg/day (Messer et al. 1973). A progressive decline in litter production was observed in both generations fed the low fluoride diet and provided deionized water. The authors suggested that fluoride enhances absorption of iron and other trace elements, and the effect at low fluoride levels was due to deficiency in these elements.

Webster mice fed 13mg fluoride/kg/day as sodium fluoride over three generations showed no effects on litter size, weight of pups, and incidence of stillbirth compared to mice fed 0.026 mg fluoride/kg/day (Tao and Suttie 1976). The mice in this study were fed the same basal diet as used by Messer et al. (1973). While no reproductive effects were seen in the animals fed high fluoride diets, a small but significant decrease in the size of the fourth litter of the second generation was observed in the group that was fed the low-fluoride diet and provided with distilled water. The authors attributed the difference between the two studies to higher iron levels in the diet of the latter study. Anemia was reported by Messer et al. (1973), but not by Tao and Suttie (1976). Reproduction was not affected in minks fed diets containing up to 9.1 mg fluoride/kg/day as sodium fluoride (Aulerich et al. 1987).

In order to determine whether reproductive problems at a kennel were due to fluoride, Sheltie dogs of proven fertility were fed untreated dog food (50 ppm fluoride) or food to which rock phosphate was added to a level of 460 ppm fluoride (11.5 mg fluoride/kg/day) (Shellenberg et al. 1990). Fluoride bioavailability was not determined. Decreased estrus rate and increased incidence of missed pregnancies were observed in the high fluoride groups. However, these changes were also observed in groups provided with distilled water rather than well water. It is not clear whether the effect could be attributed to high fluoride, along with nutritional deficiencies in

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the distilled water groups, or whether there was some other cause. Overall reproductive performance was stated by the authors as "good" in an extended two-litter reproduction study in UPj:TUC(SD)spf rats (two litters from each dam). No major differences were reported between rats fed diets containing 2.8 mg fluoride/kg/day and those fed 23 mg fluoride/kg/day (Marks et al. 1984). The fluoride source in the high-fluoride feed was rock phosphate which had been added to the feed as a mineral supplement. The rats absorbed enough fluoride to develop dental fluorosis, but the total bioavailability of fluoride in the diet was not determined.

Additional evidence for an effect of fluoride on female reproduction comes from avian studies. Single Comb White Leghorn hens, Shaver Starcross-288 variety exhibited treatment-related decreased egg production and decreased shell size in the absence of maternal toxicity (Guenter and Hahn 1986). Similarly, screech owls fed diets containing fluoride had decreased hatching success and decreased egg size (Hoffman et al. 1985). Decreased calving rate (Van Rensburg and de Vos 1966) and decreased milk production (Maylin and Krook 1982) have been reported in cows that ingested large amounts of fluoride.

Male CD rats fed 5 or 10mg fluoride/kg/day as sodium fluoride exhibited a significant increase in the thickness of the peritubular membrane of the seminiferous tubules (Araibi et al. 1989). Both treated'groups also exhibited a significant decrease in the percentage of seminiferous tubules containing spermatozoa and a significant decrease in serum testosterone. As a result, there were fewer pregnancies and fewer offspring among treated animals.

These data are not supported by a study that found that oral administration of up to 84 mg fluoride/kg as sodium fluoride to adult male Sprague-Dawley rats did not induce deoxyribonucleic acid (DNA) strand breaks in testicular cells and that testicular fluoride levels were only 10%-20% of plasma levels. This suggests that even at high doses (84 mg/kg body weight is the LD_{01}, or dose that has been calculated to cause death in 1% of exposed animals, for this species), fluoride does not accumulate in the testes (Skare et al. 1986). However, actual effects on reproductive performance were not investigated in this study. $B6C3F_1$ mice administered sodium fluoride by gavage at doses up to 32 mg fluoride/kg/day for 5 days and killed 30 days later showed no sperm head abnormalities (Li et al. 1987a). Slides were coded prior to evaluation to eliminate bias. Bone fluoride levels (1,375 ppm in the high-dose group) indicated that the fluoride was absorbed. Similarly, another well-conducted study (Dunipace et al. 1989) found that $B6C3F_1$ mice administered up to 23 mg fluoride/kg/day as sodium fluoride in water did not accumulate fluoride in the testes and did not have an increased incidence of abnormal sperm morphology. Bone fluoride levels (7,405 ppm in the humeri of the high-dose group) showed that the fluoride was well-absorbed.

The highest NOAEL values and all reliable LOAEL values for reproductive effects for each species and duration category are recorded in Table 2-3 and plotted in Figure 2-3.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans following oral exposure to fluorine, hydrogen fluoride, or fluoride were located. Oral exposures in Swiss mice and Chinese hamsters have shown both positive and negative results for chromosome aberrations and other measures of genotoxicity. The doses that show positive results have been high enough to produce clinical signs of toxicity and occasionally death (e.g., 59 mg fluoride/kg body weight in Chinese hamsters) (Li et al. 1987b). The evidence to date suggests that fluoride may be genotoxic via the oral route, but that the doses required are very high.

Neither the incidence of abnormal sperm morphology nor micronucleated polychromatic erythrocytes were increased in $B6C3F_1$ mice fed a low-fluoride diet and provided water containing fluoride as sodium fluoride for 21 weeks. Control animals were provided distilled water. Four treatment levels up to 22.8 mg fluoride/kg/day (calculated on the basis of water intake) were tested. There was no adverse effect of fluoride on body weight; no other clinical signs were reported. This was a well-conducted test performed with coded slides and appropriate controls. An increased frequency of chromatid breaks was observed when Swiss mice were dosed with 18 mg fluoride/kg as sodium fluoride for 24 hours (Pati and Bhunya 1987). Only one dose was tested, the number of animals used was not specified, and the study authors did not indicate whether the slides were coded. In another study, Chinese hamsters received gavage doses of sodium fluoride at levels up to 59 mg fluoride/kg body weight, and the rate of sister chromatid exchange in isolated bone marrow cells was determined. At the high dose, 3/8 animals died. Sister chromatid exchange was not increased, but cell cycle progression was impeded. Slides were coded prior to analysis. The results imply that fluoride's primary effect at these doses is a general cellular toxicity rather than interaction with DNA (Li et al. 1987b).

Other genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

Numerous epidemiological studies have examined the issue of a connection between fluoridated water and cancer. The weight of the evidence indicates that no such connection exists. However, all of the investigations were ecologic studies, and the sensitivity limit of even the most sensitive analysis in these studies appears to be a 10%-20% increase. Since any carcinogenic effect of fluoride at the levels found in water supplies would probably be below this level of sensitivity, a National Toxicology Program (NTP) cancer bioassay was conducted to assess the effect of fluoride on cancer incidence in animals (Bucher et al. 1991; NTP 1990). The NTP study found equivocal evidence of a fluoride-related increase in osteosarcomas in male rats, and no evidence of any fluoride-related neoplasm in female rats or male

or female mice. A study sponsored by Proctor and Gamble (Maurer et al. 1990) found no evidence of fluoride carcinogenicity in either male or female rats. Both studies contain limitations that preclude strong conclusions. The NTP is presently carrying out additional experiments on the relationship, if any, between fluoride and cancer. The International Agency for Research on Cancer (IARC) reviewed the literature on fluoride carcinogenicity in 1982. It concluded that there is no evidence from epidemiological studies of an association between fluoride ingestion and human cancer mortality, and the available data are inadequate for an evaluation of the carcinogenicity of sodium fluoride in experimental animals (IARC 1982). Several major cancer bioassays of fluoride have been conducted since the IARC review.

Data suggesting that increased fluoride exposure from drinking water supplies is associated with an increase in cancer incidence come from the study published by Yiamouyiannis and Burk (1977) comparing the cancer incidence rates in 10 U.S. cities with artificial fluoridation and 10 cities without fluoridation. The authors of the study interpret these data as showing that cancer mortality was higher in the cities with artificially fluoridated water. Data from this study have been re-analyzed several times in an attempt to further explore the hypothesis that fluoridation of water supplies causes cancer (Chilvers 1982, 1983; Doll and Kinlen 1977; Hoover et al. 1976; Kinlen and Doll 1981; Oldham and Newell 1977; Taves 1977). None of these re-analyses provided evidence of a positive association between fluoridation of water supplies and cancer of any of the sites considered. The re-analyses attributed the positive association between fluoride exposure and cancer reported by Yiamouyiannis and Burk (1977) to dissimilarities in age, race, sex and demographic factors for the populations studied. Other studies of large populations, both in the United States and Great Britain, have identified no relationship between artificially or naturally occurring fluoride in drinking water and an increase in cancer incidence (Griffith 1985; Hoover et al. 1991; Kinlen 1975). An inverse relationship between fluoride levels and cancer of the oral cavity and pharynx has been reported to occur in Norway in populations whose drinking water contained low levels of fluoride (0.05-0.5 mg/L) (Glattre and Wiese 1979). Although the authors offered no detailed mechanism for the apparent protective effect, and did not conduct a formal analysis of possible confounding factors, they did present data indicating that biases due to tobacco consumption, rural and urban differences, and differences in the population sizes of the examined communities could.not be the cause of the reduced cancer rates.

A recent epidemiological study (Hoover et al. 1991) examined >2,300,000 cancer deaths and >125,000 cancer cases in U.S. counties exposed to artificially fluoridated drinking water for up to 35 years. Taking into account the results of the NTP study described below, detailed analyses were conducted of cancers of the joints and bones (especially osteosarcomas), and cancers of the oral cavity and pharynx. The statistical evaluation was based on analysis of time trends in the observed/expected (O/E) ratios relative to duration of fluoridation. While elevated O/Es were observed for osteosarcomas

in males, the O/E ratio was inversely related to duration of fluoridation. Thorough analyses of incidences of oral cancers and cancers at a variety of other sites were conducted by means of very sensitive statistical tests that were designed to detect changes as small as 10-20%. No consistent correlation between cancer incidence or mortality and duration of fluoridation was found. An addendum to the report noted that the age-adjusted national incidence of osteosarcoma increased by 18% in males for the years 1973-1980 and 1981-1987; most of the increase was due to a 53% increase in males under 20 years of age, and there was a larger increase in fluoridated than nonfluoridated areas. A similar time-trend analysis to that done in the main report found no correlation between the cancer incidence O/E ratio and duration of fluoridation. Additional analyses also failed to find a relationship between osteosarcoma incidence in males and exposure to fluoridated water.

In general, occupational fluoride exposures result in much higher intake rates than does ingestion of artificially fluoridated drinking water. Actual absorbed doses from occupational exposure are not available, but urinary fluoride levels can reach 5.68 mg/L (Dinman et al. 1976c), compared with normal levels of about 1 mg/L (Spencer et al. 1970). Studies regarding cancer from occupational inhalational exposure to hydrofluoric acid fumes and dust from cryolite were discussed in Section 2.2.1.8.

The NTP conducted two chronic oral bioassays of fluoride administered as sodium fluoride (0, 25, 100, or 175 ppm) in drinking water, using F344/N rats and B6C3F$_1$ mice (Bucher et al. 1991; NTP 1990). The first study was considered compromised for reasons that will be discussed below. However, pathology data from the first study were used in determining the doses for the second study. The diet used in the second study was specially formulated to be low in fluoride, and contained 8.6 ppm fluoride; daily fluoride amounts administered in the food for control and experimental groups was 0.43 mg/kg/day in rats and 1.1 mg/kg/day in mice. Based on the total amount of fluoride ingested and the amount in the feces, and apparently assuming that none of the fluoride found in the feces was absorbed, Bucher et al. (1991) calculated that the average bioavailability of fluoride in the food over the course of the experiment was 60%. Assuming complete absorption of fluoride in the water, they estimated total fluoride intake (including fluoride in both water and diet) of control, low-, medium-, and high-dose male rats as 0.2, 0.8, 2.5, and 4.1 mg/kg/day, respectively. Similarly, the high doses for female rats, male mice, and female mice were 4.5, 8.1, and 9.1 mg/kg/day, respectively.

The study found osteosarcomas in the bone of 1/50 male rats in the middose group and 3/80 of the high-dose male rats. An additional high-dose male had an extraskeletal osteosarcoma in subcutaneous tissue. Examination of radiographs did not reveal a primary site in bone for the extraskeletal tumor, suggesting that it was a soft-tissue tumor that later ossified. No osteosarcomas were found in the low-dose or control rats. One of the osteosarcomas in the high-dose group was missed on radiographic examination

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and in the necropsy, and found only on microscopic examination. Three of the
tumors were in the vertebra and only one was in a long bone. This is unusual,
as Bucher et al. (1991) stated that chemically induced osteosarcomas usually
appear in the long bones, rather than in the vertebrae. Statistical analysis
found a significant dose-response trend in the four osteosarcomas of the bone
(p=0.027), but no significant difference (p=0.099) in a pairwise comparison of
the controls with the high-dose group. The probability value for the trend
test was decreased (p=0.010) when the extraskeletal osteosarcoma was included,
but the pairwise test was still not significant (p=0.057). Osteosarcomas are
rarely observed in control male rats in NTP studies; the historical incidence
is 0.6% (range 0%-6%). The rate in the high-dose group in this study was
3.75% or 5%, depending on whether the extraskeletal tumor is included. Tumor
rates could not be compared with the historical controls because the diet
generally used for NTP studies contains >20 ppm fluoride. Assuming the same
bioavailability of 60%, the study report states that this would place the
historical controls between the low- and mid-dose groups in the fluoride
study. Conversely, the more extensive bone examinations used in the fluoride
study, both at the macroscopic level and histologically, could have led to
higher bone tumor levels being observed than in historical controls.

The average fluoride level in the bones of male rats in the high-dose
group was 5,260 ppm. While similar bone fluoride levels were found in the
bones of female rats and male and female mice, there was no evidence of
treatment-related osteosarcomas in these groups. Osteosclerosis was observed
in high-dose female rats, suggesting a stimulatory or mitogenic effect on
osteoblasts (Marie and Hott 1986). Osteosclerosis was not observed in mice,
despite the higher dose. Osteosarcomas were observed in one low-dose male
mouse, one low-dose female mouse, and one control female mouse. There was
also one osteoma in a control female mouse. No osteosarcomas were observed at
mid- or high-dose levels in female rats or male or female mice. The study
authors stated that the absence of treatment-related osteosarcomas in female
rats and male and female mice may have limited relevance to the findings in
male rats. Results in the literature are mixed as to whether there is a sexlinked
response in bone tumor formation (Litvinov and Soloviev 1973; NC1 1978, both as cited in
NTP 1990).

Increased tumor incidence in rats or mice was noted in a few other
tissues, but was not considered biologically significant. For example, the
combined incidence of squamous cell papillomas and carcinomas in the oral
mucosa was marginally increased in the high-dose male and female rats and
thyroid follicular cell neoplasms were marginally increased in the high-dose
male rats. Neither increase was statistically significant, and both types of
neoplasms lacked a supporting pattern of increased pre-neoplastic lesions.
Similarly, increased levels of keratoacanthomas were observed in high-dose
female rats, but were not considered biologically significant because other
benign neoplasms arising from stratified squamous epithelium was found in the
controls. Malignant lymphoma and histiocytic sarcoma incidence in female
high-dose mice was marginally increased (combined rate 30%), but the increase

was not considered biologically significant. The incidence was well within the range of historical controls at the study laboratory (18%-48%) and at all NTP laboratories (10%-74%). The incidence of hepatocellular neoplasms in male and female mice of the treatment and control groups was higher than in historical controls. The study authors noted similar increases in other NTP studies that were conducted contemporaneously, and suggested that they may be associated with increased animal weight. Hepatocholangiocarcinomas, which are rare liver neoplasms, were identified in the original pathology examination in five treated male mice, four treated female mice, and one control female mouse. The Pathology Working Group reclassified all of the neoplasms (except one in a high-dose female mouse and one in a control female mouse) as hepatoblastomas, because they contained well-defined populations of cells that resembled embryonal liver cells more closely than they did biliary cells. The dose levels at which the reclassified hepatocholangiocarcinomas were found were not reported.

Interpretation of this study is further complicated because higher doses might have been tolerated in both the rat and the mouse studies (NTP 1990). Fluoride-related tooth abnormalities found in the study included dental attrition in males of both species that was dose-related in rats but not in mice, dentine dysplasia in both genders of both species, and tooth deformities in male rats. No other treatment-related toxic effects were found in any group, and there was no evidence of decreased body weight gain in any group. Higher fluoride levels may have affected the teeth of the male rats so severely as to interfere with the animals' ability to eat. However, it appears that the mice and possibly the female rats could have tolerated a higher dose.

Based on the finding of a rare tumor in a tissue known to accumulate fluoride, but not at the usual site for chemically-associated osteosarcomas, a weakly significant dose-related trend, and the lack of supporting data in female rats and mice of either gender, the NTP concluded that there was "equivocal evidence of carcinogenic activity of sodium fluoride in male F344/N rats." NTP defined equivocal evidence of carcinogenic activity to be a situation where the results show "a marginal increase in neoplasms that may be chemically related." NTP further concluded that there was no evidence that fluoride was carcinogenic at doses up to 4.73 mg/kg/day in female F344/N rats, or at doses up to 17.8 and 19.9 mg/kg/day in male and female B6C3F$_1$ mice, respectively.

The first chronic study in this series conducted by NTP was a 2-year cancer study in B6C3F$_1$ mice and F344/N rats using a semisynthetic diet containing 2.1 ppm fluoride and fluoride provided, in drinking water as sodium fluoride at 0, 10, 30, or 100 ppm. Several non-treatment-related clinical signs developed in rats, including corneal lesions and head tilt. Analysis of the diet revealed marginal to marked deficiencies in manganese, chromium, choline, and vitamins B$_{12}$ and D. Based on these findings, the study was considered compromised, but the results were used to aid in dose selection for

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the second study. Only the following unverified pathology findings were reported: (1) one osteosarcoma in the occipital bone of one low-dose male rat; (2) one osteoma in the vertebra of a male control mouse; (3) one subcutaneous osteosarcoma in one female high-dose mouse; and (4) no osteosarcomas were found in female rats (male mice were not mentioned).

A study sponsored by Proctor and Gamble examined the carcinogenic potential of sodium fluoride administered in feed to Sprague-Dawley rats (Maurer et al. 1990). One group of controls was fed laboratory chow, and another control group was fed a semisynthetic low-fluoride diet. The control group fed the low-fluoride diet received 0.14 (males) or 0.18 (females) mg fluoride/kg/day as sodium fluoride. The fluoride level in the laboratory chow was not determined. Treatment groups ingested 1.8, 4.5, or 11.3 mg fluoride/kg/day in the diet as sodium fluoride. Fluoride bioavailability was not determined and water fluoride levels were not reported. However, the high dose (11.4 mg fluoride/kg/day) was probably close to the MTD, since there was a 30% decrease in body weight gains of both sexes. The study was terminated early because of high mortality in all treatment and control groups. The cause of the elevated level of mortality was not determined. Fluoride-related toxicity was observed in the teeth, stomach, and bones.

Evidence of fluoride toxicity in the Maurer et al. study included doserelated hyperostoses in males and females, tooth abnormalities, and stomach inflammation. Fluoride levels in the bone ash of the high-dose males and females were 16,761 and 14,438 ppm, respectively. Primary tumors in target tissues as reported by the study authors 'were one fibroblastic sarcoma with areas of osteoid formation in a high-dose male, one osteosarcoma in a low-dose female, one chordoma in a mid-dose male, one chondroma each in a mid-dose male and a low-dose female, one odontoma in a laboratory-chow control, and one stomach papilloma in a low-fluoride control. Re-examination of tissue slides as part of a review of the study by the Carcinogenicity Assessment Committee, Center for Drug Evaluation and Research, Food and Drug Administration (CAC/CDER/FDA) revealed an additional osteosarcoma in a low-dose female and one osteosarcoma in a high-dose male. Statistical analysis of the incidence of bone tumors found no dose-response relationship (CDER 1991).

Several limitations of the study were not apparent in the study report, but were noted in the CAC review (CDER 1991). The low-fluoride diet may not have allowed normal growth and development, since pale livers and gastric hairballs were observed in all study animals except those fed laboratory chow. The diet and water were often above specifications for minerals, ions, and vitamins. A virus was found during the pretest period and its continued presence during the study was suspected; this may have compromised the health of the animals. The finding of bone tumors missed by the contract laboratory raised questions about the adequacy of the examination at gross necropsy. Finally, bone sections from only 50%-80% of the mid- and low-dose animals were analyzed microscopically. The CAC review concluded that there are "flaws and uncertainties in the studies that keep them from providing strongly reassuring

data." However, the committee concluded that the study results reaffirm the negative finding of the NTP study in female rats, and do not reinforce the equivocal finding in male rats.

2.2.3 Dermal Exposure

Several human and animal studies investigating the health effects following accidental dermal exposure to hydrofluoric acid were located. In addition, many of the human and animal studies investigating the health effects of inhalation exposure to fluorine or hydrogen fluoride found dermal/ocular effects due to the irritating effects of these chemicals. (In this section, hydrogen fluoride refers to the gas while hydrofluoric acid refers to the liquid.) One study regarding dermal exposure to sodium fluoride was located. Fluorine causes severe irritation of the eyes and skin and can severely burn the skin at high concentrations. Hydrofluoric acid is a caustic acid and can produce severe tissue damage either as the water solution, or in the anhydrous form (hydrogen fluoride). The fluoride ion in hydrofluoric acid can also rapidly penetrate the skin and cause systemic effects, especially cardiac arrhythmias. If left untreated, death can result.

2.2.3.1 Death

Hydrofluoric Acid. Fatalities from dermal fluoride exposure occur most frequently from accidental exposure to hydrofluoric acid in an occupational setting. The actual systemic doses are seldom known. However, the extent and severity of the burns, and occasionally, clinical chemistry values are reported. Death following hydrofluoric acid burns to the extremities, in the absence of inhalation exposure, is due to cardiac arrhythmias, with pronounced hypocalcemia, hyperkalemia, and hypomagnesemia. Ion pump disruption is thought to be the mechanism of systemic toxicity. Hydrofluoric acid exposure of the face has also resulted in death due to respiratory insufficiency, but the respiratory effects are likely to be due to concurrent inhalation exposure. Depending on the extent of the body surface exposed and the effectiveness of medical treatment, death usually occurs within a few hours (Chan et al. 1987; Chela et al. 1989; Kleinfeld 1965).

A patient with hydrofluoric acid burns on his leg involving 8% of his body surface area died from intractable cardiac arrhythmia, presumably secondary to the depletion of ionized calcium by the fluoride ion (Mullett et al. 1987). Serum fluoride level 4 hours after the burn injury was reported to be 9.42 µg/mL, about 400 times the value reported as normal for that age and sex. A 23-year-old man who sustained second and third degree burns of his thighs, covering 9%-10% of his body surface area died of cardiac arrhythmia 17 hours after exposure (Mayer and Gross 1985). Serum fluoride was 4.17 µg/mL.

The death of a chemist who sustained first-and second-degree burns of the face, hands, and arms when a vat containing hydrofluoric acid accidentally

broke has been reported (Kleinfeld 1965). This 29-year-old male died 10 hours after admission to the.hospital. Postmortem examination showed severe tracheobronchitis and hemorrhagic pulmonary edema. A petroleum refinery worker was splashed in the face with 100% anhydrous hydrofluoric acid (Tepperman 1980). The burn produced acute systemic fluoride poisoning with profound hypocalcemia and hypomagnesemia. The patient died less than 24 hours after exposure. A young woman splashed in the face with hydrofluoric acid died a few hours after exposure occurred (Chela et al. 1989). The autopsy revealed severe burns of the skin and lungs, with pulmonary hemorrhagic edema produced by hydrofluoric acid and its vapor.

No studies were located regarding lethality in humans after dermal exposure to fluorine or fluoride, and no studies were located regarding lethality in animals after dermal exposure to fluorine, hydrofluoric acid, or fluoride.

2.2.3.2 Systemic Effects

No studies were located regarding gastrointestinal, hematological, or musculoskeletal effects in humans or animals after dermal exposure *to* fluorine, hydrofluoric acid, or fluoride.

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category of exposure to fluorine are recorded in Table 2-4. The highest NOAEL and all reliable LOAEL values for systemic effects in each species and duration category of exposure to hydrogen fluoride or hydrofluoric acid are recorded in Table 2-5. All reliable LOAEL values for systemic effects in each species and duration category for fluoride are recorded in Table 2-6.

Respiratory Effects

Hydrofluoric Acid. Respiratory effects including pulmonary edema, tracheobronchitis, and pulmonary hemorrhagic edema have been reported in humans following acute dermal exposure of the face to hydrofluoric acid. (Chela et al. 1989; Kleinfeld 1965). However, the pulmonary effects are likely to be due to concomitant inhalation of the acid vapor. As two of these cases were occupational accidents and the third was a homicide, no doses could be estimated from the information provided.

No studies were located regarding respiratory effects in humans after dermal exposure to fluorine or fluoride, and no studies were located regarding respiratory effects in animals after dermal exposure to fluorine, hydrofluoric acid, or fluoride.

Cardiovascular Effects. Cardiac arrhythmias are found following acute dermal exposure to hydrofluoric acid in humans (Mayer and Gross 1985; Mullett

TABLE 2-4. Levels of Significant Exposure to Fluorine - Dermal

Species	Exposure duration/ frequency	System	NOAEL (mg F_2/m^3)[a]	LOAEL (effect)		Reference
				Less serious (mg F_2/m^3)[a]	Serious (mg F_2/m^3)[a]	

ACUTE EXPOSURE

Systemic

Human	1 d 1min/d	Derm/Oc		104 (ocular and nasal irritation)		Keplinger and Suissa 1968
Human	1 d 3min/d	Derm/Oc	16	78 (slight eye and nose irritation)		Keplinger and Suissa 1968
Human	1 d 5min/d	Derm/Oc	16	36 (slight eye irritation)		Keplinger and Suissa 1968
Human	1 d 15min/d	Derm/Oc	16			Keplinger and Suissa 1968
Rat	1 d 5min/d	Derm/Oc	132	263 (irritation of eye and nose)		Keplinger and Suissa 1968
Rat	1 d 15min/d	Derm/Oc	147	303 (irritation of eye and nose)		Keplinger and Suissa 1968
Rat	1 d 30min/d	Derm/Oc	105	210 (irritation of eyes and nose)		Keplinger and Suissa 1968
Mouse	1 d 5min/d	Derm/Oc	119	263 (irritation of eye and nose)		Keplinger and Suissa 1968

TABLE 2-4 (Continued)

| | Exposure | | | LOAEL (effect) | | |
| | duration/ | | NOAEL | Less serious | Serious | |
Species	frequency	System	(mg F_2/m^3)[b]	(mg F_2/m^3)[b]	(mg F_2/m^3)[b]	Reference
Mouse	1 d 15min/d	Derm/Oc	131	292 (irritation of eye and nose)		Keplinger and Suissa 1968
Mouse	1 d 30min/d	Derm/Oc	101	175 (irritation of eye and nose)		Keplinger and Suissa 1968
Mouse	1 d 60min/d	Derm/Oc	75	117 (irritation of eye and nose)	;	Keplinger and Suissa 1968

[a]Concentrations expressed as mg fluorine/m^3 for consistency with ACGIH guidelines.

d = day(s); Derm/oc = dermal/ocular; LOAEL = lowest-observed-adverse-effect level; min = minute(s); NOAEL = no-observed-adverse-effect level

TABLE 2-5. Levels of Significant Exposure to Hydrogen Fluoride/Hydrofluoric Acid - Dermal

Species	Exposure duration/ frequency	System	NOAEL (mg F/m^3)[a]	LOAEL (effect)		Reference
				Less serious (mg F/m^3)[a]	Serious (mg F/m^3)[a]	
ACUTE EXPOSURE						
Systemic						
Rat	1 d 5min/d	Derm/Oc		582 (mild irritation of eyes and nose)		Rosenholtz et al. 1963
Rat	1 d 15min/d	Derm/Oc		238 (slight irritation of eyes and nose)		Rosenholtz et al. 1963
Rat	1 d 30min/d	Derm/Oc			1072 (severe conjunctival and nasal irritation)	Rosenholtz et al. 1963
Rat	1 d 60min/d	Derm/Oc		80 (slight irritation of eyes and nose)		Rosenholtz et al. 1963
Rabbit	1 d 1-4hr/d	Derm/Oc	2% per min		2% (necrotic lesions) per hr	Derelanko et al. 1985
INTERMEDIATE EXPOSURE						
Systemic						
Human	15-50 d 6 hr/d	Derm/Oc		1.1 (stinging sensation in skin and eyes)		Largent 1960
Rat	5 wk 6d/wk 6hr/d	Derm/Oc		7 (subcutaneous hemorrhages)		Stokinger 1949

TABLE 2-5 (Continued)

Species	Exposure duration/ frequency	System	NOAEL (mg F/m^3)[a]	LOAEL (effect)		Reference
				Less serious (mg F/m^3)[a]	Serious (mg F/m^3)[a]	
Mouse	5 wk 6d/wk 6hr/d	Derm/Oc		24 (subcutaneous hemor- rhage)		Stokinger 1949
Dog	5 wk 6d/wk 6hr/d	Derm/Oc		24 (inflammation of scrotal epithelium)		Stokinger 1949

[a]Concentrations expressed as mg fluoride/m^3 for consistency with ACGIH guidelines.

d = day(s); hr = hour(s); Derm/oc = dermal/ocular; LOAEL = lowest-observed-adverse-effect level; min = minute(s); NOAEL = no-observed-adverse-effect level; wk = week(s)

TABLE 2-6. Levels of Significant Exposure to Sodium Fluoride - Dermal

Species	Exposure duration/ frequency	System	NOAEL[a]	LOAEL (effect) Less serious	LOAEL (effect) Serious	Reference	Chemical Species
ACUTE EXPOSURE							
Systemic							
Rat	1 d 24hr/d	Derm/Oc		0.5% (superficial necrosis, moderate edema, PMN infiltration)	1% (extensive necrosis, marked edema, degenerating mast cells)	Essman et al. 1981	NaF

[a]Doses concentrations expressed as % fluoride.

d = day(s); Derm/oc = dermal/ocular; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; NaF = sodium fluoride; NOAEL = no-observed-adverse-effect level; PMN = polymorphonuclear leukocytes

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et al. 1987). A man who received a hydrofluoric acid burn on the arm covering 5% of the body experienced repeated ventricular fibrillation episodes, but survived following administration of intravenous calcium chloride, subcutaneous calcium gluconate, and excision of the burn area (Buckingham 1988). These cardiovascular effects are believed to result from the strong binding of fluoride to calcium, which produces hypocalcemia. Serum calcium is critical for proper ion transport in neuromuscular synapses; hypocalcemia can cause the ventricles not to contract properly.

No studies were located regarding cardiovascular effects in humans after dermal exposure to fluorine or fluoride, and no studies were located regarding cardiovascular effects in animals after dermal exposure to fluorine, hydrofluoric acid, or fluoride.

Hepatic Effects

Hydrofluoric Acid. Elevated SGOT, serum glutamic pyruvic transaminase (SGPT), and lactate dehydrogenase levels were found in a man who was splashed in the face and on the neck with a mixture of 10% hydrofluoric acid and sulfuric acid (Braun et al. 1984). The elevated SGOT and SGPT levels were attributed to either muscle necrosis or temporary liver damage caused by toxic metabolic products from necrotic tissue.

Renal Effects

Hydrofluoric Acid. A 49-year-old man who was splashed in the face and on the neck with a mixture of hydrofluoric acid and sulfuric acid became oliguric for a brief period on the day after the accident, and then became anuric (Braun et al. 1984). Concomitant inhalation exposure is likely, and the effect of the sulfuric acid is unknown.

Dermal/Ocular Effects. Skin, nose, and eye irritation have been reported following dermal exposure to fluorine or hydrogen fluoride gas. Longer contact with these chemicals, brief contact with high concentrations of hydrofluoric acid, and longer contact with lower concentrations of hydrofluoric acid can cause severe burns.

Fluorine. Volunteers (19-50 years of age) were exposed to 16 mg/m^3 fluorine for 15 minutes without discomfort or irritation of the eyes or nose (Keplinger and Suissa 1968). However, repeated exposures at this level for 3-5 minutes every 15 minutes over a 2-3 hour period caused slight eye and nose irritation. Exposure was through a face mask that covered the eyes and nose but not the mouth. Slight eye irritation was reported following exposure to 36 mg/m^3 for 5 minutes. Exposure to 78 mg/m^3 for 3 minutes caused eye irritation and slight nose irritation. Exposure to concentrations ≥104mg/m^3 were very irritating and became uncomfortable after a few seconds. After exposure to 155 mg/m^3 for 1 minute, the eyes burned and felt as though they

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were covered by a skin. The skin felt sticky and slightly irritated. The only effect of exposure to 155 mg/m^3 for 30 seconds was severe eye and nose irritation. Less irritation was reported when exposure was repeated at weekly intervals. The study is limited by the small number of subjects and incomplete description of exposure protocol.

Osborne-Mendel rats exposed to concentrations greater than or equal to ~25% of the LC$_{50}$ (i.e., 263 mg/m^3) for 5 minutes exhibited eye irritation (Keplinger and Suissa 1968). In experiments with exposure for durations of 15-60 minutes, eye and nose irritation was reported only at ~50% of the LC$_{50}$. Similar results were obtained with Swiss-Webster mice, New England guinea pigs, and New Zealand rabbits.

When the shaved backs of New Zealand rabbits were exposed to fluorine gas under 40 pounds of pressure for 0.2-0.6 seconds at distances of 0.5-1.5 inches, the resulting burn appeared to be thermal, rather than chemical in nature (Stokinger 1949). Exposure for 0.2 seconds produced an ischemic area about ¼ inch in diameter, surrounded by an erythematous area. This became a superficial eschar that sloughed off within 4 days, revealing normal epidermis. The longer exposures produced a flash of flame that resulted in combustion of hair, singeing, and erythema over an area several times the area of the primary burn. Coagulation necrosis and charring of the epidermis was also reported. The wound healed within 13 days. The burns resembled those produced by an oxyacetylene flame, rather than those made by hydrofluoric acid, and so were characterized as thermal, rather than chemical. However, it is not clear if the difference from the hydrofluoric acid burn is due to the shorter exposure to fluorine.

Rats exposed to 25 mg/m^3 fluorine for 21 days, 5-6 hours/day exhibited irritation of the eyes and of the nasal and buccal mucosa, and stiffened fur (Stokinger 1949). Similar, but weaker symptoms appeared following exposure under a similar regimen to 8 or 3 mg/m^3,but no symptoms were seen following exposure to 0.8 mg/m^3. Few details were provided regarding the severity of symptoms seen at different exposure levels.

Hydrogen Fluoride/Hydrofluoric Acid. Dermal exposure to hydrogen fluoride can cause irritation of the skin and mucous membranes. Severe dermal effects have not been reported from dermal exposure to hydrogen fluoride gas, but it is not clear if this is because the gas does not cause such effects, or because concentrations high enough to cause severe effects were not tested. Dermal exposure to hydrofluoric acid results in extensive skin burns (Chela et al. 1989). Hydrofluoric acid quickly penetrates into soft tissues and causes necrosis. As a result of cell membrane destruction, the fluoride ion has easy access to lymph and the venules, can be distributed rapidly, and can cause significant adverse effects such as inhibition of glycolytic enzymes, hypocalcemia, and hypomagnesia. Untreated burns of the fingers can result in loss of fingers.

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Marked conjunctival irritation and "smarting" of exposed skin occurred in humans within 1 minute of exposure to hydrogen fluoride at about 95 mg fluoride/m^3 (Machle et al. 1934). This was the highest concentration that two male volunteers could tolerate for more than 1 minute. At 48 mg fluoride/m^3, conjunctival and nasal irritation were still marked, and tickling and discomfort of the nasal passages were reported. A concentration of 24.7 mg fluoride/m^3 produced mild irritation of the nose and eyes and irritation of the larger air passages. This concentration could be tolerated for "several" minutes (at least 3 minutes). The authors of this study reported some difficulties with their measurements of exposure. Repeated exposures did not reveal any habituation. Mild eye irritation was observed in five volunteers exposed 6 hours per day for 10 days, to hydrogen fluoride at concentrations averaging from approximately 2 to 4 mg/m^3 (Largent 1960). This study is limited by the inadequacy of both the experimental details and the description of effects observed.

There are many reports of hydrofluoric acid skin burns in humans. In one case, a 23-year-old man received fatal second- and third-degree burns over 9%-10% of his body from a 70% hydrofluoric acid spill (Mayer and Gross 1985). The patient died 17 hours after exposure due to cardiac arrhythmias. Two case studies of accidental dermal exposure of the hands to hydrofluoric acid (5%-7%) reported serious dermal injury following exposures from 45 minutes to 6 hours (Roberts and Merigian 1989). Topical treatment with calcium gluconate prevented loss of nails. Other case reports are discussed in Section 2.2.3.1.

Some evidence of delayed ocular damage due to persistence of the fluoride ion was observed 4 days after a 3-year-old girl accidentally sprayed a hydrofluoric-acid-containing product in her eyes (Hatai et al. 1986). Opacification of the corneal epithelium and thrombosis of the conjunctival vessels were seen. These changes were not permanent; after 30 days, the eyes returned to normal, and vision was 20/20. However, it is difficult to generalize from this report as the product contained both hydrofluoric acid and phosphoric acid at unspecified concentrations.

Hydrogen fluoride produces irritation of the eyes, skin, and conjunctivae in rats, and the severity of the effect is related to the exposure concentration and duration (Rosenholtz and Ford 1962; Rosenholtz et al. 1963; Wohlslagel et al. 1976). Levels approaching the LC_{50} can cause corneal opacity and lesions of the face (Haskell Laboratory 1988), while slight ocular and nasal irritation was observed in rats exposed to levels as low as 6% of the LC_{50} (Rosenholtz et al. 1963). Rats exposed to hydrogen fluoride (whole body) at a concentration of approximately 1,084 mg fluoride/m^3 for 60 minutes were observed to have erythema of an unspecified severity of the exposed skin (Wohlslagel et al. 1976).

Subcutaneous hemorrhages around the eyes and on the feet developed in rats exposed to 7 or 24 mg/m^3 for 6 hours/day, 6 days/week for 30 days (Stokinger 1949). The effect was more severe at the higher exposure level. Dogs exposed to 24 mg/m^3 for the same time periods developed inflammation of the scrotal epithelium.

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The concentration of hydrofluoric acid and the length of exposure affect the severity of dermal lesions (Derelanko et al. 1985). Rabbits exposed to a hydrofluoric acid solution of 0.01% for 5 minutes had visible skin lesions, whereas exposure to 2% hydrofluoric acid for 1 minute did not produce lesions. A longer exposure of 1-4 hours to 2% hydrofluoric acid solution produced necrotic lesions on the backs of rabbits (Derelanko et al. 1985). In similar experiments involving the exposure of the conjunctivae of rabbit eyes to hydrofluoric acid, McCulley et al. (1983) concluded that the greater severity of hydrofluoric acid injuries compared to injuries from other inorganic acids at comparable strengths probably results from the destruction of the cornea1 epithelium allowing substantial penetration of the fluoride ion into the cornea1 stroma and underlying structures.

The application of 0.2 mL of a 47% hydrofluoric acid solution to the shaved backs of New Zealand rabbits over a surface of 1¼ inches produced no immediate reaction (Stokinger 1949). The material was held in place by lanolin and allowed to dry for 24 hours. Within a few days of exposure, erythema and dark spots of liquefaction necrosis appeared. Multiple eschars were formed in the necrotic areas. These wounds healed more slowly than those produced by fluorine gas. Healing did not near completion until 27 days after exposure.

Fluoride. Sodium fluoride applied topically to the abraded skin of Sprague-Dawley rats (0.5% or 1.0%) for 24 hours produced both morphological and biochemical changes (Essman et al. 1981). At 0.5%, the abraded surface showed focal superficial necrosis of the epidermis. At l.0%, the abraded surface showed edema and vacuolization. There was marked edema of the dermis with inflammation. Skin histamine concentrations were also increased following application of 0.5% or 1% sodium fluoride to shaved-only or epidermally abraded skin, although the variance of these measurements was quite high.

The highest NOAEL values and all reliable LOAEL values for dermal/ocular effects of fluorine exposure for each species and duration category are recorded in Table 2-4. The highest NOAEL and all reliable LOAEL values for dermal/ocular effects of hydrogen fluoride exposure for each species and duration category are recorded in Table 2-5. All reliable LOAEL values for dermal/ocular effects of fluoride exposure are recorded in Table 2-6. No studies were located regarding the following effects in humans and animals after dermal exposure to fluorine, hydrofluoric acid, or fluoride:

2.2.3.3 Immunological Effects
2.2.3.4 Neurological Effects
2.2.3.5 Developmental Effects
2.2.3.6 Reproductive Effects
2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

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2.2.3.8 Cancer

No studies were located regarding cancer in humans or animals after dermal exposure to fluorine, hydrofluoric acid, or fluoride.

2.3 TOXICOKINETICS

The majority of data on the toxicokinetics of fluoride focus on sodium fluoride and hydrofluoric acid. Data regarding the toxicokinetics of calcium fluoride and other fluorides in human or animals are limited. While radioactive isotopes are useful in toxicokinetic studies, this use is limited in studies of fluoride because the fluorine isotope ^{18}F has a short half-life (Wallace-Durbin 1954). Only one animal study and no human studies were located regarding the toxicokinetics of fluorine.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Data providing information on absorption rates exist on the inhalation exposure of humans to mixtures of hydrogen fluoride and fluoride dusts, and inhalation exposure of animals to hydrogen fluoride. Animal data also exist showing that fluorine is absorbed.

Fluorine. No data were located regarding the absorption of fluorine in humans. Hepatic and renal effects were observed in mice following exposure to fluorine for periods up to 60 minutes (Keplinger and Suissa 1968). This indicates that the fluoride ion was systemically available following the exposure. Fluoride, rather than fluorine, is the agent that is toxicologically active systemically, since fluorine is too reactive to be absorbed unchanged. Similarly, the finding of elevated fluoride levels in bones, teeth, and urine during intermediate-duration exposure to fluorine indicates that fluoride is absorbed under these conditions (Stokinger 1949). No information on absorption rate or extent is available.

Hydrogen Fluoride. A study in rats suggests that hydrogen fluoride is absorbed primarily by the upper respiratory tract, and that removal of hydrogen fluoride from inhaled air by the upper respiratory tract approaches 100% for exposures that range from 30-176 mg fluoride/m^3 (Morris and Smith 1982). Furthermore, it is apparent that distribution to the blood is rapid. Immediately following 40 minutes of intermittent exposure, plasma fluoride concentrations correlated closely (correlation coefficient=0.98; p<0.01) with the concentration of hydrogen fluoride in the air passed through the surgically isolated upper respiratory tract. Plasma levels were not measured at time points less than 40 minutes.

Hydrogen Fluoride and Fluoride Dusts. The absorption in humans of inhaled hydrogen fluoride and fluoride dusts was demonstrated by Callings et

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al. (1952). Their study was conducted on two subjects exposed in the laboratory to an atmospheric concentration of 5.0 mg fluoride/m^3 as hydrogen fluoride during an 8-hour period. Absorption of fluoride was evaluated by monitoring urinary excretion of fluoride during and after exposure. Analysis of 2-hour serial urine samples showed a peak fluoride level 2-4 hours after cessation of exposure, which decreased to base levels within 12-16 hours after exposure. Similar results were obtained using the same protocol to measure urinary fluoride following exposure to air containing 5.0 mg fluoride/m^3 as rock phosphate dust (Collings et al. 1951). Another study reported clinical observations of employees in the production of phosphate rock and triple superphosphate (Rye 1961). Three employees were exposed to airborne fluoride (2-4 ppm) composed of approximately 60% dust and 40% hydrogen fluoride gas. Within 2-3 hours after exposure began, urinary fluoride levels increased from 0.5 to 4.0 mg/L and peaked 10 hours (7-8 mg/L) following cessation of exposure. None of the subjects had prior occupational exposure to fluoride. Although these studies demonstrate absorption of fluoride, none measure the extent of fluoride absorption.

The data presented above show that the fluoride ion, as hydrogen fluoride in fluoride-containing dusts, is absorbed by humans and animals following acute inhalation exposure. The degree of absorption in humans has not been determined. However, the demonstration that virtually 100% of airborne hydrogen fluoride is deposited in the upper respiratory tract of rats, combined with the appearance of fluoride in the urine of humans within at least 2 hours and in the plasma of rats at least 40 minutes following initiation of exposure, indicates that both forms of fluoride are rapidly and completely absorbed by humans by this route. This conclusion is confirmed by data presented in case reports of systemic effects following inhalation (combined with dermal) exposure to hydrogen fluoride/hydrofluoric acid, as discussed in, Sections 2.2.1 and 2.2.3.

Furthermore, although the data presented concern only acute exposures, it is expected that virtually complete absorption would also be observed during long-term exposure to low levels of fluoride in the air.

2.3.1.2 Oral Exposure

Data exist on absorption following oral exposure of humans and animals to fluoride as sodium fluoride, calcium fluoride, and in bone meal. Data on absorption rates exist only for sodium fluoride.

Fluoride. Ingested dietary fluoride is readily absorbed from the gastrointestinal tract as the undissociated HF molecule by passive absorption (Whitford and Pashley 1984). Since the neutral undissociated inconsistent molecule can penetrate cell membranes and be absorbed much better than the fluoride ion, decreasing the stomach pH increases absorption. The absorption of soluble fluoride in humans is rapid and extensive (97%) (Carlson et al. 1960a;Ekstrand et al. 1977b, 1983; McClure et al. 1945) with maximum plasma fluoride

concentrations attained as early as within 30 minutes following exposure (Ekstrand et al. 1977b).

Absorption of ingested fluoride has been investigated in humans in a number of studies. In a study by Carlson et al. (1960a), oral administration of 1 mg fluoride (as sodium fluoride containing ^{18}F) in 250 mL water resulted in a maximum plasma fluoride concentration of 0.13-0.17 mg/L within 60 minutes. At 150 minutes following exposure, ^{18}F was no longer detected in the stomach. In another study, the plasma fluoride concentration after oral administration of 4.5-10 mg fluoride as sodium fluoride tablets or gelatin capsules to eight subjects peaked within 30 minutes of administration (Ekstrand et al. 1977b). Similar observations were reported in children receiving 0.5 mg fluoride as sodium fluoride tablets in water (Ekstrand et al. 1983). Gastrointestinal absorption of fluoride in five men receiving a diet supplemented with sodium fluoride and calcium fluoride in water and food, and bone meal and cryolite in food was determined over a 5-day period (McClure et al. 1945). Fecal excretion data indicated that sodium fluoride in food and water, and calcium fluoride in water were extensively absorbed, while fluoride in bone meal, cryolite, and calcium fluoride in food were not as completely absorbed. About 13%-16% of the ingested fluoride was in the feces for the well-absorbed species, while 30%-56% of the ingested dose of the poorly-absorbedspecies appeared in the feces. As described below in Section 2.3.4.2, more recent data indicate that a smaller percent of a sodium fluoride dose appears in the feces than was reported here.

However, additional factors can affect absorption. The absorption of fluoride as calcium fluoride is increased when the material is given with meals (Trautner and Einwag 1987). The suggested explanation was that increased residence time in the upper gastrointestinal tract increases absorption. Fluoride is more completely absorbed from liquids than from solid foods (McClure et al. 1945; Trautner and Siebert 1986). Concurrent ingestion of other salts can increase or decrease absorption. Ingestion of 1320 mg calcium/day as calcium carbonate reduced the absorption of fluoride (30 mg/day as sodium fluoride, or 0.42 mg fluoride/kg/day) by 22% (Jowsey and Riggs 1978). This result could be due either to inhibition of absorption by calcium, such as due to the insolubility of calcium fluoride, or due to the alkalizing effect of the carbonate. Magnesium (Spencer et al. 1978b) and aluminum antacids (Spencer et al. 1980a, 1980b) decreased absorption in humans. In Sprague-Dawley rats, calcium and magnesium decreased absorption, while phosphate and sulfate increased absorption (Stookey et al. 1964; Weddle and Muhler 1954). Aluminum also decreased absorption in Sprague-Dawley rats (Weddle and Muhler 1954). The effects of salts on fluoride absorption is discussed further in Section 2.8.

Absorbed fluoride is likely to be passed on to the developing human fetus. Placental accumulation of fluoride in humans has been demonstrated following consumption of drinking water containing 0.55 ppm fluoride (Gedalia et al. 1961). Furthermore, the fluoride concentration in the placenta

(0.15 ppm) was higher than that in maternal blood (0.09 ppm). Fluoride measurements from maternal uterine vessels and umbilical blood at caesarean section revealed no difference between maternal and fetal levels (Armstrong et al. 1970). However, a partial placental barrier may exist at high maternal fluoride levels (Gedalia 1970). The use of fluoride supplements markedly increased placental fluoride levels, while fluoride levels in fetal blood remained almost constant. Placental transfer of fluoride to the developing fetus has been demonstrated in rats (Theuer et al. 1971). A high dietary level of fluoride (10 mg fluoride/kg/day) administered to pregnant rats as sodium fluoride resulted in significantly higher fluoride levels in fetuses than in the placenta.

Soluble fluorides are also rapidly and extensively absorbed from the gastrointestinal tract of animals. Rats were administered 0.2 mg fluoride (0.57 mg/kg/day) as sodium fluoride in solution, and absorption was monitored at time points up *to* 90 minutes. Half of the ,dose was absorbed with 30 minutes and 86% of the dose was absorbed within 90 minutes (Zipkin and Likins 1957). Oral administration of radiolabeled fluoride (0.08 mg fluoride/kg) to male rats resulted in 89%-90% absorption after 8-10 hours (Ericsson 1958).

In summary, existing data indicate that all common forms of inorganic fluoride are rapidly and extensively absorbed by humans. However, there are differences in the extent of absorption between different forms of fluoride and between fluoride in solution and fluoride incorporated in food, and the presence of other ions can affect absorption. The highest degree of absorption (virtually 100%) is seen with aqueous solutions of sodium fluoride. Evidence from humans and animals indicates that absorption begins quickly following ingestion, with studies in animals showing absorption beginning as early as 30 minutes following exposure. Furthermore, the absorbed fluoride is passed to the human fetus during pregnancy.

Most of the existing studies examine acute absorption of fluoride, and there is no indication that absorption of fluoride would be less extensive following low-level, long-term exposure. In the absence of such data, it is expected that absorption would be virtually complete following chronic oral exposure to low levels of most soluble forms of fluoride.

2.3.1.3 Dennal Exposure

Data exist on dermal absorption of hydrofluoric acid in humans and animals, and limited quantitative rate data are available in animals.

Fluorine. Systemic effects have been observed following whole-body exposure to fluorine (Keplinger and Suissa 1968; Stokinger 1949). However, these effects are likely to be due to inhalation exposure, rather than dermal exposure.

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Hydrofluoric Acid. Dermal application of hydrofluoric acid results in rapid penetration of the fluoride ion into the skin. Sufficiently large amounts cause necrosis of the soft tissue and decalcification and corrosion of bone in humans (Browne 1974; Dale 1951; Dibbell et al. 1970; Jones 1939; Klauder et al. 1955). Systemic fluoride poisoning has been reported following accidental dermal exposure to anhydrous hydrogen fluoride (Buckingham 1988; Burke et al. 1973). Although the extent of the contribution of inhalation exposure in these cases is not known, the reports suggest that hydrogen fluoride is quickly absorbed into the body following dermal exposure. However, these studies did not provide useful information concerning the extent of fluoride absorption, or information on absorption of smaller doses.

Dermal absorption of hydrofluoric acid in albino mice of the d.d. strain was inferred in a study by Watanabe et al. (1975). Mice were painted with 0.02 mL of 50% hydrofluoric acid, and the residual acid was wiped off after 5 minutes. The mice were then injected intraperitoneally with [^{14}C]glucose and analyzed by whole body radiography. Radioactivity levels in the liver, renal cortex, lungs, and blood were elevated 30 minutes after injection. This suggests that fluoride was absorbed through the skin and interfered with the tissue distribution of glucose, No data were located on the extent of absorption of fluoride in animals exposed dermally to hydrofluoric acid.

These studies indicate that fluoride as hydrofluoric acid is absorbed through the skin in humans and animals. However, the degree of absorption is not known, nor is it known whether other forms of fluoride would be absorbed, and to what extent. Furthermore, it is expected that the relationship between duration or concentration and degree of absorption would be affected by the corrosive action of hydrofluoric acid. Therefore, prediction of the extent of absorption following exposure to a low concentration of hydrofluoric acid cannot be made based on the existing data.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

Fluorine. No data were located regarding the distribution of fluoride following the inhalation exposure of humans to fluorine. In rats exposed to 25 mg/m^3 fluorine for about 5 hours/day, 6 days/week for 21 days, markedly elevated fluoride levels were observed in teeth and bone, the only tissues that were analyzed (Stokinger 1949). Tooth fluoride levels were about 14 times the levels in controls and fluoride levels in the femur were about 6 times those in the controls. Similar concentration-related increases in bone and tooth fluoride levels were observed at the lower concentrations (3 and 0.8 mg/m^3.

Hydrogen Fluoride. No data were located regarding the distribution of fluoride in humans following exposure to only hydrogen fluoride. Evidence from studies in animals supports the inference from occupational studies of

exposure to hydrogen fluoride and fluoride dust that fluoride is distributed to the rest of the body when inhaled. Duration- and concentration-related increases in tooth and bone fluoride levels were reported in the rat following exposure to 7 or 24 mg/m^3 for 6 hours/day, 6 days/week for up to 30 days (Stokinger 1949). Fluoride levels in new bone were up to twice the levels in old bone. The distribution of the fluoride ion was studied in the tissues of rabbits, a guinea pig, and a monkey exposed to hydrogen fluoride at various concentrations (1.5-1,050 mg/m^3) and exposure times (Machle and Scott 1935). The observation period ranged from 9 to 14 months. As might be expected, based on the following discussion of human occupational exposure to fluoride compounds, the fluoride ion accumulated chiefly in the skeleton of all three species.

Several studies in animals have demonstrated that fluoride is widely available through the blood, although actual concentrations in tissues other than blood have, for the most part, not been reported. For example, whole body exposure of male rats to levels ranging from 11 to 116 mg fluoride/m^3 as hydrogen fluoride for 6 hours resulted in a dose-dependentincrease in lung and plasma fluoride concentrations (Morris and Smith 1983). In another study, rats exposed to 84 mg fluoride/m^3 as hydrogen fluoride by whole body exposure had significantly elevated levels of fluoride in plasma and lungs 6 hours post-exposure (Morris and Smith 1983).

Intermittent high level exposures may result in greater accumulation of fluoride in bones and teeth than continuous exposure. Daily exposure of rats to airborne concentrations of 8 mg hydrogen fluoride/m^3 for a total of 124 hours resulted in a fluoride content of pooled teeth and bone 1.5-1.8 times the fluoride content of similarly pooled teeth and bones in a group exposed to the same concentration on alternate days for a total of 62 hours (Stokinger et al. 1950). If exposure durations were simply additive the ratio between fluoride concentrations in teeth and bone at the two durations would be expected to be 2.0, rather than 1.5-1.8.

Hydrogen Fluoride and Fluoride Dusts. Limited information was located on the distribution of inhaled fluoride in humans. However, reports of skeletal fluorosis (Chan-Yeung et al. 1983b; Czerwinski et al. 1988; Kaltreider et al. 1972) and elevated bone fluoride levels (Baud et al. 1978; Boivin et al. 1988) after occupational exposure to hydrogen fluoride and fluoride dusts indicate that fluoride is distributed to bone and accumulates there.

Fluoride deposition in bone occurs mainly in regions undergoing active ossification or calcification. If the source of fluoride exposure has been removed, fluoride levels in bone decrease as the bone undergoes remodelling. Areas of fluoride deposition during high-level exposure are distinguished by highly elevated fluoride levels even after the average fluoride level of the bone has returned to normal (Baud et al. 1978).

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Studies located indicate that the fluoride ion is distributed rapidly in the bloodstream following inhalation exposure. Evidence in humans and animals indicates that fluoride may be preferentially distributed to bones and teeth following inhalation exposure.

2.3.2.2 Oral Exposure

Fluoride. Ingested soluble fluoride is rapidly absorbed and distributed in humans. Epigastric counts were monitored by Carlson et al. (1960a) in subjects who consumed sodium fluoride containing ^{18}F in water (250 mL at 1 mg/L). Two-and-a-half hours after dosing, the remaining epigastric (abdominal) counts were attributable to fluoride in the spine. Counts in contracted biceps declined 50 minutes after ingestion and were undetectable after approximately 4 hours. In contrast, counts in the femur declined only 15% from their peak value (at 50 minutes) after 4 hours.

Teeth and bone readily take up fluoride following oral exposure (Machle and Largent 1943; McClure and Likins 1951; Suttie et al. 1958). While the rate of fluoride uptake in human teeth may decrease with age (Jackson and Weidmann 1959), it is apparent that the total fluoride content of teeth and bone increases throughout life, and that the amount deposited is dependent on the exposure concentration. A linear relationship was observed between subject age and fluoride concentration in bone ash of lifetime residents of an area with a drinking water supply containing 0.06 ppm fluoride, indicating that bone fluoride levels increase with duration of exposure (Smith et al. 1953). A linear relationship was also observed between the concentration of fluoride in drinking water (ranging from 0.1 ppm to 4 ppm) and the concentration in bone at autopsy in adult humans who had ingested the drinking water (Zipkin et al. 1958). Average fluoride levels in the iliac crest bone ash in people with drinking water fluoride levels of ≤0.3,1, and 4 ppm were 700, 2,300, and 6,900 ppm, respectively.

Long-term retention and accumulation of fluoride are primarily confined to calcified tissue in humans (Wagner et al. 1958). Soft tissue concentrations of fluoride do rise transiently following ingestion of fluoride (Carlson et al. 1960b; Hein et al. 1956). Examination of autopsy samples from 23 individuals who had lived in an area where drinking water contained l-4 ppm fluoride revealed no significant accumulation of fluoride in the heart, liver, lung, kidney, or spleen (Smith et al. 1960). Fluoride concentration in the aorta did increase with age; this was probably associated with increased calcification of the aorta with age. Kidney fluoride levels can be much greater than the levels in plasma (Whitford and Taves 1973).

Fluoride is redistributed as it is released during bone remodelling. The short-term kinetics of this process was investigated in humans by supplementing a diet of 4.4 mg fluoride/day with 9.1 mg fluoride/day as sodium fluoride for 32 days (Spencer et al. 1975b). Urinary fluoride excretion was elevated during the period of sodium fluoride supplementation, but dropped

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rapidly after it was removed. Urinary excretion returned to the presupplemented levels within 12 days. Only 9.1% of the retained fluoride was excreted during this period. .The progressive decrease over many years of bone fluoride concentrations of skeletal fluorosis patients who have been removed from the source of exposure indicates that there is a second, slower phase of fluoride redistribution (Boivin et al. 1988). Limited data suggest that this phase reduces fluoride levels by one-half in 20 years (Baud et al. 1978). This slower phase may correspond to remodelling of the trabecular bone (WHO 1984).

A limited number of studies were located that determined the distribution of fluoride in animal tissues following oral exposure. For example, in a lamb sacrificed 2 hours after a one-time ingestion of sodium fluoride containing ^{18}F, the absorbed fluoride was found to be widely distributed in the blood, bile, muscle, spleen, pancreas, liver, lymph node, and skeleton (Perkinson et al. 1955). These results are consistent with a short half-life in soft tissues.

In a study of rats exposed to 0.1% sodium fluoride in their diet for up to 113 days, analysis of fluoride content in the bone at various intervals revealed rapid uptake of the fluoride into bone (Suttie and Phillips 1959). However, final fluoride levels in bone were inversely correlated with the initial ages of the rats, suggesting that the rate of fluoride uptake decreases with age.

Evidence from one animal study indicates that fluoride deposits in bone are released as the bone undergoes normal absorption and redeposition (Guo et al. 1988). Weanling rats were exposed to high levels of fluoride (50 mg fluoride/L) in drinking water for 3 weeks to establish a baseline fluoride level in bone. Fluoride levels in bone were determined following exposure to a low-fluoride diet or a low-calcium, low-fluoride diet. Comparison of control fluoride-treated rats to those fed low calcium diets (which accelerates bone resorption and deposition) demonstrated that approximately 40% of the fluoride mobilized during bone resorption is not redeposited in the skeleton (Guo et al. 1988). About 30% of the bone fluoride was lost in a 4 week period. Presumably, the fluoride that is not redeposited is excreted. The high level of fluoride loading in the bone make it difficult to compare this study with results from studies in humans.

Fluoride accumulates at least temporarily in the soft tissues of dairy cows; however, differences between the bovine and human digestive systems preclude firm conclusions based on this information alone. Soft tissue concentrations of fluoride were measured in 20 dairy cows exposed to 0-50 ppm (equivalent to 1.4 mg/kg/day) fluoride as sodium fluoride in the feed for 5.5 years (Suttie et al. 1958). Cows exposed to 50 ppm fluoride had residues of fluoride mainly in the pancreas (4.2 ppm), kidney (19.3 ppm), and whole blood (0.67 ppm). As in humans, bone-fluoride concentration corresponded to the amount of fluoride ingested.

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Existing literature in humans indicates that continuous fluoride exposure results in a build-up of fluoride levels in bone and teeth. Furthermore, fluoride levels in bone are related directly to the level of steady state intake. With the exception of the aorta (Smith et al. 1960) and kidney (Whitford and Taves 1973), there is no evidence of accumulation or retention of fluoride in soft tissues in humans. Upon cessation of exposure, fluoride levels in bone are expected to decrease slowly; however, the time period over which this would occur in humans is not known.

2.3.2.3 Dermal Exposure

No information was located in humans or animals regarding the distribution of fluorine, hydrogen fluoride, or fluoride following dermal absorption.

2.3.2.4 Other Routes of Exposure

Based on the results of a five-compartment computer model, Charkes et al. (1978) calculated that about 60% of intravenously administered fluoride is taken up by bone and the half-time for this uptake is about 13 minutes.

Perkinson et al. (1955) found initial rates of removal of fluoride from sheep and cow blood to be 41%/minute and 32%/minute of the intravenously administered dose, respectively. These data suggest a rapid distribution of fluoride and corroborate findings reported by other routes of administration.

Fluoride distribution in rats was examined during and after continuous intravenous infusion of radiolabeled sodium fluoride at varying chemical dose rates for 3 hours (Knaus et al. 1976). Blood, kidneys, and lungs contained the highest fluoride concentrations at doses up to 3.6 mg fluoride/kg/hour, but at 6 mg/kg/hour the fluoride content of the liver, spleen, and hollow organs increased sharply, indicating that the dose exceeded the amount readily processed by the excretory mechanisms of the body. In rat pups injected intraperitoneally with 0.1 μg fluoride/g body weight as sodium fluoride solution, significant increases in the fluoride content occurred in the developing enamel and bone (Bawden et al. 1987). Thus, regardless of the route of administration, some fluoride is deposited in teeth, bone, and soft tissues of animals, and some is excreted in the urine, sweat and saliva.

2.3.3 Metabolism

Fluoride is believed to replace the hydroxyl ion (OH-) and possibly the bicarbonate ion (HCO_3^-) associated with hydroxyapatite--a mineral phase during formation of bone (McCann and Bullock 1957; Neuman et al. 1950). The resultant material is fluorapatite. Once absorbed, a portion of the fluoride is deposited in the skeleton, and the remainder is excreted in the urine, sweat, saliva, and feces within 24 hours (Dinman et al. 1976a, 1976b; McClure et al. 1945). Thus, skeletal sequestration and renal excretion are the two

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major means by which the body prevents circulation of toxic amounts of fluoride ion (Hodge 1961). Urinary excretion is markedly decreased in the presence of diminished renal function (Kono et al. 1984).

The fluoride ion carried in human blood serum exists in two forms, namely as an inorganic ion F and in combination with an organic molecule (Halton et al. 1984). The toxicological significance, if any, of the latter form is unknown. A portion of the circulating inorganic fluoride acts as an enzyme inhibitor because it forms metal-fluoride-phosphate complexes that interfere with the activity of those enzymes requiring a metal ion cofactor. In addition, fluoride may interact directly with the enzyme or the substrate. It is a general inhibitor of the energy production system of the cell (i.e., glycolytic processes and oxidative phosphorylation enzymes responsible for forming ATP) (Najjar 1948; Slater and Bonner 1952). Although much is known about enzyme inhibition by fluoride, the human health significance remains to be determined.

In rats exposed to 84 mg fluoride/m^3 as hydrogen fluoride by whole body exposure an average of 90% of recovered fluorine was nonionized (Morris and Smith 1983). This observation indicates that most of the fluorine in the plasma F-fraction of fluoride-exposed animals is in the form of nonionizable fluorine.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

Fluorine. No data were located regarding excretion of fluoride following human inhalation exposure to fluorine. Urinary fluoride levels were increased in dogs and rabbits exposed to levels as low as 0.8 mg/m^3 for 5-6 hours/day, 6 days/week for 35 days (Stokinger 1949). No quantitative data were reported at this level, but urinary fluoride levels in rabbits exposed to 3 mg/m^3 were 1.5 times normal. No further details were reported.

Hydrogen Fluoride. Studies in humans indicate that fluoride absorbed from inhaled hydrogen fluoride over an 8-hour work shift is excreted even during exposure, with urinary excretion peaking approximately 2-4 hours after cessation of exposure (about 10 hours following beginning of exposure) (Collings et al. 1951; Rye 1961). These studies have been discussed in Section 2.3.1.

Overnight urinary fluoride excretion in dogs and rabbits exposed to 7 mg/m^3 hydrogen fluoride for 6 hours/day, 6 days/week for 30 days was about 1.5 times that of controls (Stokinger 1949). No further details were reported.

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2.3.4.2 Oral Exposure

Fluoride. The principal route of excretion of ingested fluoride is via the urine as demonstrated in a variety of species. In general, urine accounts for about 50%-70% of the fluoride intake and feces accounts for 5%-10% (Machle and Largent 1943; Spencer et al. 1970). Estimates of total excretion range from about 50% (Spencer et al. 1970) to about 100% (McClure et al. 1945). These varying estimates lead to widely varying estimates of the amount of fluoride that is stored in the body. At least part of the discrepancy is due to excretion in sweat. Because excretion in sweat is rarely measured, data on the total amount of ingested fluoride that is excreted are often underestimates. About 1% of fluoride intake is excreted into saliva (Carlson et al. 1960a), although since saliva is swallowed, this amount does not enter mass balance calculations. In species other than man, there is little published information relating ingested fluoride concentrations and urine fluoride concentrations over prolonged periods.

There is a striking linear relationship between the concentration of fluoride in drinking water and in the urine of humans exposed continuously to fluoride. However, plasma fluoride levels are reflected better by the urinary fluoride excretion rate than by the concentration of fluoride in the urine (Ekstrand and Ehrnebo 1983). Large amounts of fluoride were excreted for prolonged periods by persons who lived for many years in areas with high fluoride water levels and who subsequently moved to areas with low fluoride levels (Likins et al. 1962). Individuals who had been chronically exposed to a drinking water supply containing 1 mg fluoride/L (1 ppm) and then received a single 5 mg dose of fluoride as sodium fluoride began excreting increased amounts of fluoride in their urine less than 2 hours following exposure (Zipkin and Leone 1957). Total 24-hour fluoride intake was estimated at 8.1 mg. Within 3 hours, 20% (1.6 mg fluoride) of the fluoride was excreted in the urine; 54% (4.4 mg) was excreted in the urine within 24 hours. By 9 hours after the fluoride bolus, the urinary fluoride excretion rate had almost returned to the pre-exposure rate of about 0.1 mg/hr. In persons not occupationally exposed to fluoride and not using water containing added fluoride, fecal elimination is usually less than 0.2 mg/day (NAS 1971a).

Urinary fluoride excretion generally corresponds to 50%-70% fluoride intake, depending on a number of factors (Machle and Largent 1943; Spencer et al. 1970). In one study, baseline fluoride balance was determined by monitoring fluoride in diet and water, and measuring excretion in urine and feces in 10 people for four 6-week periods (Spencer et al. 1970). Perspiration was not monitored. Average fluoride intake was 4.4 mg/day, of which an average of 1.8 mg/day (41%) was retained (range 1.6-2.2 mg/day). An average of 51% of the intake was excreted in urine, and 6.6% was excreted in feces. The diet was then supplemented with 9 mg fluoride/day as sodium fluoride for 30 days, and monitored as before. Average urinary and fecal excretion as a percent of intake were comparable to the levels found in the baseline study (54% and 6.4%, respectively). However, the ranges were larger

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during the increased fluoride intake. During supplementation, intake exceed excretion by an average of 5.4 mg/day (39% of intake). After the sodium fluoride supplementation was removed, retention of ingested fluoride dropped to an average of 32% as stored fluoride was cleared from the body. In human subjects consuming 6 mg fluoride daily in the diet (equivalent to 0.09 w/k/day), about half of the absorbed fluoride was excreted in the urine (Machle and Largent 1943). Of 10 subjects with endemic fluorosis who ingested 8-18 mg fluoride/day, the fluoride balance ranged from an excess excretion of 30% to excretion that was 40% less than intake (Jolly 1976). In another study, total fluoride intake was monitored in a healthy male subject who consumed his normal diet, and was found to be about 0.5 mg/day (Machle et al. 1942). Fluoride excretion in feces and urine were monitored and determined to be within 5% of intake. This study is limited by the use of only one subject.

Using radiolabeled fluoride, Carlson et al. (1960a) demonstrated that 51% and 63% of the fluoride filtered by the kidney was reabsorbed in two human subjects, respectively. The inefficiency of the human kidney in reabsorbing filtered fluoride results in the rapid urinary excretion of fluoride. Fluoride excretion is decreased in acidic urine, probably due to reabsorption of nondissociated HF (Ekstrand et al. 1980b). The renal fluoride clearance rate is lower in children than in adults (Spak et al. 1985). Although this study was conducted in children with suspected kidney disease or suspected renal dysfunction, the conclusion was reached based on children with normal glomerular filtration rates. Urinary fluoride concentration is markedly lower in children than in adults, and increases with age from ages one to six (Gedalia 1958). These studies indicate that children store more fluoride than adults do, due to high uptake in developing bones.

Sweat can account for a significant percentage of fluoride elimination. Subjects who ingested 3.7 mg fluoride in one day, of which 3 mg were from naturally fluoridated water or water to which sodium fluoride had been added, excreted about 19% of the ingested fluoride in sweat under comfortable conditions (McClure et al. 1945). Under hot-moist conditions, the excretion in sweat increased to 42%. Although water ingestion increased, the provided drinking water was low fluoride, so fluoride retention decreased. In the only other study located where fluoride in sweat was measured, up to 50% of fluoride excretion under hot conditions was in sweat. Both studies were compromised by the small number of subjects.

Limited data were located on excretion of ingested fluoride in animals. The data support the observations in humans that fluoride is rapidly excreted in urine. This was demonstrated by Chen et al. (1956), who measured renal clearance of fluoride in female dogs. In dogs receiving drinking water containing fluoride at 1 ppm, the renal fluoride clearance was 2.7 ml/minute, and the fluoride:chloride clearance ratio was 19:1.

Evidence from studies in humans and animals demonstrates that excretion of ingested fluoride occurs primarily in the urine, and to a lesser extent in

the feces, sweat, and saliva. This excretion is rapid, occurring over a period of hours (McClure et al. 1945; Spencer et al. 1970). As discussed previously, a portion of the absorbed fluoride is sequestered in bone. Continued secondary excretion of this pool of fluoride is expected based on animal studies. It is also expected that this excretion would occur in the urine.

2.3.4.3 Dermal Exposure

No studies were located regarding excretion of fluorine, hydrogen fluoride, or fluoride in humans or animals following dermal exposure. However, in the absence of evidence to the contrary, it is expected that dermally absorbed fluoride would be sequestered in bone and excreted in urine in a manner similar to that observed following oral or inhalation exposure.

2.4 RELEVANCE TO PUBLIC HEALTH

This section discusses the public health effects of fluorine, hydrogen fluoride, and fluoride. Where data exist for more than one of these compounds for a specific effect, the data will be discussed separately by chemical.

Fluorine. Limited data exist on the toxicity of fluorine, but similar effects have been observed in humans and animals. Fluorine exposure occurs only by inhalation or dermal exposure to the fluorine gas, and is most likely to occur as occupational exposure. Because fluorine is highly reactive, exposure at a hazardous waste site is likely to happen only if someone comes in direct contact with material leaking from a pressurized container. Fluorine can be lethal because of its highly corrosive nature.

Hydrogen Fluoride. Hydrogen fluoride (and the form as dissolved in water, hydrofluoric acid) produces effects in humans and animals similar to those produced by fluorine. The main health concern regarding hydrofluoric acid is from occupational exposure. Because hydrofluoric acid reacts rapidly to form fluoride salts, exposure to hydrofluoric acid at a hazardous waste site is likely to happen only if someone comes in direct contact with material leaking from a drum. Hydrofluoric acid can be lethal due both to its highly corrosive nature and the propensity of the fluoride ion to be rapidly absorbed and cause cardiac arrhythmias.

Fluoride. Exposure to fluoride at hazardous waste sites could result from contamination of groundwater by fluoride salts or hydrogen fluoride. The main health concern regarding sodium fluoride is likely to be from chronic oral exposure in drinking water. Acute oral exposure to very large doses of sodium fluoride as a result of accidental or intentional poisoning can produce gastrointestinal effects and death at high doses, but the dosage in such cases is often difficult to estimate. One study reported that a dose of about 16 mg/kg body weight to a child was lethal (Eichler et al. 1982). Chronic exposure to fluoride can result in mottling of teeth and skeletal fluorosis.

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The severity of mottling increases with fluoride dose and ranges from almost invisible opaque white spots to teeth with brown spots and pitting. Chronic exposure to fluoride in drinking water at doses above 2 ppm during development of the deciduous and permanent teeth, coupled with additional fluoride exposure from food and dental products, can result in visible mottling. Recent studies have found small white spots in about 20% of the children exposed to water containing 1 ppm fluoride; <l% may have brown spots (DHHS 1991). Mild dental fluorosis is considered a cosmetic effect; it is not necessarily a precursor to skeletal fluorosis, but may be the most sensitive clinical indicator of overexposure of children to fluoride. Due to the deposition of significant amounts of fluoride in bone, the primary target system for intermediate and chronic exposures of both humans and several animal species is the skeletal system. Recent epidemiological studies suggest that elderly women and men in communities with fluoridated water may have an elevated risk of hip fractures (Cooper et al. 1991; Danielson et al. 1992; Jacobsen et al. 1990; Sowers et al. 1991). The estimated safe and adequate dietary intake of fluoride is 1.5-4.0 mg/day for adults and 2.5 mg/day for children (NRC 1989).

An MRL of 0.05 mg/kg/day was calculated for chronic oral exposure based on a LOARL of 0.48 mg/kg/day for increased nonvertebral fracture rate in osteoporotic women (Riggs et al. 1990). No MRLs were derived for intermediate or acute oral exposure to fluoride, or inhalation exposure to fluoride for any exposure duration or system category. This is because the human exposure data are not well quantified with respect to individuals and the animal data do not provide reliable NOAELs or LOAELs. For the same reasons, no MRLs have been derived for inhalation or oral exposure to fluorine or hydrogen fluoride for any exposure duration or system category. Furthermore, the animal data providing reliable NOAELs and LOAELs for inhalation exposure to fluorine or hydrogen fluoride are based on exposures of one hour or less. No MRLs have been derived for acute, intermediate, or chronic duration dermal exposure to fluorides or hydrofluoric acid because appropriate MRL methodology has not been developed.

In response to public health concerns raised by equivocal findings of carcinogenicity in male rats in a chronic oral NTP sodium fluoride study (discussed below), the U.S. Department of Health and Human Services assembled a committee of scientists to evaluate the risks and benefits of oral exposure to fluoride (DHHS 1991). The report concluded that:

> "Extensive studies over the past 50 years have established that individuals whose drinking water is fluoridated show a reduction in dental caries. Although the comparative degree of measurable benefit has been reduced recently as other fluoride sources have become available in nonfluoridated areas, the benefits of water fluoridation are still clearly evident. The health and economic benefits of water fluoridation accrue to individuals of all ages and socioeconomic groups, especially to poor children."

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The policy recommendations offered by the report include:

"The U.S. Public Health Service should continue to recommend the use of
fluoride to prevent dental caries."

"The U.S. Public Health Service should continue to support optimal
fluoridation of drinking water. Currently, the optimal level for water
fluoridation is between 0.7-1.2 parts per million, depending on mean
daily air temperature for a geographic area."

"The U.S. Public Health Service should sponsor a scientific conference
to recommend both the optimal level of total fluoride from all sources
combined (including drinking water) and the appropriate usage of fluoride
containing dental products in order to achieve the benefits of reduced
dental caries and to minimize the occurrence of dental fluorosis."

"In accordance with prudent health practice of using no more than the
amount necessary to achieve a desired effect, health professionals and
the public should avoid excessive and inappropriate fluoride exposure."

"The U.S. Food and Drug Administration should review the labeling
required for toothpaste and other fluoride containing products to ensure
that the public has adequate knowledge to make informed decisions about
their use, especially for young children (those under six years of
age)."

"Communities with high natural fluoride levels in the public drinking
water supply should comply with EPA regulations as mandated by the Safe
Drinking Water Act. The current primary and secondary maximum
contaminant levels are 4 and 2 parts per million, respectively."

Death. Animal data show that acute-duration (Keplinger and Suissa 1968;
Stokinger 1949) or intermediate-duration (Stokinger 1949) exposure to fluorine
can cause death due to its caustic effects on the respiratory tract. The
lethal concentration depends on the exposure duration. Although no data regarding lethal
effects of fluorine on humans were located, such effects would
be expected based on the chemical properties of fluorine and its observed
irritating effects on humans (Keplinger and Suissa 1968). There is some
animal data indicating that pre-exposure to low fluorine concentrations may
provide some resistance to the lethal effects of fluorine (Keplinger 1969).

Dermal exposure to hydrofluoric acid combined with inhalation of
hydrofluoric acid fumes can be fatal due to pulmonary edema or cardiac
arrhythmias (Kleinfeld 1965; Tepperman 1980). Dermal exposure only to
hydrofluoric acid can cause death due to cardiac arrhythmias (Mayer and Gross
1985; Mullett et al. 1987). The amount of hydrofluoric acid needed to produce
death is dependent on the strength of the acid, the percentage of the body
exposed, and the length of the exposure. Oral exposure to small amounts of
hydrofluoric acid can cause death or severe injury (corrosion of the
gastrointestinal tract, cardiovascular effects) (Menchel and Dunn 1984).

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Animal data support these results, but variations in the levels of inhalation exposure to hydrofluoric acid resulting in death in animal studies preclude the determination of levels that would cause death in humans (Rosenholtz et al. 1963; Wohlslagel et al. 1976).

Human data indicate that at high doses, ingestion of sodium fluoride can be fatal due to respiratory arrest or cardiac arrest. The certainly lethal dose has been estimated at 32-64 mg fluoride/kg body weight (Hodge and Smith 1965). However, ingestion of less than one gram (14 mg/kg) has produced cases of severe poisoning (Bell 1936; Greenwood 1940). Although precise levels can not be established, clinical case studies and anecdotal reports indicate that drinking water levels of fluoride as low as approximately 40 ppm (and probably lower) cause nausea, vomiting, and diarrhea in humans. At higher levels these symptoms and others may become severe enough to warrant hospitalization. It is difficult to predict a level of fluoride in drinking water that will result in death, because in most cases the ingested dose will be quickly ejected (vomited), so that most of the dose exits without being absorbed into the body. It is also difficult to predict the maximal volume of water that could be ingested before nausea and vomiting would occur. Animal data provide supporting evidence for the lethal effects of sodium fluoride following acute oral exposure.

The amounts of fluorine, hydrogen fluoride, and fluoride found at waste sites vary; each site should be evaluated on a case-by-case basis. However, since hydrogen fluoride reacts rapidly with salts present in the soil and is readily neutralized in dilute solutions, the public would be exposed to hydrogen fluoride only by direct contact with material leaking from a waste drum or its fumes. Instead, hydrogen fluoride at a waste site would normally result in exposure to the fluoride ion.

Systemic Effects

Respiratory Effects. Inhalation exposure to fluorine has been observed to cause respiratory tract irritation in people, and dyspnea and lung congestion in animals (Keplinger and Suissa 1968). Pulmonary and nasal irritation has also been reported following repeated exposures for about 30 days (Stokinger 1949). However, human (Lyon 1962) and animal (Keplinger 1969) data suggest that pre-exposure to lower levels can reduce the respiratory effects.

Acute lethal inhalation exposure of humans to hydrofluoric acid has produced pulmonary edema (Chan et al. 1987; Chela et al. 1989; Tepperman 1980). Animal data provide supporting evidence for the respiratory effects of hydrofluoric acid observed in humans. Acute inhalation exposure to hydrofluoric acid has produced nasal irritation, respiratory distress, pulmonary congestion, and intraalveolar edema in rats, rabbits, and guinea pigs (Haskell Laboratory 1988; Rosenholtz et al. 1963; Wohlslagel et al. 1976). Similarly, intermediate-duration inhalation exposure caused pulmonary hemorrhage and signs of inflammation (Machle and Kitzmiller 1935; Stokinger

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1949). The respiratory effects of hydrofluoric acid are attributed to its highly corrosive properties.

Workers chronically exposed by inhalation to hydrogen fluoride and cryolite dust have had decreased respiratory function measurements (Chan-Yeung et al. 1983a).

Pulmonary edema observed after oral exposure to lethal quantities of sodium fluoride (Sharkey and Simpson 1933) may be due to aspiration of the gastric contents.

Cardiovascular Effects. Cardiovascular effects of systemic fluoride poisoning are attributed to a combination of hypocalcemia and hyperkalemia due to the poisoning of potassium pumps. Serum potassium levels are often not measured in cases of fluoride poisoning, so much of the evidence for the effect on potassium pumps comes from in vitro experiments and from the results of intravenous administration of fluoride. However, hyperkalemia and cardiac effects have been reproduced by the oral administration of sodium fluoride to dogs (Baltazar et al. 1980). In dogs administered sodium fluoride intravenously, the onset of ventricular fibrillation was better temporally associated with increased serum potassium levels than with decreased calcium levels. Exposure of erythrocytes to 10 mM sodium fluoride in vitro for 5 minutes produced a 50% increase in extracellular potassium levels measured 12 hours later (McIvor et al. 1987). This suggests that a mechanism of fluoride toxicity involves hyperkalemia induced by poisoning of the potassium Pump.

Severe cardiovascular effects have occurred in humans after dermal or oral exposure at or approaching lethal levels of hydrofluoric acid or sodium fluoride (Abukurah et al. 1972; Buckingham 1988; Mayer and Gross 1985). As described above, cardiac arrhythmias in humans are thought to be caused by a combination of hypocalcemia and hyperkalemia. No data are available on whether inhalation exposure only to hydrogen fluoride could cause cardiovascular effects, although there is one inconclusive report of myocardial necrosis and congestion in rabbits exposed to hydrogen fluoride for an unstated period (Machle et al. 1934). If it does, inhalation of large amounts of hydrogen fluoride in contaminated air would be necessary to pose risk of severe cardiovascular effects. However, these effects could occur, for example, from dermal exposure to hydrofluoric acid found around hazardous waste sites, depending on the strength of the acid solution.

Data from sodium fluoride poisonings support the mechanisms and effects described above with hydrogen fluoride (Baltazar et al. 1980). Ingestion of large amounts of fluoride in contaminated water would be necessary to pose a risk of severe cardiovascular effects.

Gastrointestinal Effects. Data were not located regarding gastrointestinal effects following ingestion of hydrofluoric acid, but due to

its recognized caustic properties, it is assumed that severe gastrointestinal effects (e.g., tissue necrosis) would result. There is an unconfirmed report of nausea and gastrointestinal distress following inhalation exposure in humans (Waldbott 1979), suggesting that this effect is not route-specific. Ingestion of hydrofluoric acid clearly poses a risk of gastrointestinal effects to humans. However, ingestion of hydrogen fluoride would probably only occur in the event of a child eating material around a leaking waste container in which hydrogen fluoride was discarded. Otherwise, hydrogen fluoride contamination would lead to ingestion of fluoride in drinking water.

Symptoms of nausea, vomiting, and gastric discomfort have been reported in humans following the ingestion of varying levels of sodium fluoride (Hoffman et al. 1980; Rao et al. 1969). These effects are due to the combination of sodium fluoride with gastric hydrochloric acid, which forms hydrofluoric acid. Supporting evidence for gastrointestinal effects comes from observations of marked stomach irritation (ulcers, necrosis) in F344/N rats administered high levels of fluoride for 6 months (NTP 1990). Effects have also been observed in sheep (Kessabi et al. 1985) and rabbits (Susheela and Das 1988), but these animals may not be appropriate models for gastrointestinal effects in humans. Ingestion of sodium fluoride clearly poses a risk of gastrointestinal effects to humans, although this risk is dose-dependent. Large-scale contamination of a water supply could raise water fluoride levels high enough to cause gastrointestinal effects.

Hematological Effects. No studies on hematological effects of fluorine in humans were located. However, no effects were seen on complete blood cell count parameters in rats at exposure levels up to 50% of the LC_{50} (Keplinger and Suissa 1968).

No signs of hematological effects as measured by routine blood counts were seen in a large cohort of aluminum workers exposed to total fluoride levels below 2.5 mg/m^3 (Chan-Yeung et al. 1983b). However, anemia was observed in an outdated occupational cohort study (Moller and Gudjonsson 1932). No white cell changes were noted.

Very limited animal data indicate that hematological effects may result from exposure to fluoride (Hillman et al. 1979; Pillai et al. 1988; Susheela and Jain 1983). Decreased red blood cell counts were reported in three species (cows, rabbits, and mice) after gavage or oral dosing, suggesting that there may be some risk for fluoride-induced anemia, depending on level of exposure. White blood cells were increased in mice and decreased in rabbits following oral fluoride exposure (Pillai et al. 1988; Susheela and Jain 1983).

There is no evidence that the hematopoietic system is a primary target for fluoride, but the quality of most relevant studies is very low. Hematologic changes could result from high exposures to hydrogen fluoride or fluoride.

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Musculoskeletal Effects. The one intermediate-duration study of inhalation exposure to fluorine found increased fluoride levels in bones and teeth in rats exposed to fluorine for 21 days (Stokinger 1949). This suggests that prolonged exposure to elevated fluorine levels could cause skeletal fluorosis in humans. However, the high reactivity of fluorine means that prolonged exposure at a hazardous waste site is highly unlikely.

Exposure to total fluoride levels of about 2.5 mg/m^3 as hydrogen fluoride or fluoride dusts for several years can cause skeletal fluorosis (Chan-Yeung et al. 1983b; Kaltreider et al. 1972). This effect is supported by the increased tooth and bone fluoride levels found following inhalation exposure of rats to hydrogen fluoride for 30 days (Stokinger 1949). Such exposure is not likely to occur at a hazardous waste site.

Human and animal data clearly indicate that fluoride accumulates in the teeth and skeleton. Levels of up to about 1 ppm in drinking water have been associated with a decreased number of dental cavities (DHHS 1991). Early studies found fluoride treatment for Type I osteoporosis to be effective (Pak et al. 1989). However, there is some evidence that although fluoride increases bone mass, the newly formed bone may have reduced elasticity. A carefully controlled four-year prospective study of postmenopausal osteoporotic women receiving chronic oral fluoride doses of 34 mg/day found an increase in non-vertebral fractures (Riggs et al. 1990). An chronic oral MRL of 0.05 mg/kg/day was calculated from this study based on a LOAEL of 0.48 mg/kg/day. Ecologic epidemiological studies have also found suggestive evidence that elderly women and men in communities with fluoridated water may have an increased hip fracture rate (Cooper et al. 1991; Danielson et al. 1992; Jacobsen et al. 1990; Sowers et al. 1991). Skeletal fluorosis may result when humans are exposed to chronic, high levels of fluoride; severe cases are generally associated with malnourishment (Pandit et al. 1940). Tooth mottling occurs in children orally exposed to fluoride during development of their deciduous and/or permanent teeth (Heifetz et al. 1988; Mann et al. 1987). Animal data for similar exposure conditions support the human evidence (Uslu 1983). Therefore, adults may be at risk of developing skeletal fluorosis and children may be at risk of developing mottled teeth if exposed to fluoride for long periods of time. Fluoride causes mottled enamel by interfering with osteocytes and impairing the work of ameloblast cells. There is no clear evidence that dental fluorosis necessarily progresses to skeletal fluorosis.

Hepatic Effects. No studies were located regarding hepatic effects of fluorine inhalation by humans. Liver histopathology findings in Swiss-Webster mice exposed to fluorine included coagulation necrosis, periportal hemorrhages, and diffuse cloudy swelling (Keplinger and Suissa 1968). It is not known whether such effects would be found in humans. Exposure of humans to fluorine at hazardous waste sites is unlikely.

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No changes in levels of total bilirubin, SGOT, or alkaline phosphatase were observed in workers exposed at levels below 2.5 mg/m^3 (Chan-Yeung et al. 1983b).

No oral human data and very limited oral animal data exist on hepatic effects following fluoride exposure. Mice administered 0.95 mg fluoride/kg/day in drinking water for >7 days had pale, granular hepatocytes (Greenberg 1982a). Enlarged liver cells were seen in B6C3F$_1$ mice that died after receiving 26 or 52 mg fluoride/kg/day as sodium fluoride in drinking water for 6 months (NTP 1990). No liver effects were seen in F344/N rats administered up to 19 mg/kg/day under the same regimen, or in rats or mice given total fluoride (amount added to water plus endogenous fluoride in the food) doses up to 4.5 mg/kg/day (rats) or 9.1 mg/kg/day (mice). Liver congestion was observed in sheep given a single intragastric dose of fluoride as low as 9.5 mg fluoride/kg and mild serum increases of liver enzymes were found in sheep administered 38 mg fluoride/kg (Kessabi et al. 1985). However, the different gastrointestinal systems of ruminants make it difficult to determine the relevance of this study to human health.

The hepatotoxicity of fluoride in humans cannot be fully assessed at this time.

Renal Effects. No studies were located regarding renal effects of fluorine inhalation by humans. Kidney histopathology findings in Swiss-Webster mice exposed to fluorine included focal areas of coagulation necrosis in the renal cortex and focal areas of lymphocyte infiltration in the cortex and medulla (Keplinger and Suissa 1968). It is not known whether such effects would be found in humans. Exposure of humans to fluorine at hazardous waste sites is unlikely.

Severe renal effects (anuria, elevated serum creatinine levels) were reported in workers splashed in the face with hydrofluoric acid (Braun et al. 1984). Concurrent dermal and inhalation exposure in these cases is likely. The weight of evidence from studies of workers who were chronically exposed to hydrogen fluoride and fluoride dusts indicates that no renal toxicity is seen at the exposure levels that have existed for the past 20 years. Toxicity was measured using renal function tests and assays for albuminuria (Chan-Yeung et al. 1983b; Dinman et al. 1976a; Kaltreider et al. 1972).

Very limited human and animal data exist on the renal effects of fluoride (Kessabi et al. 1985; Lantz et al. 1987; NTP 1990). However, studies indicate that persons with impaired renal clearance may be unusually susceptible to the effects of fluoride (Juncos and Donadio 1972; Spencer et al. 1980a). While there is evidence that fecal excretion of fluoride may be increased in those with lower renal clearance, it is not clear whether the increase is enough to compensate for decreased renal excretion. A case report of one man may provide evidence that renal insufficiency may be linked to high intake of fluoride (up to 0.48 mg/kg/day) (Lantz et al. 1987). Acute

nephrosis was considered the main cause of death in mice administered 26 or 52 mg fluoride/kg/day as sodium fluoride in water (NTP 1990). No renal pathology has been seen in animals maintained for long periods on high levels of fluoride in drinking water.

Weanling Sprague-Dawley rats injected intraperitoneally with 14 or 22 mg fluoride/kg as sodium fluoride exhibited altered renal function and histopathological changes (Daston et al. 1985). Profound diuresis and decreased urinary osmolality were observed, particularly in the first 48 hours posttreatment. Glucosuria and hematuria also were observed, as were renal tubular lesions. Only minor changes were observed in suckling rats injected under the same protocol. The control rats were untreated, rather than being injected with a control substance, so the changes could be due to the high level of salts injected.

Since elevated fluoride levels appear in the kidney (Whitford and Taves 1973) and the kidney plays a major role in fluoride excretion (Machle and Largent 1943; Spencer et al. 1970), one might expect the kidney to be a target organ for fluoride toxicity. Renal pathology definitively and specifically attributed to exposure to fluorine, hydrogen fluoride, or fluoride has never been reported in healthy humans. However, the animal data suggest that fluorine or fluoride at near lethal levels may damage the kidney (Keplinger and Suissa 1968; NTP 1990). Pre-existing renal impairment affects the excretion of fluoride.

Dermal/Ocular Effects. Results from human exposure show that fluorine is highly irritating to the eyes and nose (Keplinger and Suissa 1968). Similar results have been obtained from animal experiments (Keplinger and Suissa 1968). However, exposure of humans to fluorine at hazardous waste sites is unlikely.

Dermal and ocular effects have occurred in humans exposed to hydrofluoric acid dermally and to atmospheric hydrogen fluoride. Because hydrofluoric acid is caustic and the fluoride ion is rapidly absorbed through the skin, severe burns, tissue damage, and even death can result. The severity of the damage depends on a number of factors (e.g., the length of exposure, the strength of the acid solution, the percentage of the body exposed, and the treatment utilized) (Buckingham 1988; Chela et al. 1989; Hatai et al. 1986). Animal data support the human data and indicate that hydrofluoric acid produces severe skin and ocular damage, which if severe enough is not reversible. Cleanup workers and members of the public who come in direct contact with material leaking from waste drums could be at risk of the effects of dermal exposure to hydrofluoric acid.

Immunological Effects. Very limited human and animal data were located to evaluate the immunological effects of fluoride. The American Academy of Allergy has reviewed a number of cases of human fluoride exposure and

concluded that none of the health effects seen with oral exposure to fluoride constitute an immune reaction. One animal study reported reduced antibody titers in rabbits administered 10 mg fluoride/kg/day for 9 months. No other doses were tested, and no mechanism proposed. The existing database does not permit a complete assessment of the immunotoxic potential of fluoride.

Neurological Effects. There are few data on the neurological effects of fluorine, hydrogen fluoride, or fluoride exposure in humans or animals. Dogs exposed to lethal concentrations of fluorine for up to 30 days had seizures before they died (Stokinger 1949).

Inhaled hydrogen fluoride produced a significant increase in the sensitivity to light at a dose of 0.03 mg/m^3 for periods of 5-40 minutes, but the effect may have been due to irritation of mucous membranes by hydrofluoric acid. These data are supported by animal data that showed that rats continuously exposed for an intermediate duration to a low concentration exhibit histological changes in the synapses of nerve cells (Sadilova et al. 1965). There are some data suggesting that,nonspecific neurological effects (headaches, paresthesia, vertigo) occasionally occur in cases of fluorosis (Waldbott 1979).

The nervous system in humans does not appear to be a major target for fluorides, although convulsions and paresthesia have been observed in cases of acute fluoride poisoning. Hypocalcemia produced when fluoride binds with serum calcium may be a cause of these effects.

Developmental Toxicity. Fluoride crosses the placenta in limited amounts and is found in fetal and placental tissue (Gedalia et al. 1961; Theuer et al. 1971). An epidemiological study of water fluoridation found no increase in birth defects in fluoridated areas (Erickson et al. 1976). No conventional well-designed studies regarding developmental toxicity of fluoride were located, and the existing animal literature contains conflicting results. Very limited animal data were located on the developmental effects of fluoride. One reproductive study indicated no change in the number of abnormal pups born to rats orally exposed to 21 mg fluoride/kg/day (Ream et al. 1983). Calves exposed to fluoride deposited on forage from aluminum plant emissions were stunted (Maylin and Krook 1982) and lame (Krook and Maylin 1979). The relevance to public health cannot be ascertained at this time.

Reproductive Toxicity. No data exist on the reproductive effects of fluoride in humans. Studies that reported an increased incidence of Down's syndrome in areas of high fluoridation have been refuted on reanalysis with consideration of place of residence and age of mother (Berry 1958; Erickson et al. 1976; Needleman et al. 1974). No data on reproductive effects in occupational cohorts exposed to higher-than-background levels of fluoride were found. Data from animal studies are inconsistent. One animal study found that the reproductive system of male rats is a target for fluorides (Araibi et

al. 1989), while others found that fluoride does not accumulate in the male reproductive system (Skare et al. 1986) and does not cause sperm abnormalities (Dunipace et al. 1989; Li et al. 1987a). There is some evidence that fluoride at toxic levels can lower fertility in mice (Messer et al. 1973). Adverse reproductive effects of fluoride have also been observed in cows (Van Rensburg and de Vos 1966), dogs (Shellenberg et al. 1990), and various avian species (Guenter and Hahn 1986; Hoffman et al. 1985). At this time, reproductive toxicity resulting from exposure to fluoride cannot be fully assessed or ruled out due to inadequacies in the database, including conflicting findings.

A decline in litter production was observed in mice fed a low-fluoride diet (Messer et al. 1973). This result was not replicated by Tao and Suttie (1976). These authors suggested that the results of Messer et al. (1973) were due to an iron deficiency that was partially corrected by fluoride enhancing absorption of trace elements.

Genotoxicity. In general, positive genotoxicity findings occurred at doses that are highly toxic to cells and whole animals. Lower doses were generally negative for genotoxicity. Tables 2-7 and 2-8 present the results of the most recent assays. All in vitro experiments discussed in this section were conducted with sodium fluoride or potassium fluoride. All doses are given as amount of fluoride.

A dose-related increase in chromosome aberrations was observed in bone marrow cells isolated from Swiss mice that received intraperitoneal doses of sodium fluoride (4.5, 9.1, and 18 mg fluoride/kg) for 6, 24, or 48 hours (Pati and Bhunya 1987). Increases were seen in the frequency of chromatid breaks, fragments, and exchanges. The study authors included gaps in their analysis, but the biological significance of gaps is unclear. However, the dose-related increase in aberration frequency remained when gaps were not included. There was no indication of the number of animals used, or whether the slides were coded prior to analysis. This study also reported increased levels of micronucleated polychromatic erythrocytes at all intraperitoneal doses tested (i.e., ≥4.5mg fluoride/kg).

While sodium fluoride has been shown to be mutagenic in both mouse lymphoma L5178Y cells and human lymphoblasts without S9 activation, the lowest significant doses of chemical were 400 μg/mL for the mouse cells and 440 μg/mL for the human cells (Caspary et al. 1988). Potassium fluoride was positive for mutagenic activity at the thymidine kinase locus in mouse lymphoma cells both with and without S9 activation. Approximately three-fold increases in mutant frequency were observed for concentrations in the 500-700 μg/mL range that reduced the relative total growth to approximately 10% (Caspary et al. 1987).

As part of the NTP cancer assay, the induction of chromosome aberrations by sodium fluoride in Chinese hamster ovary cells was assayed by two

TABLE 2-7. Genotoxicity of Sodium Fluoride In Vitro

Species (test system)	End point	Results With activation	Results Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium	Histidine reversion	-	-	Martin et al. 1979
	Histidine reversion	-	-	Tong et al. 1988
	Histidine reversion	-	-	NTP 1990
Eucaryotic organisms:				
Human lymphocytes	Chromosome aberrations	No data	+	Albanese 1987
	Sister chromatid exchange	No data	-	Tong et al. 1988
	Chromosome aberrations	No data	-	Thomson et al. 1985
	Sister chromatid exchange	No data	-	Thomson et al. 1985
Human fibroblasts	Unscheduled DNA synthesis	No data	+	Tsutsui et al. 1984c
Syrian hamster embryo cell	Chromosome aberrations	No data	+	Tsutsui et al. 1984b
	Sister chromatid exchange	No data	+	Tsutsui et al. 1984b
	Unscheduled DNA synthesis	No data	+	Tsutsui et al. 1984b
	Morphological transformation	No data	+	Tsutsui et al. 1984b
Mouse lymphoma	Reversion assays	No data	(+)	Cole et al. 1986
	Forward mutation	+	+	Caspary et al. 1987
	Forward mutation	+	+	Caspary et al. 1988
Chinese hamster ovary	Sister chromatid exchange	No data	-	Li et al. 1987b
	Chromosome aberrations	+	+	Aardema et al. 1989
	Chromosome aberrations	-	+	NTP 1990
	Sister chromatid exchange	No data	-	Tong et al. 1988
	Sister chromatid exchange	+	+	NTP 1990
Rat hepatocytes	DNA repair	No data	-	Tong et al. 1988
Rat liver epithelium	HGPRT mutation	No data	-	Tong et al. 1988
Human lymphoblasts	Thymidine kinase mutation	+	+	Caspary et al. 1988

- = negative result; + = positive result; (+) = weakly positive result; DNA = deoxyribonucleic acid; HGPRT = hypoxanthine guanine phosphoribosyl
transferase

Species (test system)	End point	Results	Reference	Form
Mammalian cells:				
Rat bone marrow	Chromosome aberrations	+	Voroshilin et al. 1975	HF
	Micronuclei	-	Albanese 1987	NaF
Rat testis	DNA strand breaks	-	Skare et al. 1986	NaF
Mouse (C57B1)	Dominant lethal	-	Voroshilin et al. 1975	HF
Mouse (Harlan Sprague-Dawley)	Sperm head abnormality	-	Li et al. 1987a	NaF
Mouse bone marrow and testis	Chromosome aberrations	-	Martin et al. 1979	NaF
Mouse bone marrow, intraperatoneal dose	Chromosome aberrations	+	Pati and Bhunya 1987	NaF
	Micronuclei	+	Pati and Bhunya 1987	NaF
	Sperm abnormality	+	Pati and Bhunya 1987	NaF
Mouse	Chromosome aberrations	-	Kram et al. 1978	NaF
	Sister chromatid exchange	-	Kram et al. 1978	NaF
Chinese hamster bone marrow	Sister chromatid exchange	-	Li et al. 1987b	NaF

+ = positive result; - = negative result; DNA = deoxyribonucleic acid; HF = hydrogen fluoride; NaF = sodium fluoride

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independent laboratories (NTP 1990). The study was well-designed, and slides were coded prior to analysis. An increased aberration frequency was reported by one laboratory at doses ≥182µg fluoride/ml. The type of aberrations was not reported. The second laboratory only tested doses up to 91 µg/mL, and did not see a positive effect. Increased levels of breaks and gaps were observed in Syrian hamster embryo cells exposed for 16 hours to 45 µg/mL fluoride (Tsutsui et al. 1984b). As noted earlier, the biological significance of gaps is questionable. There was no indication that slides were coded prior to analysis. Evidence of a clastogenic effect of sodium fluoride was also observed in Chinese hamster ovary (CHO) cells (Aardema et al. 1989). Sodium fluoride, at fluoride concentrations up to 57 µg/mL, did not produce chromosome aberrations in cultured human lymphocytes (Thomson et al. 1985). Another study reported increased chromosome aberrations at 9 and 18 µg fluoride/mL as sodium fluoride (Albanese 1987).

Tests for sister chromatid exchanges have been negative in much of the recent work on fluoride genotoxicity (Li et al. 1987b; Thomson et al. 1985; Tong et al. 1988). However, sister chromatid exchanges were increased at fluoride doses ≥31µg/mL in a well-conducted assay using coded slides (NTP 1990). Sodium fluoride inhibited cell cycle progression; a delayed harvest time was necessary in order to observe a positive result. Harvest time may not be able to fully account for the different results, since at least one of the recent assays with a negative result also used a delayed harvest time (Li et al. 1987b). In general, sister chromatid exchange assays are more sensitive but less informative than chromosomal aberration, unscheduled DNA synthesis, or DNA repair assays. The mechanism and ultimate significance of sister chromatid exchange formation is not yet understood. Sodium fluoride also induced unscheduled DNA synthesis in cultured human diploid fibroblasts (Tsutsui et al. 1984c).

Negative results have generally been obtained in the Salmonella typhimurium/mammalian microsome reverse mutation assay (Martin et al. 1979; NTP 1990; Tong et al. 1988). However, the validity of this assay for studying fluoride is questionable because the high concentration of chloride ions in the agar medium used in the assay may interfere with fluoride uptake.

While the genotoxic status of fluoride appears to be contested, a more generally-accepted mechanism for the effects of fluoride suggests that fluoride acts as a general "protein poison" at high doses, possibly inhibiting DNA repair enzymes (Caspary et al. 1987, 1988). This would be consistent with high-dose effects, delayed cell cycle kinetics, and an effect on DNA repair enzymes, all of which have been seen with doses of fluoride higher than 10 µg/mL. Alternative theories suggest that fluoride may hydrogen-bond with thymine in DNA, distorting the structure of the DNA strand. The mixed results of the genotoxicity studies indicate that further assessment of the effect of fluoride on enzymes in metabolic pathways may be warranted.

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Cancer. Although excess cancer rates have been reported in some occupational groups exposed to hydrogen fluoride and fluoride dusts, these studies were not controlled for the multiple substance exposures to which industrial workers are generally exposed (Andersen et al. 1982; Cecilioni 1972; Gibbs and Horowitz 1979; Milham 1979; Rockette and Arena 1983). An increase in the lung cancer rate was reported in cryolite workers, but comparison with the surrounding city rather than nationwide rates removed this effect (Grandjean et al. 1985). Because of these multiple exposures and the problems inherent in all occupational studies in identifying appropriate referent populations, only limited evidence from such studies is specifically relevant to the investigation of possible carcinogenic effects of long-term dermal exposure to hydrofluoric acid and inhalation exposure to hydrogen fluoride and/or fluoride dusts in human beings.

Cancer mortality rates in areas with low or high fluoride levels in drinking water have been compared in several studies (Griffith 1985; Hoover et al. 1976; Kinlen 1975; Oldham and Newell 1977). When these populations are compared with appropriate adjustments made for differences in demographic composition, degree of industrialization, and confounding exposures from other natural or man-made sources of fluoride, these studies provide no statistically significant evidence that an increased level of fluoride in water is associated with an increase in cancer mortality.

Animal data on the carcinogenicity of fluoride are limited. The results of the chronic oral sodium fluoride carcinogenicity study conducted in rats and mice by the NTP (Bucher et al. 1991; NTP 1990) have been reviewed and judged to show equivocal evidence of carcinogenicity in male rats of one strain (based on the dose-related presence of the rare bone cancer osteosarcoma), and no evidence of carcinogenicity in female rats and male and female mice. The NTP considers evidence of carcinogenic activity to be equivocal when the results show a marginal increase in neoplasms that may be chemically related. A number of factors influence the relevance of these studies to human health. As with most animal cancer studies, administered doses were much higher than those to which humans would be exposed. However, since fluoride accumulates in the bone over time, the fluoride levels in the high-dose male rats after a 2-year exposure was similar to the levels reported in people with a lifetime exposure to water with 4 ppm fluoride (Zipkin et al. 1958). Bone development also occurs over a larger proportion of the lifetime in rats than in humans. While ossification in humans is generally complete by 18 years of age, or less than a third of the human lifetime, ossification in rats is not complete until after the first year of life (half the life-span). Finally, the fluoride levels in the diet of the control animals meant that the controls ingested several times more fluoride on a mg/kg body weight basis than is ingested by people whose drinking water is fluoridated. While this could limit the study's sensitivity, no osteosarcomas were observed in the control group. Another cancer bioassay in rats (Maurer et al. 1990) found no evidence of carcinogenicity in male or female rats in a study of fluoride added to a semi-synthetic low-fluoride diet. Although the fluoride dose of

the controls was lower, the control animals still received more fluoride than do most people in fluoridated areas. Several limitations affect the strength of the conclusions from this study, including high mortality in treatment and control groups, evidence that the diet may have been inadequate, and possible inadequacies in the pathological examination.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to fluoride are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic,or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by fluoride are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

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2.5.1 Biomarkers Used to Identify and/or Quantify Exposure to Fluorine, Hydrogen Fluoride and Fluoride

There is extensive literature regarding fluoride levels in biological tissues such as urine, teeth, and bone as indices of exposure. Since it does not produce any metabolites, the fluoride ion itself is the measured indicator. The most commonly used medium for identifying fluoride exposure is urinary levels (Ekstrand et al. 1983). Several investigators have used this parameter to detect exposure to sodium fluoride through drinking water (Zipkin et al. 1956) or by ingestion (i.e., toothpaste or diet) (Ekstrand et al. 1983). Occupational exposure to hydrogen fluoride is also evaluated from urine fluoride levels (Yoshida et al. 1978).

Urinary fluoride levels are generally around ≤1mg/L when the water supply contains ≤1ppm fluoride (Schamschula et al. 1985; Venkateswarlu et al. 1971; Zipkin et al. 1956). Only one report was located of urinary fluoride levels following acute poisoning. Following dermal exposure to about 5 g hydrofluoric acid over 2.5% of the body surface (along with concomitant inhalation exposure), the urinary fluoride level in the first sample obtained 3.5 hours after the accident was 87.0 mg/L (Burke et al. 1973). It is difficult to determine urine levels that are associated with chronic effects such as skeletal fluorosis, because no studies that report urinary fluoride levels, accurate exposure levels, duration of exposure, and health effects were located. Probably the most complete study reports average urinary fluoride levels of 9 mg/L following inhalation exposure to 2.4-6.0 mg/m^3 for an unspecified period of time (Kaltreider et al. 1972). Marked evidence of fluorosis was seen in these workers. In another study (Dinman et al. 1976c), the average postshift urinary fluoride level after 3-5 working days was 5.7 mg/L (range, 2.7-10.4). No exposure levels were available, but they were reported to be lower than in the plant where urinary fluoride levels were 9 mg/L. In spite of 10-43 years of occupational exposure, no signs of skeletal fluorosis were seen. This study may provide urinary fluoride levels that are not associated with skeletal fluorosis, but any sensitive workers may have left such work and not been included in the study. These studies are describe in more detail in Section 2.2.1.2. Urinary fluoride levels up to 13.5 mg/L have been reported in areas of India where skeletal fluorosis due to high water fluoride levels (up to 16.2 ppm) is prevalent (Singh et al. 1963).

Other media that have been used to measure fluoride exposure include plasma (Ekstrand et al. 1983), saliva (Peterson et al. 1987), and tooth enamel (McClure and Likins 1951). Plasma fluoride is often employed as an indicator; however, it does not always show a clear correlation to fluoride exposure, even when measurements are conducted soon after exposure (Whitford and Williams 1986). The normal plasma fluoride level is about 0.01 mg/L (Ikenishi et al. 1988; NAS 1971a). A plasma fluoride level of 35.2 mg/L was measured in a case of fatal oral hydrofluoric acid poisoning (Manoguerra and Neuman 1986). No studies regarding normal serum fluoride levels were located, but a level of 2 mg/L was reported in a case of severe oral poisoning with 53 g fluoride as

sodium fluoride (Abukurah et al. 1972). Multiple episodes of ventricular fibrillation and tetany occurred, but the patient recovered following stomach lavage and treatment.

The biomarkers mentioned above can be used for acute exposure to fluoride. Concentrations can peak within 1 hour after exposure since fluoride is rapidly absorbed from all routes of exposure. Fluoride salts possess a peculiar "soapy-salty" taste that enables some individuals to recognize that they are consuming large quantities of fluoride. With chronic exposures, such as from drinking water containing fluoride, urinary fluoride levels initially increase, and then reach a constant level. In workers, post-shift urinary levels differ from pre-shift levels since fluoride exposure during the work day is absorbed rapidly into the body. However, these measurements may not always be useful for quantifying chronic exposure because fluoride can accumulate in bones (Carlson et al. 1960a). It may be retained in the skeletal tissues for a long period after the end of exposure, and later reenter circulating blood to be reabsorbed or excreted in urine. Furthermore, background tissue/fluid levels may affect these measurements since fluoride is prevalent in the environment from dietary sources. Calcium, which is a major element in the body, may interfere with biological fluoride measurements due to its ability to bind fluoride (Richards et al. 1982). This may prevent the quantitation of exposure, because plasma and urine fluoride levels may be unaffected. An important factor in biological fluid fluoride concentration is pH (Ekstrand et al. 1980a). When urine is alkaline, fluoride urine excretion increases and is followed by a decline in plasma fluoride.

Bone fluoride levels can be used to quantitate long term fluoride exposure (Boivin et al. 1988; Baud et al. 1978). However, this requires a bone biopsy, so bone fluoride levels are most frequently measured after clinical signs appear. As described in Section 2.2.2.2, the fluoride level found in bone varies between bones and increases with age. That section also describes fluoride levels in normal bone, and levels associated with various effects.

2.5.2 Biomarkers Used to Characterize Effects Caused by Fluorine, Hydrogen Fluoride, and Fluoride

Because soft tissues do not accumulate significant levels of fluoride over long periods of time, effects of chronic exposure to fluoride first appear in the musculoskeletal system. Chronic oral fluoride exposure can produce dental fluorosis (Duxbury et al. 1982), and higher levels of oral or inhalational exposure can lead to skeletal effects (Kaltreider et al. 1972; Leone et al. 1955). Dental fluorosis is characterized by mottling and erosion of the enamel. Children are particularly susceptible since their teeth are still developing. Thus, teeth mottling, staining, erosion, hypoplasia, and excessive wear are possible markers of effect for fluoride exposure (Walton 1988). In recent studies, about 22% of children exposed to 0.7-1.2 ppm fluoride in drinking water had very mild to mild dental fluorosis,

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characterized by small white spots on the teeth (DHHS 1991). Brown spots appeared on the teeth .of 7.6% of the children exposed to 2 ppm fluoride in water. In adults, skeletal changes may occur from prolonged exposure. Alteration in bone density or derangement of trabecular structure can be detected by radiographs, and can indicate fluoride toxicity. However, these are nonspecific changes and can be associated with other exposures. Other metals can sequester in the skeleton, and produce similar changes observed in radiographs. Exostosis, apposition of new bone, ossification of ligaments and tendon insertions, and metastatic aberrant growth of new bone appear to be much more specific and constant findings in fluorosis (Vischer et al. 1970). Skeletal fluorosis has been reported following inhalation exposure to 2.4-6.0 mg/m^3 for an unspecified duration (Kaltreider et al. 1972). As discussed in Section 2.2.2.2, nutritional status plays a large role in determining the oral fluoride exposure levels that lead to this effect. In the few cases of skeletal fluorosis in the United States for which doses are known, they are generally 15-20 mg/day for over 20 years (Bruns and Tytle 1988; Sauerbrunn et al. 1965).

No well-documented information was located regarding biomarkers of effect for fluoride, although there are studies in which cellular changes occurred after fluoride exposure. Increases in glucose or lipid metabolism have been reported in tissues after exposure to fluorides (Dousset et al. 1984; Shearer 1974; Watanabe et al. 1975). Changes in erythrocyte enzyme activities including enolase, pyruvate kinase, and ATPase were found in chronically exposed workers in conjunction with slightly increased fluoride levels in the body (Guminska and Sterkowicz 1975). These alterations may explain the decreased red blood cell counts observed in other studies (Hillman et al. 1979; Susheela and Jain 1983). However, none of these enzyme alterations are specific to fluoride exposure. No information is available regarding how long these effects last after the last exposure. The enzymatic effects were measured within a few hours of a single fluoride treatment, while the red blood cell effects were seen as a result of chronic exposure.

There is evidence that in patients with skeletal diseases the proportion of dialyzable and nondialyzable hydroxyproline peptides serves as an index of bone collagen turnover. A decreased proportion of nondialyzable hydroxyproline peptides in the urine of fluorosis patients indicates either a decreased rate of synthesis of new collagen or an increased utilization of newly formed collagen for matrix formation. This marker offers potential for an early, although nonspecific, indication of altered bone metabolism after long-term fluoride exposure (Anasuya and Narasinga Rao 1974). No information is available regarding how long this lasts after chronic exposure. Sudden hyperkalemia and hypocalcemia are effects seen with fluoride intoxication due to the marked potassium efflux from intact cells caused by fluoride (McIvor et al. 1985). These ionic shifts are the only serologic marker of effect that have been identified, and these changes are not unique to fluoride. They last for a few hours after exposure. Polydypsia and polyuria are also nonspecific markers of effect.

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2.6 INTERACTIONS WITH OTHER CHEMICALS

The absorption of fluoride from the gastrointestinal tract of humans and/or animals is affected by the presence of several minerals including calcium, magnesium, phosphorus, and aluminum (Rao 1984). These effects are discussed in Section 2.8. No reliable data on interactions that exacerbate negative effects of fluoride were located.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Existing data indicate that subsets of the population may be unusually susceptible to the toxic effects of fluoride and its compounds. These populations include the elderly, people with deficiencies of calcium, magnesium, and/or vitamin C, and people with cardiovascular and kidney problems.

Because fluoride is excreted through the kidney, people with renal insufficiency would have impaired renal clearance of fluoride (Juncos and Donadio 1972). Fluoride retention on a low-protein, low-calcium, and lowphosphorus diet was 65% in patients with chronic renal failure, compared with 20% in normal subjects (Spencer et al. 1980a). Serum creatinine levels were weakly correlated (r=0.35-0.59) with serum fluoride levels (Hanhijarvi 1982). People on kidney dialysis are particularly susceptible to the use of fluoridated water in the dialysis machine (Anderson et al. 1980). This is due to the decreased fluoride clearance combined with the intravenous exposure to large amounts of fluoride during dialysis. Impaired renal clearance of fluoride has also been found in people with diabetes mellitus and cardiac insufficiency (Hanhijarvi 1974). People over the age of 50 often have decreased renal fluoride clearance (Hanhijarvi 1974). This may be because of the decreased rate of accumulation of fluoride in bones or decreased renal function. This decreased clearance of fluoride may indicate that elderly people are more susceptible to fluoride toxicity.

Poor nutrition increases the incidence and severity of dental fluorosis (Murray and Wilson 1948; Pandit et al. 1940) and skeletal fluorosis (Pandit et al. 1940). Comparison of dietary adequacy, water fluoride levels, and the incidence of skeletal fluorosis in several villages in India suggested that vitamin C deficiency played a major role in the disease (Pandit et al. 1940). Calcium intake met minimum standards, although the source was grains and vegetables, rather than milk, and bioavailability was not determined. Because of the role of calcium in bone formation, calcium deficiency would be expected to increase susceptibility to effects of fluoride. No studies in humans supporting this hypothesis were located. Calcium deficiency was found to increase bone fluoride levels in a two-week study in rats (Guggenheim et al. 1976) but not in a 10-day study in monkeys (Reddy and Srikantia 1971). Guinea pigs administered fluoride and a low-protein diet had larger increases in bone fluoride than those given fluoride and a control diet (Parker et al. 1979). Bone changes in monkeys following fluoride treatment appear to be more marked

if the diet is deficient in protein or vitamin C, but the conclusions are not definitive because of incomplete controls and small sample size (Reddy and Srikantia 1971). Inadequate dietary levels of magnesium may affect the toxic effects of fluoride. Fluoride administered to magnesium-deficient dogs prevented soft-tissue calcification but not muscle weakness and convulsions (Chiemchaisri and Philips 1963). In rats, fluoride aggravated the hypomagnesemia condition, which produced convulsive seizures. The symptoms of magnesium deficiency are similar to those produced by fluoride toxicity. This may be because of a fluoride-induced increase in the uptake of magnesium from plasma into bone.

Some people with cardiovascular problems may be at increased risk of fluoride toxicity. Fluoride inhibits glycolysis by inhibiting enolase (Guminska and Sterkowicz 1975; Peters et al. 1964). It also inhibits energy metabolism through the tricarboxylic acid cycle by blocking the entry of pyruvate and fatty acids and by inhibiting succinic dehydrogenase (Slater and Bonner 1952).

There is evidence that daily doses of 34 mg fluoride (0.48 mg/kg/day) increases the risk of nonvertebral fractures in women with postmenopausal osteoporosis (Riggs et al. 1990). Postmenopausal women (Danielson et al. 1992; Sowers et al. 1991) and elderly men (Danielson et al. 1992) in fluoridated communities may also be at increased risk of fractures.

2.8 MITIGATION OF EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to fluorine, hydrogen fluoride, and fluoride. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to fluorine, hydrogen fluoride/hydrofluoric acid, or fluoride. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

In all cases of acute high-level exposure to fluorine, hydrogen fluoride/hydrofluoric acid, or fluoride, the focus of mitigation is to limit further absorption and to complex or remove the free fluoride ions from the blood while maintaining the proper electrolyte balances. The majority of relevant acute high-level exposure situations for which mitigation information is available involve dermal and/or inhalation exposure to hydrofluoric acid or gaseous hydrogen fluoride. Some information is also available regarding mitigation of chronic oral exposure to fluoride.

Fluorine. Inhalation exposure to fluorine is treated very similarly to inhalation exposure to hydrogen fluoride. The source of exposure is removed and water used to decontaminate the patient. The eyes are washed with saline if necessary, and magnesium oxide paste can be applied (Bronstein and Currance 1988; Stutz and Janusz 1988).

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Hydrogen Fluoride/Hydrofluoric Acid. In cases of dermal and inhalation exposure, the exposed persons are first removed from the source of exposure, and any particles or.excess liquids are removed by brushing or blotting (Bronstein and Currance 1988). Thorough irrigation with cold water or saline is then done to further limit absorption through exposed skin and eyes. Irrigation is followed by washing the affected skin with an alkaline soap and water (Bronstein and Currance 1988; Dibbell et al. 1970). Persistent pain is an indication that large amounts of free fluoride ions remain. In such cases, magnesium oxide paste is applied or the exposed skin is soaked in cold solutions of magnesium sulfate, calcium salts, or quaternary ammonium compounds (benzalkonium chloride, benzethonium) (Browne 1974; Goldfrank et al. 1990; Haddad and Winchester 1990). However, the evolving standard of treatment for mild to moderate burns involves massaging the affected area with a penetrating calcium gluconate gel, to avoid problems with magnesium oxide precipitating (Borak et al. 1991; Browne 1974; Goldfrank et al. 1990).

In cases of subungual invasion or moderate to severe burns in which there is immediate tissue damage, intradermal injections of calcium gluconate solution (Ellenhorn and Barceloux 1988; Goldfrank et al. 1990; Haddad and Winchester 1990), along with surgical debridement of the saturated skin (Buckingham 1988; Dibbell et al. 1970; Goldfrank et al. 1990) will limit the local and systemic toxic effects. However, intra-arterial infusions of calcium gluconate are often preferred to intradermal injections due to the ability of the infusions to deliver more calcium to the burn site, better distribution of calcium in the tissues, and the need for only a single injection, as opposed to an injection for every square centimeter of affected dermal tissue (Haddad and Winchester 1990). Additionally, in burns involving the hands, multiple intradermal injections pose the risk of elevating tissue pressures and forcing the removal of the nails (Ellenhorn and Barceloux 1988; Goldfrank et al. 1990). One source reports that calcium gluconate injection was successfully used in at least 96 cases without causing damage (Browne 1974). The therapeutic effects of calcium gluconate, magnesium acetate, and magnesium sulfate on hydrofluoric acid burns of shaved Sprague-Dawley rats were compared using intradermal and subcutaneous injection (Harris et al. 1981). Although this study found that injection of calcium gluconate, but not the magnesium compounds, was irritating in the absence of a burn, and the duration, depth, and area of lesions were reduced with the magnesium compounds compared with calcium gluconate, no reports were located of using intradermal injection of magnesium compounds in humans. It is not clear if this contradicts the results of Browne (1974), and if any difference is due to species differences. The presence of unbound fluoride ions indirectly results in nerve stimulation, and thus pain is the best indicator of when further treatment is required (Browne 1974; Dibbell et al. 1970). Therefore, anesthetics are not used, except in those cases of subungual exposure that require the removal of the nail (Browne 1974).

In cases of severe burns affecting large areas (>20%) of the body surface, the patient is monitored for signs of systemic fluoride poisoning,

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including hypocalcemia, hypomagnesemia, and hyperkalemia, which may cause life-threatening neuromuscular paralysis. In such cases, calcium and magnesium supplements, temporary cardiac pacing, and intravenous injections of calcium gluconate, diazepam, and lidocaine are used (Abukurah et al. 1972; Goldfrank et al. 1990; Haddad and Winchester 1990). Intravenous injection of sodium bicarbonate and dextrose/insulin, along with oral administration of sodium polystyrene sulfonate, which may slowly reduce the body burden of potassium, can counteract hyperkalemia (Haddad and Winchester 1990). Fluoride is rapidly excreted by the kidney. The excretion is increased by alkalinizing the urine using intravenous sodium bicarbonate; sodium bicarbonate also combats acidosis (Haddad and Winchester 1990). Hemodialysis is reserved for severe cases due to renal failure or severe hyperkalemia (Haddad and Winchester 1990; Morgan 1989). Strong diuretics such as furosemide or ethacrynic acid also help protect against renal failure and enhance fluoride excretion (Abukurah et al. 1972).

Fluoride. Ingested fluoride is rapidly absorbed from the gastrointestinal tract, but calcium and magnesium salts, antacids, and milk interfere with the absorption by binding the fluoride ion and removing the residual fluoride from the esophagus (Ellenhorn and Barceloux 1988; Goldfrank et al. 1990; Haddad and Winchester 1990; Morgan 1989). Gastric lavage with solutions of calcium gluconate, calcium carbonate, calcium lactate, calcium chloride, calcium hydroxide, calcium- or magnesium-based antacid, or aluminum hydroxide gel aid in decontaminating the gastrointestinal tract due to their action in precipitating the fluoride in the gut (Ellenhorn and Barceloux 1988; Haddad and Winchester 1990; Morgan 1989). No attempt is made to neutralize the acid with orally administered sodium bicarbonate, due to the resulting exothermic reaction (Bronstein and Currance 1988). Most authorities discourage emesis due to the formation of hydrofluoric acid in the stomach (Bronstein and Currance 1988; Haddad and Winchester 1990). As in cases of severe hydrofluoric acid burns, the patient's electrolyte balance and electrocardial signs are monitored for indications of acute fluoride poisoning, and calcium gluconate is administered intravenously if a large dose was ingested (Abukurah et al. 1972; Ellenhorn and Barceloux 1988; Haddad and Winchester 1990).

The major treatment strategies for long-term, low-level exposure to fluorides are removal of the source of exposure and administration of compounds that reduce intestinal absorption. Skeletal fluorosis has been reported to be partially reversed 8-15 years after the elevated exposure ended (Grandjean and Thomsen 1983). Sclerosis of the trabecular bone in ribs, vertebral bodies, and pelvis faded, but calcification of muscle insertions and ligaments was not altered. The absorption of fluoride from the gastrointestinal tract of humans and/or animals is affected by the presence of several minerals including calcium, magnesium, phosphorus, and aluminum (Rao 1984). With the exception of aluminum hydroxide, no studies were located regarding the therapeutic use of these materials in humans.

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Humans administered aluminum hydroxide (as antacid) had a significant increase in the fecal fluoride excretion and a decrease in the urinary excretion of fluoride Spencer and Lender 1979; Spencer et al. 1980a). These results can be explained by a reduction in gastrointestinal absorption of fluoride due to aluminum's ability to form fluoride complexes (Spencer et al. 1981). This effect also occurred in persons with chronic renal failure, suggesting antacids could be used to counteract adverse effects of fluoride in this population.

Calcium binds with fluoride after oral exposure, which reduces the bioavailability of fluoride. In humans, calcium and/or phosphorus administration (as bone meal, cryolite, or calcium fluoride) decreased the absorption of fluoride (Machle and Largent 1943; McClure et al. 1945). In another study, added calcium had only a limited effect on the intestinal absorption of fluoride in humans (Spencer et al. 1975c, 1980b). The discrepancy between these studies may be due to differences between the absorption of fluoride in calcium fluoride or in a form that must first be homogenized, and the absorption of fluoride in the presence of added calcium.

Plasma fluoride concentrations were higher in pigs fed calcium-deficient diets than in pigs fed diets with calcium (Richards et al. 1982). Administration of both calcium and phosphorus reduced the skeletal uptake of fluoride in rats compared to that following high calcium administration (McClure and Mitchell 1931).

Magnesium may decrease the intestinal absorption of fluoride because it tends to form slightly soluble complexes with fluoride (Kuhr et al. 1987). The results of human and animal studies investigating this interaction appear to differ. Several studies have found no significant effect from orally administered magnesium oxide on either fecal or urinary fluoride excretion in humans (Spencer et al. 1977a, 1977b, 1978a). Humans administered magnesium along with fluoride as therapy for osteoporosis had diminished joint pain and resorbed periarticular calcium phosphate deposits (Kuhr et al. 1987). Magnesium appeared to reduce the adverse effects of fluoride when it was used as a treatment for osteoporosis.

Simultaneous gavage administration of magnesium and fluoride reduced skeletal uptake of fluoride in rats (Stookey et al. 1964; Weddle and Muhler 1954). Administration of both magnesium and calcium reduced the deposition of fluoride in bones (Stookey et al. 1964). Another study in rats found that the level of dietary magnesium is a significant factor in the bioavailability of dietary fluoride (Cerklewski 1987). These differences between humans and animals may be attributed to the route of administration and/or age of the subjects.

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Techniques that increase bone turnover or bone resorption might be effective in reversing skeletal fluorosis. However, no information on such techniques were located.

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA-and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of fluorides is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of fluorides.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.9.1 Existing Information on Health Effects of Fluorine, Hydrogen Fluoride, and Fluoride

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to fluorine, hydrogen fluoride, and fluoride are summarized in Figures 2-4 through 2-6, respectively. The purpose of these figures is to illustrate the existing information concerning the health effects of fluorine, hydrogen fluoride, and fluoride. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information.

There are many case reports and epidemiological studies investigating the health effects of hydrogen fluoride in humans by the inhalation and dermal routes, and the health effects of fluoride compounds by the inhalation and oral routes. There are also limited data from experimental human exposure to fluorine. Most human studies of the health effects of oral exposure to fluoride are case reports of acute and chronic oral exposure to sodium fluoride, and human studies of the health effects of dermal exposure to fluorides are generally case reports of acute dermal exposure to hydrofluoric acid.

Human fatalities have resulted from both oral exposure to sodium fluoride and dermal exposure to hydrofluoric acid. Dermal exposure to hydrofluoric acid is often accompanied by inhalation of hydrofluoric acid

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FIGURE 2-4. Existing Information on Health Effects of Fluorine

HUMAN

ANIMAL

● Existing Studies

FIGURE 2-5.   Existing Information on Health Effects of Hydrogen Fluoride/Hydrofluoric Acid

HUMAN

ANIMAL
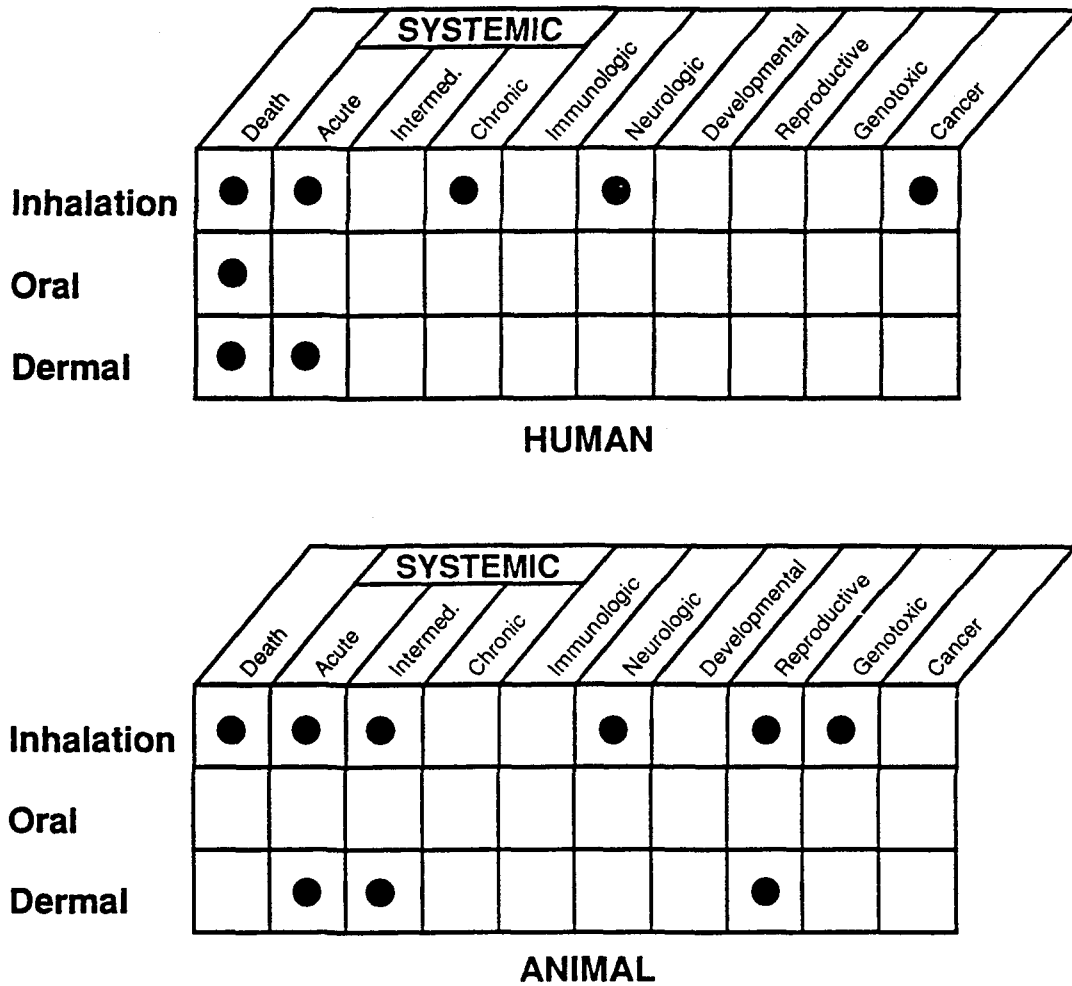
● Existing Studies

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FIGURE 2-6. Existing Information on Health Effects of Fluoride

HUMAN

ANIMAL

● Existing Studies

fumes. Human studies and case reports have investigated the effects of nonlethal oral doses of sodium fluoride, although only after acute exposure. These exposures have resulted in mostly gastrointestinal effects and consequences of hypocalcemia (e.g., nervous system and cardiovascular effects). Exposure to fluorine gas causes respiratory, ocular, and dermal irritation in humans after acute exposure. One study on chronic exposure to fluorine was located. Chronic human studies have generally examined health effects in workers exposed to hydrogen fluoride or fluoride-containing dusts by inhalation, and populations exposed to ionic fluoride through drinking water. These studies have investigated the relationship between fluoride and neurological and reproductive effects and cancer.

Studies conducted on animals have been fairly extensive, and have focused on the health effects following inhalation of hydrogen fluoride and oral exposure to fluoride. A few studies on inhalation exposure to fluorine also exist. Dermal studies in animals are limited to those investigating dermal and ocular effects from exposure to fluorine, hydrofluoric acid and sodium fluoride. A number of studies on the genotoxicity of fluoride were located.

2.9.2 Data Needs

The following section will discuss data needs by category and by chemical (fluorine, hydrogen fluoride, and fluoride). Although the toxicological data on fluorine are severely limited, such data are not needed, since fluorine is so reactive that human exposure at hazardous waste sites is unlikely.

Acute-Duration Exposure. Inhalation of fluorine can cause respiratory irritation, dyspnea, and death (Keplinger and Suissa 1968; Stokinger 1949). Inhalation of concentrated hydrofluoric acid fumes can cause pulmonary edema, hyperkalemia, hypocalcemia, and death (Chela et al. 1989; Kleinfeld 1965; Tepperman 1980). Acute dermal exposure to hydrofluoric acid will cause burns (Chela et al. 1989; Kleinfeld 1965; Mullett et al. 1987; Tepperman 1980). Gastrointestinal upset (Hoffman et al. 1980; Rao et al. 1969), cardiovascular disturbances, or death can result from accidental consumption of large amounts of sodium fluoride or other soluble fluoride salts (Eichler et al. 1982; Sharkey and Simpson 1933). The toxicity and pharmacokinetic data at the present time are not sufficient to derive acute duration MRLs for inhalation of fluorine or hydrogen fluoride or oral exposure to sodium fluoride because the exposure data in humans are not well quantified. Regarding acute oral toxicity, it should be mentioned that because the rat does not vomit, this would not be an appropriate model to use to determine levels of exposure that cause gastrointestinal distress. In addition, there is no way of determining if the animal is suffering from gastrointestinal discomfort. Further information concerning the levels of oral exposure to sodium fluoride, calcium fluoride, or hydrofluoric acid that cause acute effects in humans such as

gastrointestinal distress would be useful because there are populations surrounding hazardous waste sites that might be exposed to these forms of fluoride for brief periods.

Intermediate-Duration Exposure. Target organs for intermediate exposure of humans to fluorine, hydrogen fluoride or sodium fluoride are not known, although data from animal experiments provides some indication. Intermediateduration inhalation exposure to fluorine or hydrogen fluoride can cause respiratory effects in animals similar to those seen following acute exposure (Stokinger 1949). Bone and tooth fluoride levels were elevated, suggesting that these could also be target organs for intermediate exposure to fluorine or hydrogen fluoride. One might also expect that the musculoskeletal system may be a target of intermediate-duration oral exposure to fluoride. Studies in mice (Greenberg 1986; NTP 1990) suggest that the kidney may also be a
target of near-lethal fluoride levels, but there is no data from such high exposures in humans. The toxicity and pharmacokinetic data at the present time are not sufficient to derive MRLs or identify target organs for either inhalation or oral exposure because the exposure data in humans are not well quantified. Further information concerning the levels of oral exposure to sodium fluoride or calcium fluoride, and inhalation exposure to hydrogen fluoride that cause effects such as fluorosis in humans would be useful because there are populations surrounding hazardous waste sites that might be exposed to these forms of fluoride for intermediate duration's.

Chronic-Duration Exposure and Cancer. Small amounts of ionic fluoride given chronically in the drinking water are recognized as being beneficial to human teeth (DHHS 1991), but the mechanism of action is not well understood. Chronic exposure of children to excessive amounts of fluoride can result in mottled teeth (fluorosis) (Hodge and Smith 1972; Mann et al. 1987), but variations in methods of reporting dental fluorosis make it difficult to thoroughly compare studies. The development of a method for quantitating dental fluorosis that is sensitive, specific, reliable, and acceptable to the public would help in determining the fluoride doses leading to varying degrees of fluorosis. Epidemiological evidence exists that the incidence and severity of fluorosis has increased in the United States (DHHS 1991; Heifetz et al. 1988). Further examination of the etiology and trends in prevalence may be useful. Chronic inhalation exposure to high levels of hydrogen fluoride and fluoride dusts, or chronic oral exposure to high doses of fluoride can cause skeletal deformities and joint pain (Bruns and Tytle 1988; Goldman et al. 1971; Fisher et al. 1981; Kemp et al. 1942; Leone et al. 1955; Moller and Gudjonsson 1932; Pandit et al. 1940; Sauerbrunn et al. 1965; Singh et al. 1963). Some data from case studies are available regarding nutritional states that exacerbate fluorosis (Kemp et al. 1932; Pandit et al. 1940). Epidemiological studies addressing the effect of nutrition on the prevalence and severity of dental and skeletal fluorosis may be useful. Recent studies indicate that fluoride may increase the rate of hip fractures in elderly men and women (Danielson et al. 1992; Sowers et al. 1991), particularly women with

osteoporosis (Riggs et al. 1990). A chronic oral MRL was derived for fluoride based on increased risk of nonvertebral fractures. Analytical epidemiological studies of the association, if any, between bone fractures and factors such as fluoride intake, fluoride blood levels, diet, and body levels of nutrients such as calcium may be useful. Target organs other than bones and teeth for chronic exposure to fluoride for humans are not known. There is some evidence of hepatic (Greenberg 1982a) and renal (Daston et al. 1985; Kessabi et al. 1985) effects of fluoride in animals, but minimal information regarding possible effects in humans. Additional studies specifically addressing effects on these systems may be useful, especially since people with renal dysfunction are sensitive to fluoride.

The osteosarcoma rate in males living in fluoridated areas has increased markedly in recent years, but thorough statistical analyses concluded that the effect is not due to fluoridation (Hoover et al. 1991). Nonetheless, analytical epidemiology studies to determine the risk factors for osteosarcoma may be useful. Such studies should include analysis of fluoride exposure and bone levels of fluoride. Case-control studies of people with osteosarcoma could be particularly useful. The NTP oral carcinogenicity study for sodium fluoride concluded that there is equivocal evidence that fluoride is a carcinogen in male rats, but not in female rats or mice of either gender (NTP 1990). Higher doses may have been attainable in female rats and mice of both genders. Another rat carcinogenicity study found no evidence that fluoride is a carcinogen (Maurer et al. 1990), but was limited in several different aspects. Additional animal cancer bioassays may be useful in addressing this issue. Additional systemic effects may be understood after further investigation. The toxicity and pharmacokinetic data at the present time are not sufficient to derive chronic MRLs for inhalation of fluorine, hydrogen fluoride or other fluoride compounds, because the exposure data in humans are not well quantified with respect to individuals. Further information concerning the levels of oral exposure to sodium fluoride or calcium fluoride, and inhalation exposure to hydrogen fluoride that cause effects in humans such as fluorosis would be useful because there are populations surrounding hazardous waste sites that might be exposed chronically to these forms of fluoride.

The existing data do not demonstrate that fluoride is a human carcinogen. The epidemiological studies indicate that a carcinogenic effect of fluoride is not likely to be a health risk. However, evidence of genotoxicity suggests that further mechanistic data would be useful (Caspary et al. 1987; Caspary et al. 1988; NTP 1990).

Genotoxicity. There is a significant database on the genotoxicity of fluoride compounds in several species and several cell types. However, the results from well-characterized systems are much more limited and additional well-designed experiments would be useful in resolving contradictory data.

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The results have been inconsistent in many instances, but a consensus is developing that at toxic levels (greater than 10 µg/mL, and usually seen at greater than 40 µg/mL), there may be a general inhibition of enzymes, including the DNA polymerases (Caspary et al. 1987, 1988). While sodium fluoride may not be directly reactive with DNA, biochemical studies would be useful for establishing a mechanism for the cellular toxicity seen at high doses of fluoride compounds.

Reproductive Toxicity. No definitive data were located regarding reproductive effects in humans of hydrogen fluoride inhalation or oral exposure to fluoride. Reports of an increased incidence of Down's syndrome have been refuted (Berry 1958; Erickson et al. 1976; Needleman et al. 1974). Reduced fertility was seen after exposure of female mice to fluoride levels at or above the maximum tolerated dose (Messer et al. 1973). Sixty days of oral exposure to sodium fluoride was observed to cause changes in the seminiferous tubules of CD rat testes and a decreased number of offspring (Araibi et al. 1989). The significance to reproduction in humans of histological changes observed in rats is not known. Sperm abnormalities were not increased in $B6C3F_1$ mice exposed to fluoride in water (Dunipace et al. 1989; Li et al. 1987a), but were increased in Swiss mice that received intraperitoneal injections of sodium fluoride (Pati and Buhnya 1987). Additional support for an adverse effect of high fluoride levels on reproduction comes from studies in dogs and birds (Guenter and Hahn 1986; Hoffman et al. 1985; Shellenberg et al. 1990; Van Rensburg and de Vos 1966). Further data concerning reproductive organ pathology following a 90-day oral or inhalation study would be useful to clarify the current data on reproductive effects, given that there are populations surrounding hazardous waste sites that might be exposed to fluoride compounds.

Developmental Toxicity. There are no studies in humans or animals regarding the developmental effects of inhaled hydrogen fluoride. Similarly, there are no recent studies of conventional design in animals of the developmental effects of oral fluoride. There was no difference in the incidence of birth defects between fluoridated and nonfluoridated towns in one epidemiological study (Erickson et al. 1976). There was no fluoride-induced increase in the number of abnormal offspring in a two-generation reproduction study in Sprague-Dawley rats that drank water containing sodium fluoride (Ream et al. 1983). Adverse developmental effects of oral fluoride exposure have also been observed in calves (Krook and Maylin 1979; Maylin and Krook 1982) and mink (Aulerich et al. 1987). However, there is a general paucity of data concerning developmental endpoints for fluoride compounds. Further data concerning exposure to fluoride compounds by the oral and inhalation routes for developmental endpoints would be useful.

Immunotoxicity. A review of human studies has shown that fluoride in drinking water has no adverse effects on immunologically mediated reactions or allergies (Austen et al. 1971). This suggests that the immune system is not a

sensitive target for fluoride toxicity following oral exposure. Additional information is probably not needed at this time.

Neurotoxicity. Because fluoride interacts with calcium ions needed for effective neurotransmission, fluoride can affect the nervous system. However, while acute effects on the nervous system have been observed in humans, it is not known whether chronic exposure to hydrogen fluoride or fluoride can cause nervous system effects. Human and animal studies have shown minor changes in neurological function after inhalation exposure to hydrogen fluoride. Overt signs or behavioral signs of neurotoxicity were not noted, except for alterations in conditioned responses and evidence of depression observed in rats (Sadilova et al. 1965). Further neurological testing may be warranted to ascertain the conditions involved and the extent to which the nervous system is a target organ for fluoride toxicity.

Epidemiological and Human Dosimetry Studies. Since fluoride is available in the drinking water in many communities, many epidemiological studies have been conducted regarding its health effects. Epidemiological studies of people who have been exposed to hydrogen fluoride and other fluoride compounds occupationally have also been performed (Czerwinski et al. 1988; Chan-Yeung et al. 1983a; Chan-Yeung et al. 1983b; Kaltreider et al. 1972). Because of the wide use of fluoride in industry and dental hygiene, it is likely that subpopulations vary in their level of exposure to fluoride. Human dosimetry studies exist that indicate that fluoride levels in the urine can be used as an indication of recent exposure (Carlson et al. 1960a; Collings et al. 1952; Machle and Largent 1943). Additional studies correlating environmental measurements of fluoride with urinary excretion data and health effects would be useful for establishing a dose response for health effects in humans.

Biomarkers of Exposure and Effect. The level of fluoride in urine is the best biomarker of acute exposure (Ekstrand et al. 1983; Hodge and Smith 1977). However, because chronic exposure to fluoride results in sequestration in bone, levels in the urine cannot be correlated with levels of chronic exposure (Carlson et al. 1960a). This biomarker is specific for acute and intermediate duration exposure to this chemical.

The most sensitive biomarkers of effect for fluoride are alterations in teeth and bones following chronic exposure (Knaus et al. 1976). Of these, tooth alterations are more sensitive, but they occur only during childhood (DHHS 1991; Heifetz et al. 1988). Changes in glucose or lipid metabolism (Dousset et al. 1984; Shearer 1974; Watanabe et al. 1975), and in erythrocyte enzyme activities (Guminska and Sterkowicz 1975) have been noted following acute exposure. Specific biomarkers of effects following acute exposures have not been well identified, and would be useful in monitoring short-term effects, such as might be expected to occur in hazardous waste site workers.

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Absorption, Distribution, Metabolism, and Excretion. Data exist that indicate that a high percentage of hydrogen fluoride is rapidly absorbed following acute inhalation exposure (Collings et al. 1952; Rye 1961). Rates of absorption differ between human studies, because the reported times to peak urinary fluoride levels are different (2-4 hrs vs. 10 hrs) (Collings et al. 1952; Rye 1961). One human study reports absorption of fluoride from acute inhalation of rock phosphate dust, with time to peak urinary fluoride of 10 hours, and similar excretion kinetics to that found following hydrogen fluoride inhalation (Rye 1961). One acute animal study described the rate and extent of absorption following inhalation exposure to hydrofluoric acid (Morris and Smith 1982). Data on chronic absorption, extent of absorption, and potential for saturation were not located but would be useful for predicting potential effects in persons exposed to hydrogen fluoride or fluoride dusts at low levels over extended periods of time.

Soluble fluoride is rapidly and almost completely absorbed following oral exposure of humans or animals (Armstrong et al. 1970; Carlson et al. 1960a; Ekstrand et al. 1977b, 1983; Ericsson 1958; McClure et al. 1945; Whitford and Pashley 1984; Zipkin and Likins 1957). However, the degree of absorption is affected by a number of other factors (Rao 1984).

Although dermal absorption has not been studied per se, toxicity following acute dermal exposure to hydrofluoric acid (e.g., hypocalcemia) provide adequate evidence that this is a significant route of exposure (Browne 1974; Dale 1951; Dibbell et al. 1970). However, it should be noted that in some cases the effects reported for dermal exposure may have been caused by inhalation of hydrofluoric acid fumes as well as injury to skin. The existing data on dermal exposure to sodium fluoride (Essman et al. 1981) are not sufficient to determine absorption. Because hydrofluoric acid readily dissolves in water, and reacts readily with a number of compounds and metals, contamination of water or the ground would result in the formation of fluoride salts. Therefore, populations surrounding hazardous waste sites would be more likely to be exposed dermally to fluoride salts than to hydrofluoric acid. However, cleanup workers or members of the public who came into contact with leaking drums could be dermally exposed to hydrofluoric acid. Additional animal studies regarding rate and extent of absorption following dermal exposure would be useful for clarifying the effects seen following dermal or inhalation exposure.

The development of systemic effects following whole body exposure to fluorine indicates that fluorine is absorbed (Stokinger 1949). The rate and extent of absorption are not known.

Regardless of the route of administration, fluoride is found in the plasma (Morris and Smith 1983; Perkinson et al. 1955), and accumulates in bones and teeth. Elevated fluoride levels are also found in the kidney (Whitford and Taves 1973) and aorta (Smith et al. 1960). Further information

2. HEALTH EFFECTS

concerning distribution would be useful to determine if there are target organs of fluoride exposure in addition to the skeletal, gastrointestinal, and cardiovascular systems. In addition, while it is known that elevated bone fluoride levels decrease with time if the exposure source is removed, more information about the kinetics of this process would be useful.

Fluoride interacts with other elements, particularly in bone formation (McCann and Bullock 1957; Neuman et al. 1950). The ion is also known to interact with enzymes in the body (Capozzi et al. 1967; Cimasoni 1966; Halton et al. 1984; Smith et al. 1959). Although there are extensive data on in vitro inhibition of enzymes, very few data exist regarding the biological significance of these interactions. Several glycolytic enzymes are inhibited at fluoride concentrations of 38 ppm (Capozzi et al. 1967). A few enzymes have been identified that are inhibited at in vitro concentrations <lO ppm (Cimasoni 1966; Smith et al. 1959). Further information on the biological significance of these enzyme reactions would be useful for assessing the mechanisms by which fluoride affects human health.

The excretion of fluoride in the urine of humans following inhalation or oral exposure is well characterized in its relationship to recent fluoride exposure (Ekstrand et al. 1983; Hodge and Smith 1977). However, while it is known that bone fluoride concentration increases with age (Smith et al. 1953), the total steady-state excretion level when people are chronically exposed to low-levels of fluoride is not well characterized. Reliable data are also lacking regarding the contribution of sweat to fluoride excretion. Data are lacking concerning excretion following dermal exposure; however, there is no evidence to suggest that excretion following dermal exposure would differ from that following oral or inhalation exposure.

Comparative Toxicokinetics. Because fluoride is frequently available in the drinking water, abundant human data exist concerning the kinetics of fluoride in humans. Fewer data were located for animals that are considered to be appropriate models for humans. Human and animal data exist that indicate that the most likely target organs (bones and teeth) are similar across species for intermediate and chronic duration exposures (Derryberry et al. 1963; Machle and Scott 1935; Wagner et al. 1958). However, as mentioned before, the lack of a vomit reflex in rats may preclude their use as an animal model for acute oral exposure to fluoride compounds.

There is good evidence that there are marked species and strain differences regarding tolerance to increased levels of oral fluoride. For example, beef and dairy heifers show susceptibility to levels as much as 100 times lower than those causing some degree of pathology in laying and breeding hens (Suttie 1980). Additional data from studies that provide directly comparable pharmacokinetic data from several species would be useful for establishing the best species for extrapolating to human effects.

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Mitigation of Effects. Methods have been published for limiting oral and dermal absorption of fluoride compounds (Bronstein and Currance 1988; Goldfrank et al. 1990; Haddad and Winchester 1990) and for counteracting the hypocalcemia, hypomagnesemia, and hyperkalemia that are produced by fluoride in acute high-level exposure situations (Abukurah et al. 1972; Ellenhorn and Barceloux 1988; Haddad and Winchester 1990). Although there is a report in an animal model that intradermal injection of magnesium acetate or magnesium sulfate is more effective than injection of calcium gluconate (Harris et al. 1981), a report of human case studies found that the calcium gluconate method was 100% effective and did not cause tissue damage (Browne 1974). Therefore it is not clear whether intradermal injection of magnesium acetate or magnesium sulfate should be explored. The only information located on treatment strategies for long-term exposures to excessive amounts of fluorides involved reducing exposure either by removing the source or reducing absorption. Fluoride excretion can be increased by the administration of aluminum hydroxide as antacid (Spencer et al. 1980a). Other studies show that fluoride absorption is decreased in the presence of calcium (Machle and Largent 1943; McClure et al. 1945), especially in combination with carbonate (Jowsey and Riggs 1978), although these studies were not designed to develop treatment strategies. Strategies for increasing bone turnover might also be useful, but no investigations of such methods were located. Research on using dietary supplements or increasing bone turnover for mitigating adverse effects of chronic exposure to fluoride would be helpful, especially in the case of chronic exposure to drinking water which has been contaminated with fluoride.

2.9.3 On-going Studies

On-going research on human health effects of fluoride is summarized in Table 2-9

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TABLE 2-9. On-going Studies on the Health Effects of Sodium Fluoride

Investigator	Affiliation	Research description
Aoba, T.	National Institute of Dental Research	Enamel formation
Baylink, D.J.	VA Medical Center, Loma Linda, California	Osteoporosis therapy
Bauman, A.A.	Institute for Medical Research and Occupational Health, Yugoslavia	Occupational study
Bawden, J.W.	University of North Carolina	Enamel formation; placental transfer
Bucher, J.	National Toxicology Program	Repeat carcinogenicity assay
Burt, B.	University of Michigan	Prevention of osteoporosis
Cerklewski, F.	Oregon State University	Pharmacokinetics
Debensten, P.	Forsythe Dental Center, Boston	Enamel formation
Dunipace, A.	Indiana University School of Dentistry	Clastogenicity and mutagenicity
Eisenberg, A.	Eastman Dental Center, New York	Antimicrobial activity
Freni, S.	National Center for Toxicological Research, Arkansas	Human fertility
Gillit, J.W.	Cornell University	Impact of industrial chemicals on Indian communities
Grandjean, P.	Odense University Denmark	Occupational study
Huff	National Toxicology Program	Special toxicology studies
Hughes, B.D.	Tufts University	Interaction with calcium on bone loss
Kies, C.V.	University of Nebraska Nebraska	Drinking water contaminants and all causes of mortality
Kleerekoper, M.	Henry Ford Hospital, Detroit	Osteoporosis therapy
Martin, G.R.	National Institute of Dental Research	Clastogenicity and mutagenicity
Messer, H.	University of Minnesota	Absorption
Riggs, B.L	Mayo Foundation, Rochester, Minnesota	Osteoporosis therapy
Schneider, V.	University of Texas Medical School	Metabolism
Skobe, Z.	Forsyth Memorial Hospital	Enamel growth
Unknown	Proctor and Gamble	Oncogenicity in mice
Whitford, G.M.	Medical College of Georgia	Metabolism

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

The common synonyms and other information for fluorine, hydrogen fluoride, and sodium fluoride are listed in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Important physical and chemical properties of fluorine, hydrogen fluoride, and sodium fluoride are presented in Table 3-2.

	Fluorine	Hydrogen fluoride	Sodium fluoride
Synonyms	Bifluoriden; Fluor; Fluorine-19; Fluoro	Anhydrous hydrofluoric acid; fluorhydric acid	Disodium difluoride; sodium hydrofluoride; sodium monofluoride; trisodium trifluoride
Trade names	No data	Antisal 2B	Alcoa sodium fluoride; Antibulit; cavi-trol; credo; Fl-Tabs; Fluorigard; Florocid; Flozenges; Fluorinse
Chemical formula	F_2	HF	NaF
Chemical structure	Not applicable	Not applicable	Not applicable
Identification numbers:			
CAS registry	7782-41-4[a]	7664-39-3	7681-49-4[a]
NIOSH RTECS	NIOSH/LM64750000	NIOSH/MW7890000	NIOSH/WB0350000
EPA hazardous waste	P056	U134	No data
OHM/TADS	No data	7216750	7216897
DOT/UN/NA/IMCO shipping	UN1045; Fluorine, 1MO 2.3; Fluorine compressed	UN1790; hydrofluoric acid UN1052; anhydrous hydrogen fluoride IMO 8.0	UN1690; 1MO 6.1
HSDB	541	0.546	1766
NCI	No data	No data	No data

All information obtained from HSDB 1989 except where noted
[a]Weiss 1985

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/ Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

TABLE 3-2. Physical and Chemical Properties of Fluorine, Hydrogen Fluoride, and Sodium Fluoride

	Fluorine	Hydrogen Fluoride	Sodium Fluoride
Molecular weight	37.99[a]	20.01[b]	41.99[b]
Color	Pale, yellow-green[c]	Colorless[d]	White[c]
Physical state	Gas[c]	Gas[b]	Cubic or tetragonal crystals[d]
Melting point	-219.61°C[a]	-83.1°C[b]; -83.55°C[d]	993°C[d]
Boiling point	-188.13°C[a]	19.51°C[d]	1695°C[e]
Density	1.5127 g/mL at -188.13°C[a]	0.991 g/mL at 19.54°C[a]	2.78 g/mL at room temperature[d]
Odor	Pungent, choking[a]	Sharp penetrating odor[f]	Odorless[e]
Odor threshold:			
Water	No data	No data	No data
Air	0.035 ppm[a]	0.03 mg/m[3g]	No data
Solubility:			
Water	No data	Miscible[f]	430 g/mL at 25°C[d]
Organic solvents	No data	Benzene; toluene; ether; m-xylene tetraline[d]	4.22 g/100 mg at 18°C[b]
Partition coefficients:			
Log Kow	No data	No data	No data
Log Koc	No data	No data	No data
Vapor pressure	1 mmHg at -223°C; 10 mmHg at -214.1°C[a]	400 mmHg at 2.5°C[a]	1 mmHg at 1077°C[a]
Henry's law constant:			
at 20°C	No data	No data	No data
at 30°C	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	Not flammable[a]	Not flammable[e]	Not flammable[e]
Flammability limits	No data	No data	No data
Conversion factors	1 mg/L=1554 ppm 1 ppm=0.64 mg/m[3h]	1 mg/L=1223 ppm; 1 ppm=0.82 mg/m[3h]	Not applicable
Explosive limits	No data	No data	No data

[a]HSDB 1989
[b]Lide 1992
[c]WHO 1984
[d]Windholz 1983
[e]Weiss 1986
[f]NIOSH/OSHA 1978
[g]Sadilova et al. 1965
[h]NAS 1971a

4 . PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Fluorine, hydrogen fluoride, sodium fluoride, and calcium fluoride form a diverse and widely used group of related chemicals. The sources of these chemicals vary. The fluoride chemical industry is based mainly on fluorspar (calcium fluoride), which has been mined since the late 18th century for use in the production of steel (Grayson 1980). This compound is found mainly in the Illinois-Kentucky region. Average annual U.S. production for the years 1972-1978 is estimated at 118,000-225,000 metric tons (Grayson 1980). Future mining is expected in Tennessee, Colorado, and Alaska. Another source of fluoride chemicals is the processing of phosphate rock, which releases fluorine as gaseous hydrogen fluoride. The preferred raw materials for hydrogen fluoride manufacture are acid-grade fluorspar and sulfuric acid. Sodium fluoride is produced by reacting hydrofluoric acid and sodium carbonate. Very pure calcium fluoride is made by the reaction of hydrofluoric acid with precipitated calcium carbonate.

The total commercial production of fluorine in the United States and Canada is approximately 5,000 tons/year, of which 70%-80% is used to produce uranium hexafluoride for nuclear power applications. The current growth rate of hydrogen fluoride production is approximately 0.5%. The rate has decreased over the past few decades, from 10% annually in the 1940s and 1950s, to 5% in the 1960s, then to 3% in the early 1970s (Grayson 1980). Information on recent production volumes of these chemicals was not located. Table 4-l shows the number of facilities in each state that manufacture and process hydrogen fluoride, the intended uses of the product, and the range of maximum amounts of hydrogen fluoride that is stored on site. The data listed in Table 4-l are derived from the Toxics Release Inventory (TRI) of EPA (TR188 1989). Because only certain types of facilities are required to report, this is not an exhaustive list. Neither fluorine nor sodium fluoride or any other fluoride salt are listed on TRI.

4.2 IMPORT/EXPORT

The United States imports more than 80% of its fluorspar, the primary source of fluorine and its compounds. The imports originate primarily from Mexico, the Republic of South Africa, Spain, and Italy. The most recent data indicate that in 1977, 885,000 metric tons were imported. In 1975, 1,200 metric tons of fluorspar were exported, primarily to Canada (Grayson 1980).

4.3 USE

Fluoride compounds are used in a wide range of fields. The steel industry is the largest consumer of fluorides, followed by the chemical industry and the glass and ceramics industry (Windholz 1976).

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

TABLE 4-1. Facilities That Manufacture or Process Hydrogen Fluoride[a]

State[b]	No. of facilities	Range of maximum amounts on site in thousands of pounds[c]	Activities and uses[d]
AL	5	1-999	3, 7, 12
AR	1	100-999	7
AZ	8 (1)[e]	0.1-999	7, 11, 12, 13
CA	60 (6)[e]	0-49,999	2, 3, 4, 7, 8, 9, 10, 11, 12, 13
CO	6 (1)[e]	1-99	11, 12, 13
CT	9	0.1-99	1, 5, 8, 11, 12, 13
DE	1	10-99	7, 8
FL	11	0-999	1, 3, 5, 6, 7, 12, 13
GA	13 (1)[e]	0.1-999	8, 9, 11, 12, 13
HI	2	1-9	12
IA	3	0-99	3, 7, 9, 11, 13
ID	2 (1)[e]	0.1-0.9	1, 5, 12, 13
IL	13	0-999	2, 3, 4, 7, 8, 9, 11, 12
IN	14 (2)[e]	0-999	5, 7, 8, 11, 12, 13
KS	8	1-9,999	7, 10, 11
KY	8 (1)[e]	0-9,999	1, 2, 3, 4, 5, 7, 10, 11, 12
LA	11	10-9,999	1, 2, 3, 4, 5, 7, 11, 12, 13
MA	15	0.1-99	8, 11, 12, 13
MD	6 (1)[e]	1-999	5, 11, 12
ME	1	10-99	12
MI	12	0.1-9,999	2, 7, 8, 11, 12, 13
MN	1	100-999	7, 13
MO	12 (1)[e]	0-99	5, 7, 8, 11, 12, 13
MS	1	1-9	13
MT	5	0-999	1, 3, 5, 11
NC	13	0-99	1, 5, 7, 11, 12, 13
ND	1	1-9	11
NJ	17 (2)[e]	0-999	1, 2, 3, 4, 5, 7, 8, 10, 11, 12, 13

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

TABLE 4-1 (Continued)

State[b]	No. of facilities	Range of maximum amounts on site in thousands of pounds[c]	Activities and uses[d]
NM	4 (1)[e]	0.1-99	11, 12, 13
NV	1	1-9	2, 7
NY	21 (2)[e]	0-9,999	1, 2, 5, 6, 7, 10, 11, 12, 13
OH	38 (6)[e]	0-999	1, 2, 3, 5, 7, 8, 11, 12, 13
OK	8 (1)[e]	10-999	1, 2, 3, 7, 11, 12
OR	8	0.1-999	1, 5, 11, 12, 13
PA	48 (2)[e]	0.1-9,999	2, 5, 7, 8, 10, 11, 12, 13
PR	7 (1)[e]	1-99	5, 11, 12, 13
RI	3 (1)[e]	0.1-99	11, 12
SC	6	0-999	5, 7, 11, 12, 13
TN	8 (1)[e]	0-9,999	1, 3, 4, 5, 6, 7, 11, 12
TX	42	0-49,999	1, 2, 3, 4, 5, 7, 11, 12, 13
UT	7	0-999	2, 3, 5, 8, 11, 12, 13
VA	3	0-99	5, 11, 12
VT	1	100-999	12
WA	16 (1)[e]	0-999	1, 5, 7, 11, 12, 13
WI	11	0.1-99	9, 10, 11, 12, 13
WV	3	0-9	2, 5, 12
WY	4 (1)[e]	10-99	5, 11

[a]TRI 1989
[b]Post office state abbreviations
[c]Data are maximum amounts on site at each facility.
[d]Activities/Uses:

1. produce
2. import
3. for on-site use/processing
4. for sale/distribution
5. as a byproduct
6. as an impurity
7. as a reactant
8. as a formulation component
9. as an article component
10. for repackaging only
11. as a chemical processing aid
12. as a manufacturing aid
13. ancillary or other use

[e]Number of facilities reporting "no data" regarding maximum amount of the substance on site.

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

Molecular fluorine has been used as an oxidizer in rocket fuels, in the production of metal1ic.s and other fluorides, and in glass, enamel, and brick production (Greenwood 1969; Windholz 1976). Currently, molecular fluorine is used by most manufacturers for the production of various inorganic fluorides. With the discontinuance of liquid fluorine as a rocket fuel oxidizer, demand for this form has virtually ceased (Grayson 1980). The fluorine-18 isotope has been found to be effective in bone scanning. When used as a replacement for the conventional x-ray process, the amount of radiation exposure received by the patient is reduced (Gerber et al. 1972).

The main use of sodium fluoride is as a drinking water additive for prevention of dental caries. It is also used as a rodenticide and insecticide (mainly for roaches and ants), as a disinfectant for fermentation apparatus in breweries and distilleries, in wood preservation, and in rimmed steel manufacture (Markuson 1947; Windholz 1976).

Calcium fluoride, the primary compound used by the fluoride chemical industry, has been used as a flux in steel manufacturing since the introduction of the open-hearth process. In 1977, the two primary uses of calcium fluoride were the production of hydrofluoric acid and steel making, accounting for 519,000 metric tons and 504,OOO metric tons of calcium fluoride, respectively. The total amount of calcium fluoride used in that year is estimated at 1,063,000 metric tons (Grayson 1980). Other uses are frosting glass and enamels, coating welding rods, transmittal of ultraviolet rays in the optical industry, fluoridation of drinking water, paint pigment, and as a catalyst in wood preservation (Windholz 1976).

Prior to 1930, hydrogen fluoride was used mainly for glass etching and polishing, foundry scale removal, and minor production of metal fluorides (Grayson 1980). In 1977, 40% of hydrogen fluoride use was devoted to aluminum production and 37% to production of chlorofluorocarbons. Other uses include uranium processing, petroleum alkylation, and stainless steel pickling (Anonymous 1970; Grayson 1980; Windholz 1976). A sharp decrease in demand for hydrogen fluoride occurred in 1978 when the United States prohibited the use of chlorofluorocarbon gases in pressure packaging (Grayson 1980).

4.4 DISPOSAL

Limited information on the required disposal practices of fluoride compounds was located. Fluorine can be disposed of by conversion to gaseous fluoride salts (Grayson 1980). No information could be located on levels disposed of via these methods. Industrial practices include reaction with solid disposal agents such as alumina, limestone, lime, and soda lime; reaction with superheated steam; and scrubbing with caustic solutions. Potassium hydroxide and sodium hydroxide are used in spray column caustic scrubbing systems. Potassium hydroxide is preferred because of the higher solubility of the resulting potassium fluoride (Grayson 1980). During the manufacture of wet-process phosphoric acid, waste liquors and slurries that

contain sodium and potassium fluorosilicates, hydrofluoric acid, and
fluorosilicic acid are.produced.
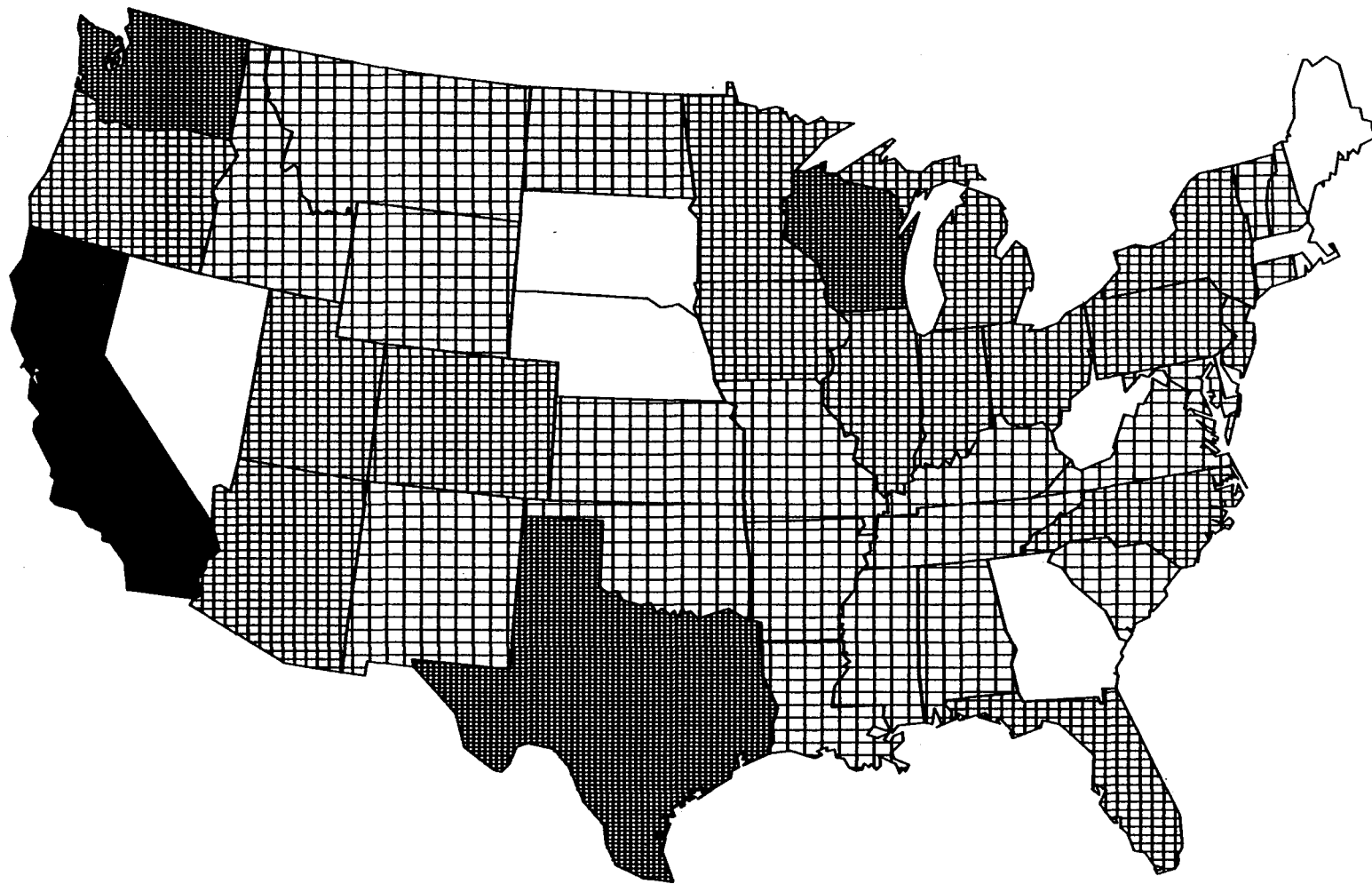
5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Fluorides enter the environment naturally through the weathering of rocks and minerals and by emissions from volcanoes. The greatest amount of the total volume of fluorides in the environment is released from natural sources, in particular volcanoes and oceans. However, the greatest concentrations are found near anthropogenic point sources. Fluorides are found in soil, air, water, and in most foods, from both natural and anthropogenic sources, though rarely as molecular fluorine. It is highly electronegative and therefore reacts vigorously with other compounds. The dominant fluoride compound in a particular medium is the most stable compound in that medium. For example, the dominant species in air is hydrofluoric acid, but even this species will not persist in the air for long periods. Anhydrous hydrogen fluoride will react with moisture in the air and form hydrofluoric acid, which will gradually settle to the ground or be dispersed with the wind. Calcium fluoride is most common in alkaline soils, and fluoroaluminate complexes are most common in acidic soils. Thus, exposure to hydrofluoric acid would occur at a hazardous waste site only if someone came in contact with material leaking from a storage container or breathed contaminated air before it was dispersed. Once in a stable form, fluoride persists in the environment for a relatively long time unless transformed to another compound or decomposed by radiation.

The general population is exposed to fluoride through consumption of drinking water, foods, and dentifrices, primarily in the form of sodium fluoride and stannous fluoride. Populations exposed to relatively high concentrations of fluoride include workers in fluoride-processing industries and individuals residing near such industries. These individuals may be exposed to higher than background concentrations as a result of the levels of hydrogen fluoride and dusts from fluoride compounds in the air, and from foodstuffs produced within the vicinity that have collected excess fluoride from the environmental media. Populations near hazardous waste sites may be exposed to high levels of fluoride by similar routes, although no information has been located to support this.

EPA has identified 1,334 NPL sites. Fluorides have been found at 130 of the sites. Fluorine and hydrogen fluoride have been found at 28 and 19 sites, respectively. Because fluorine is a gas, it could exist at a hazardous waste site only in a pressurized cylinder. Alternatively, fluoride contamination may be generically listed as fluorine contamination. We do not know how many of the 1,334 NPL sites have been evaluated. As more sites are evaluated by EPA, these numbers may change (Hazdat 1992). The frequency of these sites within the United States (including all sites with fluoride, hydrogen fluoride, or fluorine contamination) can be seen in Figure 5-l.

FIGURE 5-1. FREQUENCY OF NPL SITES WITH FLUORIDES CONTAMINATION *

FREQUENCY ▦ 1 TO 3 SITES ▦ 4 TO 7 SITES
▦ 9 TO 11 SITES ■ 21 SITES

*Derived from HAZDAT 1991

5. POTENTIAL FOR HUMAN EXPOSURE

5.2 RELEASES TO THE ENVIRONMENT

According to TRI, an estimated total of 12,934,848 pounds of hydrogen fluoride were released to the environment (air, land, water, and underground injection wells) from manufacturing and processing facilities in the United States in 1987, as can be seen in Table 5-1 (TR188 1989). Facilities are required to report releases if they are in Standard Industrial Classification (SIC) codes 20-39 and meet other reporting criteria. The quality of the TRI data must be viewed with caution since the 1987 data represent first-time, incomplete reporting of estimated releases by these facilities. Not all sources of chemical wastes are included, and not all facilities that should have reported release data have done so. Neither fluorine nor sodium fluoride or other fluorides are listed on TRI.

5.2.1 Air

Natural sources of atmospheric fluoride releases include volcanoes, minerals, and oceans. The greatest total amount of natural fluoride is contributed by volcanoes, primarily in the form of hydrogen fluoride. Passive degassing of volcanoes has been estimated to contribute between $5x10^{10}$ and $5X10^{12}$ g/year (0.067 to 6.7 million tons/year), and between $5x10^9$ and $5x10^{10}$ g (0.0067-0.067 million tons) is explosively erupted each year (Symonds et al. 1988). Weathering of fluoride-containing rocks and minerals also contributes to the atmospheric burden of fluoride in the form of soil minerals (NAS 1971a). Another source of undetermined quantity is sea salt aerosol, which releases small amounts of gaseous hydrogen fluoride and fluoride salts into the air. The marine aerosol is potentially a major source of tropospheric hydrogen fluoride, though confined to the air over the oceans (Friend 1989).

Anthropogenic releases of fluoride into the atmosphere totaled 155,300 tons/year from the major fluoride-processing industries measured between 1964 and 1970 (EPA 1980a). The major contributors were steel, brick and tile, and aluminum manufacturing, combustion of coal, and production of phosphorus and phosphate fertilizer (EPA 1980a; NAS 1971a). Since this study, regulations have been established that set emissions standards for aluminum manufacturing (EPA 1980b) and phosphate fertilizer plants (EPA 1975). No data were located on global anthropogenic fluoride releases since the emissions limits have been implemented. Fluoride can also enter the atmosphere from the manufacture and use of pesticides such as sodium fluoride, sodium fluorosilicate,barium fluorosilicate, and cryolite particularized in the form of dusts and sprays (NAS 1971a).

According to TRI, an estimated total of 11.4 million pounds of hydrogen fluoride were released to the atmosphere from manufacturing and processing facilities in the United States in 1987 (TRI88 1989). As discussed above, estimates generated by this database must be viewed with caution, particularly

State[c]	No. of facil- ities	Air	Underground injection	Water	Land	Total environment[d]	POTW[e] transfer	Off-site waste transfer
		Range of reported amounts released in thousands of pounds[b]						
AL	5	0-48	0-0	0-0	0-0	0-48	0-0	0-1.6
AR	1	6.6-6.6	0-0	0-0	0-0	6.6-6.6	0-0	0.1-0.1
AZ	8	0-2.3	0-0	0-0	0-0	0-2.3	0-78	0-16.5
CA	60	0-6.8	0-0	0-0	0-59.9	0-59.9	0-14	0-143.3
CO	6	0-0.5	0-0	0-0	0-0	0-0.5	0-4.9	0-7.5
CT	9	0-3.9	0-0	0-2.6	0-0	0-3.9	0-0.3	0-42
DE	1	2.9-2.9	0-0	0-0	0-0	2.9-2.9	0-0	0-0
FL	11	0-17.7	0-15.2	0-1.2	0-0	0-17.7	0-0.5	0-95.6
GA	13	0-0.5	0-0	0-0	0-0	0-0.5	0-62	0-0.3
HI	2	0-0	0-0	0-0	0-0	0-0	0-0	0-0
IA	3	0-1	0-0	0-0.8	0-0	0.3-1	0-0	0-0
ID	2	0.5-103	0-0	0-0	0-0	0.5-103	0-5.7	0-0
IL	13	0-82.9	0-15	0-0.3	0-0.3	0-82.9	0-31.6	0-0.3
IN	14	0-1,510	0-0	0-19.3	0-0	0-1,510	0-112	0-6.5
KS	8	0-41	0-568	0-0	0-0	0-568	0-0	0-522.6
KY	8	0.3-464.3	0-0	0-1.2	0-0	0.3-464.3	0-68.3	0-207.7
LA	11	0.1-280.2	0-0	0-0	0-0	0.1-280.2	0-110	0-0.1
MA	15	0-5.4	0-0	0-0.3	0-0	0-5.4	0-19.9	0-108
MD	6	0-250	0-0	0-0.3	0-0	0.3-250	0-5.5	0-27.7
ME	1	0.5-0.5	No Data	0-0	0-0	0.5-0.5	0-0	19.5-19.5
MI	12	0-6.1	0-0	0-0.3	0-0.3	0-6.1	0-0.3	0-297.7
MN	1	99.7-99.7	0-0	0-0	0-0	99.7-99.7	0-0	0-0
MO	12	0-270.5	0-0	0-0	0-0	0-270.5	0-55	0-54
MS	1	0-0	0-0	0-0	0-0	0-0	27.3-27.3	0-0
MT	5	3.9-252.8	0-0	0-0	0-0	3.9-252.8	0-0	0-0

TABLE 5-1 (Continued)

Statec	No. of facil-ities	Range of reported amounts released in thousands of pounds[b]						
		Air	Underground injection	Water	Land	Total environment[d]	POTW[e] transfer	Off-site waste transfer
NC	13	0-152	0-0	0-0	0-120	0-152	0-0	0-29
ND	1	3.7-3.7	0-0	0-0	0-0	3.7-3.7	0-0	0-0
NJ	17	0-3.2	0-0	0-0.1	0-0	0-3.2	0-0.3	0-1,400
NM	4	0.1-1	0-0	0-0	0-0	0.1-1	0-0	0-0.8
NV	1	0.5-0.5	0-0	0-0	0.3-0.3	0.8-0.8	0-0	0-0
NY	21	0-566	0-0	0-0.3	0-0	0-566	0-54.5	0-70.9
OH	38	0-538	0-0	0-7.9	0-290	0-538	0-20.4	0-492.2
OK	8	1.4-933	0-0	0-0.3	0-0	1.4-933.3	0-0	0-180
OR	8	0-169	0-0	0-6.2	0-0	0-169	0-2.6	0-9.1
PA	48	0-90	0-0	0-39.5	0-194.1	0-195.3	0-35.9	0-382.8
PR	7	0-0.5	0-0	0-0	0-0	0-0.5	0-16.5	0-0.1
RI	3	0-120	0-0	0-0	0-0	0-120	0-0.3	0-0
SC	6	0.3-90.3	0-0	0-4.3	0-1.3	0.3-90.3	0-0.3	0-0.5
TN	8	0.3-363.5	0-0	0-0	0-0	0.3-363.5	0-0	0-23.8
TX	42	0-670	0-0	0-0	0-0	0-670	0-0.3	0-165
UT	7	0.5-31.2	0-0	0-25	0-0	0.5-31.2	0-72.9	0-0
VA	3	0.3-3.9	0-0	0-0	0-0.3	0.3-3.9	0-0	0-0
VT	1	2.7-2.7	0-0	0-0	0-0	2.7-2.7	0-0	0-0
WA	16	0-440	0-0	0-6.2	0-0	0-440	0-0	0-16.8
WI	11	0-2.9	0-0	0-0	0-0	0-2.9	0-0.3	0-0
WV	3	0.3-266	0-0	0-0	0-0	0.3-266	0-0	0-0
WY	4	0-6.7	0-0	0-0	0-0	0-6.7	0-0	0-0

[a]TRI 1989
[b]Data are maximum amounts released by each facility. Quantities reported here have been rounded to the nearest hundred pounds, except those quantities >1 million pounds which have been rounded to the nearest thousand pounds.
[c]Post office state abbreviations used
[d]The sum of all releases of the chemical to air, land, water, and underground injection wells by a given facility
[e]Publicly owned treatment works

since approximately 16,000 tons are emitted each year from combustion processes that are probably not included in the TRI database (NAS 1971a).

5.2.2 Water

Natural sources of fluoride released to surface waters include wet deposition of atmospheric fluorides, and weathering of fluoride-containing rocks and soils through which groundwater flows. In the western regions of the United States, rocks and soils have greater than average concentrations of fluoride; as a result, greater amounts of fluorides leach into the groundwater. Leaching from alkaline igneous rocks, dolomite, phosphorite, and volcanic glasses gives rise to high-fluoride waters (EPA 1980a; NAS 1971a). The ocean is another natural source of fluoride.

Near industrial sources, precipitation provides an even greater concentration of fluorides, because of increased levels in the ambient air. In the manufacture of wet-process phosphoric acid, waste liquors and slurries are produced that contain sodium and potassium fluorosilicates, hydrofluoric acid, and fluorosilicic acid. In coastal areas, these wastes are disposed of in the sea. In other areas, large ponds are constructed to contain this waste and may contribute to the atmospheric burden by volatilization and water runoff (NAS 1971a). Fluorides are also added to many community water supplies to achieve a concentration of 0.7-1.2 ppm, which helps decrease the incidence of dental caries (DHHS 1991).

According to TRI, an estimated total of 204,544 pounds of hydrogen fluoride were released to surface waters from manufacturing and processing facilities in the United States in 1987 (TRI88 1989). However, as discussed above, these data must be viewed with caution.

Fluoride has been detected in an estimated 1.04% of the surface water samples and 3.94% of the groundwater samples analyzed for the 2,783 hazardous waste sites participating in EPA's Contract Laboratory Program (CLP); geometric mean concentrations for the positive samples were not reported (CLPSD 1988). Note that the Contract Laboratories Program Statistical Database (CLPSD) includes data from both NPL and non-NPL sites.

5.2.3 Soil

Natural sources of fluorides released to soils include weathering of minerals, precipitation of atmospheric fluorides, plant and animal wastes, and sedimentation of undissolved fluorides in water. Soils may contain fluoride in the form of several different minerals including biotite, muscovite, hornblende, apatite, and fluorspar (NAS 1971a). Man-made sources are primarily fertilizers, particularly super phosphates, and industrial releases (EPA 1980a; NAS 1971a). In a study by Oelschldger (1971), fertilization with superphosphates added to the soil 8-20 kg fluoride/hectare. Fluoride loss through seepage water averaged between 52 and 208 μg/L, depending upon levels

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of clay, lime, and fluoride in the water and the run-off (OelschMger 1971).
Fluoride-containing pesticides, mentioned above, may add significantly to soil
levels, although quantitative information on this source was not located.
Soil contamination by atmospheric fluorides near an industrial source
reflected the gradient of fluoride deposition. In one study, the total
fluoride concentration was found to decrease over a distance of 8.8 km from
2,700 to 616 µg/g fluoride and the water extractable fraction from 292 to
10 µg/g fluoride (Polomski et al. 1982).

Fluoride has been detected in an estimated 0.12% of the soil samples
analyzed for the 2,783 hazardous wastes sites participating in EPA's CLP;
geometric mean concentrations for the positive samples were not reported
(CLPSD 1988). Note that the CLPSD includes data from both NPL and non-NPL
sites.

According to TRI, an estimated total of 1.3 million pounds of hydrogen
fluoride were released to soils from manufacturing and processing facilities
in the United States in 1987 (TR188 1989). However, as discussed above, these
data must be viewed with caution.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Gaseous and particulate fluorides are transported to the atmosphere from
the earth's crust via volcanic emissions and entrainment of soil particles.
The gaseous fluorides are primarily hydrogen fluoride and silicon
tetrafluoride. Vaporization and aerosol formation are the most important
processes involved in partitioning of fluorides between surface waters and the
atmosphere. Atmospheric fluorides are transported to soils and surface waters
through wet and dry deposition processes (NAS 1971a).

Transport and partitioning of fluoride compounds depend primarily on the
availability of reactants and on the physical properties of the specific
compounds, such as water solubility and volatility. Fluorides in surface
waters that are not volatilized to the atmosphere can partition to sediments
or biota (Carpenter 1969; NAS 1971a). Precipitation of insoluble fluorides
from surface waters is dependent on the amount of calcium present for
complexing (EPA 1980a). Industrial waste ponds containing fluorosilicic acid
and hydrofluoric acid partially vaporize,, introducing silicon tetrafluoride
and hydrogen fluoride into the air. High concentrations of fluorosilicic acid
favor greater concentrations of silicon tetrafluoride (NAS 1971a).

Fluorides in soils are transported to surface waters through leaching of
particulate-bound fluorides or by addition of fluoride-containing particulate
matter to the water (NAS 1971a). Leaching removes only a small amount of
fluorides from soils. For example, Oelschldger (1971) reported that about

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0.5%-6.0% of the yearly increment of fluoride added to forest and agricultural areas was lost in the leaching process.

In soils with high calcium or aluminum content, fluorides form persistent complexes. In sandy, acidic soil, water-soluble forms predominate. Fluoride compounds with high water solubility can be absorbed into vegetation. Particulate forms of fluorides may also be, deposited on vegetation by light rains and wind. Fluoride accumulates primarily in the skeletal tissues of terrestrial animals that consume fluoride-containing foliage.

Fluorides released into marine environments have been shown to accumulate in some aquatic organisms. In a study by Hemens and Warwick (1972), toxic effects due to fluorosis were observed in species of mussel, mullet, crab, and shrimp in an estuary where waste from an aluminum plant was released. There is an no information in the literature on the movement of fluoride through the terrestrial or aquatic food chains.

5.3.2 Transformation and Degradation

5.3.2.1 Air

The predominant mode of degradation of inorganic fluorides in the air is hydrolysis. Silicon tetrafluoride, a major industrial pollutant, reacts with vapor in air to form hydrated silica and fluorosilicic acid. Molecular fluorine hydrolyzes to form hydrogen fluoride and oxygen. Hydrolysis of uranium hexafluoride, which is used in nuclear power applications, also produces hydrogen fluoride as well as nonvolatile uranyl fluoride. These compounds are then removed from the atmosphere by condensation or nucleation processes. Hydrogen fluoride is stable and the most abundant species. Fluorides emitted by industries in the form of particulate matter are stable compounds that do not hydrolyze readily. ' Particulate compounds have low solubility and usually return as dusts. Particulate compounds that persist in the atmosphere are decomposed by radiation (NAS 1971a).

5.3.2.2 Water

In dilute solutions and at neutral pH, dissolved fluorides are usually present as the fluoride ion (F^-) (Bell et al. 1970). As pH decreases, the proportion of F^- decreases, while HF_2^- and nondissociated hydrogen fluoride increase. Levels of nondissociated hydrogen fluoride also increase in concentrated solutions. In sea water, fluorides exist in equilibrium. Calcium carbonate precipitation dominates the removal of dissolved fluoride from sea water. The next most important removal mechanism is incorporation into calcium phosphates (Carpenter 1969). Undissolved fluoride is generally removed by sedimentation (EPA 1980a). The residence time of fluoride in ocean sediments has been computed at 2-3 million years (Carpenter 1969).

5. POTENTIAL FOR HUMAN EXPOSURE

5.3.2.3 Soil

Fluorides tend to persist in most soils, predominantly as aluminum fluorosilicate complexes in acidic soils and calcium fluoride in alkaline soils. The retention of fluoride in alkaline soils depends largely upon the aluminum content. Soluble fluoride compounds are almost completely fixed in soils as calcium fluoride at pH 6.5 or above if sufficient calcium carbonate is available (Brewer 1966). Sandy, acidic soils favor the development of soluble forms of fluoride (Shacklette et al. 1974). Several species of plants have the capacity to convert soluble fluoride obtained from the soil into carbon-fluorine compounds such as monofluoroacetic acid, ω-fluoro-oleic acid, ω-fluoropalmitic acid, and ω-fluoromyristic acid (Marais 1944; Ward et al. 1964).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

The amount of fluoride measured in ambient air depends on the amount of fluoride emitted from a point source, the distance from the source, the meteorologic conditions, and the topography of the area (Davis 1972). In a study by Thompson et al. (1971) of 9,175 urban air samples in the United States in 1966, 1967, and 1968, 88% registered no detectable quantity of fluorides. Only 18 measurements (0.2%) exceeded 1.00 $\mu g/m^3$, the maximum being 1.89 $\mu g/m^3$. Even lower levels were found in samples taken from rural areas. Of 7,700 air samples analyzed in the United States by the National Air Pollution Control Administration in 1966 and 1967, 97% had no detectable fluoride. The lower limit of detectability was approximately 0.05 $\mu g/m^3$ (Yunghans and McCullen 1970).

Fluoride is often concentrated in the atmosphere near industrial operations. An aluminum factory that began operating in 1958 in Oregon raised the average fluoride content of foliage in cherry and peach trees from 13 ppm to 65 and 76 ppm, respectively. The highest average values measured were 196 ppm and 186 ppm, respectively, recorded in September 1960 (NAS 1971a). In 1976, fluoride levels were measured downwind of an aluminum plant that emitted 34 kg fluoride/hour; total fluoride concentration was about 0.66 $\mu g/m^3$ (Krook and Maylin 1979). The installation of scrubber devices has reduced emissions from aluminum plants, but no data were located on ambient air levels since their installation. These high concentrations decrease with increasing distance from the industrial source.

5.4.2 Water

Fluoride levels in water vary according to location and proximity to emission sources. Surface water concentrations generally range from 0.01 to 0.3 mg/L and usually do not exceed this upper level. The fluoride content of groundwater generally ranges from 0.02 to 1.5 ppm (EPA 1980a; Fleischer 1962).

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Groundwater levels are higher than surface water levels because their content
is influenced more by the minerals and rock through which they flow (EPA
1980a; NAS 1971a; WHC 1984). Water with high salinity has higher levels of
fluoride, as in the Great Salt Lake with a fluoride concentration of 14 ppm
(EPA 1980a). Sea water contains more fluoride than fresh water, ranging from
approximately 1.4-1.5 ppm (Bowen 1966; Carpenter 1969; Goldschmidt 1954).
Levels in surface and groundwater at hazardous waste sites have not been
reported by CLPSD.

5.4.3 Soil

Fluorides are widely distributed in the earth's crust. The mean
fluoride content in mineral soils ranges from 200 to 300 ppm (Bowen 1966; NAS
1971a; Worl et al. 1973). The chief fluorine-containing minerals are
fluorspar, cryolite, and fluorapatite. In soils with high concentrations of
these minerals, the soil fluoride content is much higher and may range from 7
to 38 g/kg (Smith and Hodge 1979). Average fluoride concentrations differ
between the eastern and western United States. The average concentrations are
340 ppm in the east and 410 ppm in the west (EPA 1980a). Fluoride
concentrations also tend to increase with soil depth. Of 30 domestic soil
samples, the mean fluoride concentration at a depth of 0-3 inches was 190 ppm,
whereas the mean concentration at a depth of 3-12 inches averaged 292 ppm (NAS
1971a).

On the other hand, soils near industrialized sources show elevated
concentrations that decrease with distance from the source and depth below the
surface. Concentrations of fluoride in the top 0.5 inches of soil located
near a phosphorus extraction facility near Silver Bow, Montana, were reported
to range from 265 to 1,840 ppm (Van Hook 1974).

5.4.4 Other Environmental Media

Several factors influence the level, of fluorides in food. These include
the locality in which the food is grown, the amount of fertilizer and
pesticides applied, the type of processing the food receives, and whether
fluoridated water is used in food preparation (McClure 1949; Myers 1978;
Waldbott 1963b). Foods characteristically high in fluoride content are
certain types of seafood (1.9-28.5 mg/kg), especially those types in which the
bones are consumed, bone products such as bone meal and gelatin, and tea,
which contains approximately 0.52 mg/cup (Cook 1969; Kumpulainen and
Koivistoinen 1977). Baby formula processed with fluoridated water can contain
1 mg/kg fluoride, yielding a dose of 0.27 mg/kg/day if the formula is
reconstituted with water containing 1.2 ppm fluoride (Forsman 1977); some
manufacturers now monitor fluoride levels in baby formula and keep them within
acceptable limits (Rao 1984).

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5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Fluoride intake by the general population occurs primarily through
ingestion of food and water. Since levels in ambient air are, in most cases,
below detectable limits, the levels inhaled are generally very low except for
in areas immediately surrounding industries that emit fluorides into the air.
In a study of airborne fluoride concentrations measured in community settings,
87% of all measurements at urban stations and 97% of all measurements at
nonurban stations showed concentrations below 0.05 $\mu g/m^3$, the threshold of
detectability. The maximum measurements in one study were 1.89 $\mu g/m^3$ at an
urban location and 0.16 ,$\mu g/m^3$ at a nonurban location (Yunghans and McCullen
1970). Another study reported fluoride levels 1.5 km from an aluminum plant
(Krook and Maylin 1979). The average particulate fluoride level was 0.31 $\mu g/m^3$
(5.53 $\mu g/m^3$, 12-hour maximum), and the average gaseous fluoride level was
0.36 $\mu g/m^3$ (6.41 $\mu g/m^3$, 12-hour maximum). In an occupational setting when the
airborne concentration is frequently at the exposure limit of 2.5 mg/m^3,
fluoride intake via inhalation can be 25 mg/day (OSHA 1985).

Virtually all food contains trace amounts of fluoride; estimates of the
average daily adult fluoride intake from food in the United States range from
0.8-0.9 mg (San Filippo and Battistone 1971) to 1.2-2.7 mg (Spencer et al.
1970). Total daily fluoride from diet and water in the two studies was
2.1-2.4 mg and 2.82.9-5.9 mg, respectively. Cooking food in fluoridated water
results in increased dietary fluoride levels. In England, where much more tea
is consumed, a study found daily average intake of fluoride from tea to be
1.26 mg/day in children and 2.55 mg/day in adults (Cook 1969).

In such studies, it is important to take bioavailability into account,
and not just measure the fluoride level of the consumed material. As
discussed in Sections 2.3.1.2 and 2.8, absorption is affected by factors such
as whether the material was eaten with a meal, the chemical and physical form
of the fluoride, and the current health status of the individual (Rao 1984).
For example, the bioavailability of fluoride as sodium fluoride is high. In
contrast, absorption of calcium fluoride in the solid form is rather
inefficient, but it is increased up by administration with food. Thus, the
actual absorbed dose could be smaller than that the intake levels reported in
the above studies. In addition, since determination of fluoride content in
food is preceded by ashing the sample, it is difficult to determine the amount
that is present in an ionized or ionizable form, rather than being covalently
bound in a organic molecule.

In areas where fluoride is not added to water, the total intake from
food and water does not usually exceed 1.0 mg/day (WHO 1984). Fluoride
tablets or drops are ingested in some areas where water fluoride levels are
low, providing about 0.5 mg/day. The average total dietary intake in twelve
fluoridated U.S. cities was reported to be 2.7 mg/day (Kumpulainen and
Koivistoinen 1977). In industrial settings, oral intake may also be increased

from dust contamination of food (WHO 1984). Fluoridated dentifrices and mouth rinses are additional sources of fluoride, particularly in small children who do not have complete control of the swallowing reflex. Dentifrice ingestion was inversely correlated with age; average ingested levels per brushing for children aged 2-4, 5-7, and 11-13 was 0.30, 0.13, and 0.07 g (Barnhart et al. 1974). Average fluoride intake from these sources in children <7 years old ranged from 0.3 to 0.4 mg/use for mouth rinses, depending on the child's age, and were about 0.1 mg/brushing for fluoridated toothpaste use (Ericsson and Forsman 1969).

The National Occupational Hazard Survey (NOHS), conducted by the National Institute for Occupational Safety and Health (NIOSH) for the years 1972-1974, estimated that 68,886 workers in 6,590 U.S. plants were potentially exposed to hydrogen fluoride in the workplace in 1970 (NIOSH 1976b). For sodium fluoride, the NOHS estimate was 25,059 workers in 3,763 U.S. plants (NIOSH 197613). Preliminary data from a second workplace survey, the National Occupational Exposure Survey (NOES), conducted by NIOSH from 1980 to 1983, indicated that 185,997 workers, including 67,073 women, in 11,254 plants were potentially exposed to hydrogen fluoride in the workplace in 1980 (NIOSH 1984). Estimates from the same survey for sodium fluoride are 68,571 total employees, including 21,930 women, in 2,818 plants (NIOSH 1984). Neither the NOHS nor the NOES contain information on the frequency, concentration, or duration of exposure of workers to any of the chemicals listed therein. These surveys provide only estimates of the number of workers potentially exposed to chemicals in the workplace.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Populations in hot climates and outdoor laborers generally have a greater daily intake of fluorides because of a larger consumption of water. Populations in areas such as Asia and Great Britain, where people drink substantial amounts of tea, and in areas with high consumption of seafood, also have greater daily intakes of fluorides (WHO 1984). People are exposed to greater concentrations of fluoride in the groundwater in the southwestern United States. The highest reported water fluoride concentration in each of Nevada, southern California, Utah, New Mexico, and western Texas is at least 1.5 ppm (Fleischer 1962). People with polydipsia will also ingest larger amounts of water, and hence will have higher fluoride exposure. Populations downwind of phosphate fertilizer or aluminum plants can be exposed to higher fluoride levels in the air (Ernst et al. 1986), and workers in such plants will have occupational exposure to fluorides.

Populations living in the vicinity of hazardous waste sites may be exposed to fluorides through contact with contaminated air, water, and soil. Food grown near the source could also be contaminated. Data on the concentrations of fluorides in waste site media are quite limited, and no information was located regarding daily intake of fluorides from these sources.

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5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of fluorides is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of fluorides.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Data Needs

Physical and Chemical Properties. The physical/chemical properties of fluorides are sufficiently well characterized to enable assessment of the environmental fate of these compounds.

Production, Import/Export, Use, and Disposal. Because fluoride is ubiquitous in food and water, the potential for human exposure is substantial. Human exposure to fluorine or hydrogen fluoride is unlikely outside of an occupational setting. While fluorine, hydrogen fluoride, sodium fluoride, and calcium fluoride all have industrial uses, the latter may also be used at home. Information on recent production volumes of fluorine and hydrogen fluoride was not located. In addition, although the United States relies on imports for more than 80% of its needs, the most recent data on import and export are for 1977 (885,000 metric tons) and 1975 (1,200 metric tons), respectively (Grayson 1980). Information on disposal of fluorine, hydrogen fluoride, and fluoride compounds is limited to descriptions of large-volume industrial practices. Additional quantitative information on production, import and export of fluorides, and common disposal practices would be useful in assessing the release of, and potential exposure to, these compounds.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to EPA. The Toxics Release Inventory (TRI), which contains this information for 1987, became available in May of 1989. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

5. POTENTIAL FOR HUMAN EXPOSURE

Environmental Fate. Upon release to the environment, fluorides partition to the atmosphere, soils, and sediments. The atmosphere is the main transport medium for the compounds (NAS 1971a). Fluorides undergo transformation in the atmosphere and in soils and surface waters. Information on the environmental fate of fluorides is sufficient to permit a general understanding of the widespread transport and transformation of fluorides in the environment. More information on biotransformation by plants would be useful in developing a more complete understanding of the environmental fate of fluorides.

Bioavailability from Environmental Media. Fluorides are absorbed by humans following inhalation of workplace land ambient air that has been contaminated (Chan-Yeung et al. 1983a; Waldbott 1979), ingestion of drinking water and foods (Carlson et al. 1960a; Spencer et al. 1970), and dermal contact (Buckingham 1988; Browne 1974). Information is available on factors that influence bioavailability of ingested fluoride (Rao 1984). However, this information is rarely coupled with the available information on total ingested fluoride to determine actual bioavailable dose. Additional information on absorption following ingestion of contaminated soils would be useful in determining the bioavailability of fluorides from these routes of exposure, which may be of particular importance for populations living in the vicinity of hazardous waste sites.

Food Chain Bioaccumulation. Fluorides have been shown to accumulate in animals that consume fluoride-containing foliage (Hemens and Warwick 1972), although no information has been located on whether biomagnification occurs in tissues consumed by predators. Information on bioconcentration in terrestrial and aquatic organisms and biomagnification in food chains would be helpful in assessing the importance of bioaccumulation as a route of human exposure.

Exposure Levels in Environmental Media. Fluorides have been detected in ambient air, surface water, groundwater, drinking water, and foods (Barnhart et al. 1974; Davis 1972; EPA 1980a; Waldbott 1963b). However, hhe existing monitoring data are not current. Estimates of intake via ingestion have been made for members of the general population (Kumpulainen and Koivistoinen 1977; NAS 1971a; Spencer et al. 1970; WHO 1984). Fluorides have also been detected in a limited number of surface water, groundwater, and soil samples taken at hazardous waste sites (Van Hook 1974). Additional information is needed on concentrations in ambient air, surface water, groundwater, and soils, particularly at hazardous waste sites. This information will be helpful in estimating exposures of populations living near these sites through contact with contaminated media.

Exposure Levels in Humans. Fluorides can be measured in urine, plasma, saliva, tooth enamel, bone, and other tissues. Detection of fluoride in biological tissues, particularly urine, has been used as an indicator of human exposure to fluorides in the workplace and through consumption of fluoridated

drinking water (Chan-Yeung et al. 1983a; Kaltreider et al. 1972; Spencer et al. 1970). Additional data on fluoride levels in urine and other fluids and tissues are needed for populations living near hazardous waste sites. This information will be helpful in establishing exposure profiles for waste site populations that may be exposed to higher than background levels of fluorides through contact with contaminated media. The total human intake is of interest, since multiple sources, all of which are generally considered safe by themselves, could, under some circumstances, provide total intake that is considered to be above the "safe" level.

Exposure Registries. No exposure registries for fluorides were located. This compound is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The compound will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this compound.

5.7.2 On-going Studies

Remedial investigations and feasibility studies conducted at the 177 NPL sites known to be contaminated with fluorine, hydrogen fluoride, or fluorides may add to the existing database on exposure levels in environmental media at hazardous waste sites, exposure levels in humans, and exposure registries.

No other on-going studies pertaining to the environmental fate of fluorine, hydrogen fluoride, or fluorides were identified.

6. ANALYTICAL METHODS

The purpose of this, chapter is to describe the analytical methods that are available for detecting and/or measuring andmonitoring fluorides in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify fluorides. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect fluorides in environmental samples are the methods approved by federal agencies such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL MATERIALS

Trace levels of fluoride in biological media are determined primarily by the ion selective electrode (ISE) and gas chromatography (GC) methods. Spectrophotometry is not used as often for analysis because it is not as sensitive or quantitative as the other methods (Kakabadse et al. 1971; Venkateswarlu et al. 1971). Reported recovery for most methods is greater than 90%. Most of the methods can not distinguish among different forms of inorganic fluoride. Table 6-1 describes the analytical methods for determining fluorides in biological materials.

There is extensive literature on the ISE methodology because this potentiometric analysis is the most frequently used method for fluoride measurement in biological media. For fluoride determination in urine, NIOSH (1987) recommends the ISE technique (Method 8308). It is simple, sensitive, and rapid, with a detection limit in the ng/mL range. Recoveries of fluoride are usually greater than 90%, but this is dependent on sample preparation. The ion electrode requires the sample solution to be maintained in a specific pH range and can only detect ionic fluoride. Interference may result from ions that can complex with fluoride. Prior to analysis, preparation of the biological material generally involves dilution with total ionic strength adjustment buffer, which eliminates hydroxide interference and minimizes cation interference (NIOSH 1987; Schamschula et al. 1985; Tusl 1970).

The ISE method was modified by Venkateswarlu (1974). Fluoride was extracted as fluorosilane in the biological sample, followed by a back extraction in an alkaline solution to recover the fluoride ion. This isolation step removes most of the interfering materials. The detection of fluoride is through a hanging drop fluoride electrode assembly. An agar bridge between the fluoride electrode and the reference electrode allows detection in small samples (5 μL). Another advantage is that no dilution of

TABLE 6-1. Analytical Methods for Determining Fluoride in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine	Extract with TMCS; inject organic phase (microwave induced plasma emission detector)	Gas chromatography	4 μg/L	93%	Chiba et al. 1982
	Dilute urine with TISAB buffer	Ion selective electrode	1,000 μg/L	94%-100%	Schamschula et al. 1985; NIOSH 1987; Tusl 1970
	Add TMCS toluene solution; centrifuge; inject toluene layer	Gas chromatography	>5 ng/mL	No data	Ikenishi et al. 1988
Human serum and saliva	Absorb with calcium phosphate; centrifuge; analyze	Ion selective electrode	10 μg/L	92%-102%	Venkateswarlu et al. 1971
	Absorb with calcium phosphate; collect by diffusion; analyze (with cerium-alizarin complexan reagent)	Spectrophotometry	No data	95%-102%	Venkateswarlu et al. 1971
Saliva	Resuspend in TISAB buffer; analyze	Ion selective electrode	No data	99.8%	Peterson et al. 1987; Schamschula et al. 1985
Plasma	Add TMCS toluene solution; centrifuge; inject toluene layer and analyze	Gas chromatography	5 μg/L	91.4%	Ikenishi et al. 1988b
Biological tissues and fluids	Extraction from acidified sample as fluorosilane; reverse extraction as fluoride ion into alkaline solution	Ion selective electrode with hanging drop assembly	>0.04 ng/sample	No data	Venkateswarlu 1974
Biological tissues	Sample pulverized to fine powder; irradiate; detect gamma rays	Nuclear inelastic scattering	<10 ng/sample	No data	Rudolph et al. 1973

TABLE 6-1 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
	Decomposition of sample at 700°-1,000°C (pyrohydrolytic technique)	Spectrophotometry	1 μg/sample	No data	Kakabadse et al. 1971
Tooth enamel	Soak teeth; decalcify in $HClO_4$; add TISAB; analyze	Ion selective electrode	No data	No data	Shida et al. 1986; Schamschula et al. 1982
Plaque	Dried; microdiffusion; analyze	Ion selective electrode	No data	97%	Schamschula et al. 1985
Bone	Ash sample; dissolve in perchloric acid; add 1,2-cyclohexylenedinitro-tetraacetic acid	Ion selective electrode	No data	No data	Boivin et al. 1988
Hair/finger nail	Wash in diethylether; dry; decomposed in NaOH	Ion selective electrode	No data	94%-96%	Schamschula et al. 1985

$HClO_4$ = perchloric acid
NaOH = sodium hydroxide
TISAB = total ionic strength activity buffer
TMCS = trimethylchlorosilane

6. ANALYTICAL METHODS

the sample is required, and thus greater sensitivity (0.04 ng/sample) is obtained.

Recent studies have employed GC to measure fluoride concentrations in human urine and plasma (Chiba et al. 1982; Ikenishi and Kitagawa 1988; Ikenishi et al. 1988). Trimethylchlorosilane (TMCS) toluene solution was added to samples to produce trimethylfluorosilane (TMFS). The organic layer was injected into the GC system. The benefit of this method is its sensitivity and wide application; it can detect bound fluorine, as well as free fluoride ion, on the chromatogram. This detection of bound fluorine provides an advantage over the ISE technique, which is not suitable for bound or organic fluoride measurements. ISE samples must be initially subjected to isolation methods. It should also be noted that the aluminum ion may cause interference under the operating conditions of GC, as it does with the ISE method.

Bone fluoride levels can be measured using the ISE technique after ashing of the sample (Boivin et al. 1988). The addition of 1,2-cyclohexylenedinitrotetraacetic acid prevents interference by aluminum and iron. A method was developed by Rudolph et al. (1973) in which biological samples were subjected to irradiation followed by gamma ray identification of fluoride concentrations. This analysis has not been fully exploited, but has been tested in tooth samples and bone biopsies. The nuclear inelastic scattering technique is sensitive to trace amounts of sample and requires minimal sample preparation. Accuracy, however, is not as high as that found in the GC and ISE techniques. The instrument used for this method is equipped with a lithium-drifted germanium detector. Interference from bound fluoride or other ions has not yet been shown to occur in this irradiation technique.

Most studies describe methods for monitoring fluoride in the urine, plasma, and/or biological tissue. Little information was located regarding fluoride levels in human enamel. Shida et al. (1986) measured fluoride concentrations in different layers of the surface enamel of extracted incisors. Tooth samples were decalcified and analyzed by the ISE technique. A distribution pattern of fluoride levels on the surface layer of human enamel was shown. However, the correlation between fluoride exposure and the concentration in the tooth was not determined. A similar method was employed by Schamschula et al. (1982) on enamel of children. They found that the fluoride content of enamel did reflect fluoride exposure of the group, but variations occurred within the individuals. A scaled-down version of this method was employed by Retief et al. (1987). Instead of analyzing the whole tooth, individual surfaces could be analyzed by etching the teeth with small volumes.

The literature indicates that the ion selective electrode and gas chromatography are the most commonly available and widely used methods. Modifications of the sample preparation and the instruments themselves to improve sensitivity and recovery are frequently reported.

6. ANALYTICAL METHODS

6.2 ENVIRONMENTAL SAMPLES

The ISE method is the most widely used method for determining fluoride levels in the environmental media. Table 6-2 describes this and other methods for determining fluoride in environmental samples, The convenience, precision, and sensitivity of this method make it suitable for various sample matrices. A limitation is that the electrode can identify only free fluoride ions. Because of the inherent restriction of this technique, several approaches have been recommended to prepare the sample for analysis. Lopez and Navia (1988) assayed total fluoride (bound and free) in food and beverages by initially acid hydrolyzing samples at 100°C in borosilicate vials. This closed-system approach decreases contamination, eliminates dry ashing, and yields high recoveries. Dabeka and McKenzie (1981) employed microdiffusion to food samples in Petri dishes at 60°C for 24-48 hours. Difficulties arose in controlling contamination and fluoride loss in the Petri dishes, and low recoveries were reported. Preparation of total fluoride in dry plant material (i.e., hay, barley, straw, corn, grass) was described by Eyde (1982); samples were fused in nickel crucibles with sodium hydroxide at 350°-475°C. The ash was diluted and filtered for analysis. This method is more tedious than the others, and fluoride loss is expected from the high decomposition temperatures. All of these preparatory techniques can liberate bound fluoride from the sample matrices. It is important to prevent interference of other ions and to avoid fluoride loss at high decomposition temperatures before potentiometric analyses.

Kakabadse et al. (1971) described a pyrohydrolytic technique for tea, coca, or tobacco samples that could be employed prior to spectrophotometric or ISE fluoride analysis. Decomposition of the sample at 700°-1,000°C is mediated by a current of air or pure oxygen to evolve hydrogen fluoride. An advantage of this approach is that fluoride is collected from inorganic and organic fluorides in one operation. Ashing, which may produce loss of organic fluorine, is eliminated.

For the analysis of pollutants in the environment, EPA has approved the manual electrode procedure (Method 340.2), the calorimetric procedure (SPADNS) (Method 340.1), and the automated complexone procedure (Method No. 340.3) for determining inorganic fluoride in air, water, and vegetation (EPA 1988).

Kojima et al. (1972) evaluated fluorine levels in laboratory organic compounds of known compositions with a GC detection technique using an ISE. This combined system selectively detects organic compounds and in addition provides information on the sample composition. The sample is injected into the gas chromatograph, which can separate the organic components and cause hydrogenolysis. The hydrogen fluoride produced is absorbed and passed through the fluoride ion selective electrode. A chromatogram of fluorine compound peaks and the fluoride ion concentration are reported. This is a sensitive, stable, and rapid method. However, this technique has been tested only with

TABLE 6-2. Analytical Methods for Determining Fluoride in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Ambient air collected using teflon tubing; detect with continuous flow analyzer	Ion selective electrode	0.1 μg/L	No data	Danchik et al. 1980
	HF vapor collected with dosimeter containing polypropylene element; analyze	Ion selective electrode	100 μg/L	No data	Young and Monat 1982
	Dual cellulose filter to separate particulate and gaseous fluorides; extract; dilute in TISAB buffer; analyze	Ion selective electrode	3 μg/sample	No data	NIOSH 1990a
	Dual cellulose filter to separate particulate and gaseous fluoride; heat filters at 75°C; extract; dilute in TISAB buffer; analyze	Ion selective electrode	1.2 μg/filter	No data	Einfeld and Horstman 1979
	Sampling performed with teflon materials (in municipal incineration)	Ion selective electrode	1 ppm	No data	Candreva and Dams 1981
	Syringe-sampling; dilute with 50% (v/v) 1,2-dioxane containing Amadec-F (colorimetric)	Spectrophotometry	0.3 ppm	No data	Bethea 1974
Water	Dilute sample; add barium chloride, complex with zirconium-xylenol orange for color development (colorimetric)	Spectrophotometry	2,000 μg/L	No data	Macejunas 1969
	Extract with TMCS; analyze organic phase (microwave induced plasma emission detector)	Gas chromatography	4 μg/L	93%-100%	Chiba et al. 1982

TABLE 6-2 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
	Collect sample in polyethylene containers; centrifuge; extract; dilute; analyze	HPLC/ion exchange column	200 μg/L	No data	Hannah 1986
Food, beverage	Homogenize sample; acid hydrolysis in a closed system; analyze	Ion selective electrode	~0.1 μg/g	97%	Lopez and Navia 1988
	Sample pulverized to powder, analyze Fluorine-19 peak	Proton activation	1 μg/g dry weight	No data	Shroy et al. 1982
Tea, cocoa, tobacco	Decomposition at 700°-1,000°C in moist current of oxygen or air; collect HF; analyze as Ce(III) alizarin-complexan (colorimetric)	Spectrophotometry	>1 μg	No data	Kakabadse et al. 1971
Milk, peas, pears	Sample is dried and ground to powder; microdiffusion in Petri dish; analyze	Ion selective electrode	0.2-5 μg/g	54%-109%	Dabeka and McKenzie 1981
Vegetation	Fluorine-19 sample activation; analyze Fluorine-20 peak	Neutron activation	14 μg/sample	No data	Knight et al. 1988
	Extraction of sample	Ion selective electrode	>0.05 μg/g	>95%	Jacobson and Heller 1971
	Fusion with NaOH; dissolve in tiron buffer; analyze	Ion selective electrode	10 μg/g	No data	Sager 1987
Feed	Sample is dried and acidified; analyze by addition procedure	Ion selective electrode	15 μg/g	90%-108%	Melton et al. 1974

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TABLE 6-2 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Household products	Dilute sample, add buffer; addition procedure	Ion selective electrode	No data	98%-104%	Schick 1973
Plants	Sample dried and fused in nickel crucibles, filter, analyze	Ion selective electrode	>0.3 μg/g	87%-102%	Eyde 1982
Rainwater	Dilute sample with TISAB buffer; analyze in flow injection system	Ion selective electrode	2 μg/L	No data	Fucsko et al. 1987

Ce III = cesium ion (+3 oxidation state)
HF = hydrogen fluoride
HPLC = high pressure liquid chromatography
NaOH = sodium hydroxide
TISAB = total ionic strength activity buffer
TMCS = trimethylchlorosilane
(v/v) = volume/volume

laboratory chemicals with a known fluorine composition and has not yet been used for measuring fluorine in biological or environmental samples.

Fluoride gas or vapors in ambient air are measured primarily with the ISE method. NIOSH (1987) recommends this method (Method 7902) for gaseous and aerosol fluorides with the two forms undergoing collection on separate filters before determination. However, the best method for sampling fluoride in air depends on the form of fluoride being measured. Several modifications have been suggested for the air sample collection. Einfeld and Horstman (1979) found that gaseous fluoride, to some extent, may get trapped in the filter for particulate fluoride. They suggest that postsampling heat treatment promotes desorption of the gaseous fluoride from the particulate phase. The use of Teflon® tubing and materials in the analyzer is indicated for controlling loss of sample ions (Candreva and Dams 1981; Danchik et al. 1980).

Young and Monat (1982) developed a dosimeter to be worn on the lapel in the workplace for monitoring airborne fluoride vapor. A replaceable collection element adsorbs the fluoride vapors. Samples are desorbed with TISAR solution and analyzed on the ISE. The study authors noted its convenience, stability, retentivity, and insensitivity to moisture at 5%-88% humidity and competing sulfur dioxide vapors. Interference may occur from reactive volatile fluorine compounds (i.e., uranium hexafluoride, fluorine gas) as well as wind speed, temperature, and pressure. This dosimeter yields a sample detection range of 0.1-387 ppm fluoride in air.

Two analytical methods for fluorine determination have been developed based on irradiation activation of fluorine-19 (Knight et al. 1988; Shroy et al. 1982). Instruments equipped with lithium-drifted germanium detectors measure gamma rays for fluorine determination. This approach has a wide application since it does not depend on a specific sample matrix or chemical form. However, activated fluorine is unstable, and analysis may be time consuming. Furthermore, background peaks may overlap fluorine peaks and affect the determination.

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of fluorides is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of fluorides.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate

the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Sensitive, reproducible analytical methods are available for detecting fluorides in biological materials following short-term exposure (such as plasma and urine) and long-term exposure (i.e., bone). The most prevalent technique is the ISE method because it is reliable, simple, sensitive, and yields good recoveries (NIOSH 1987; Venkateswarlu et al. 1971). GC is also useful for detection of trace levels of fluoride in plasma and urine (Chiba et al. 1982; Ikenishi and Kitagawa 1988; Ikenishi et al. 1988). Both methods can measure samples at concentrations at which health effects may occur. Additional analytical methods are needed for evaluating bound or organic fluorides directly from the sample since most analytical methods require a sample preparation step to isolate fluoride from complexes. However, the significance to fluoride toxicology of bound or organic fluoride is unclear. Sample preparation increases the risk of contamination and low recoveries. Thus, a need also exists for refining initial isolation techniques.

Urinary fluoride concentration is a widely accepted biomarker of recent fluoride exposure and has frequently been used as an indicator of fluoride exposure in occupational studies (Chan-Yeung et al. 1983a; Kaltreider et al. 1972) and to determine exposure from drinking water (Spak et al. 1985). A minimum fluoride level of 4 mg/L in the urine using the ISE technique has been recommended as an indicator of recent fluoride exposure in workers (Derryberry et al. 1963). Other possible biomarkers of fluoride exposure include fluoride concentrations in tooth enamel (Shida et al. 1986), saliva (Peterson et al. 1987), blood (Jackson and Hammersley 1981), and bone (Baud et al. 1978; Bruns and Tytle 1988; Fisher 1981; Sauerbrunn et al. 1965) for which analytical methods are available. Except for fluoride in blood, these indices are not well established for quantitating fluoride exposure. More sensitive methods for long-term exposure to fluorides would be useful for determining the threshold levels that differentiate beneficial effects (caries prevention) and detrimental effects (fluorosis). Improving methods such as ISE and GC for other indices (plasma, tooth enamel) would be useful for more sensitive quantitative assessment of fluoride exposure and distribution.

For biomarkers of effect following chronic exposure, investigators have looked for skeletal fluorosis using radiographs. Bone density is a common index used for evaluation (Kaltreider et al. 1972). Guminska and Sterkowicz (1975) found an increase in erythrocyte enzyme activity (i.e., enolase, pyruvate kinase, ATPase) that may reflect altered glucose metabolism during prolonged fluoride exposure. These biochemical alterations are suggested for possible diagnostic purposes, but they represent a response that may be

induced in the body by a physiological change or other chemical agents.
Therefore, more specific analytical methods are needed for measuring
biomarkers of effect.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Human exposure to fluoride is most likely to occur from ingesting water or food containing high levels of fluoride. Fluoride in
ambient air is another source of exposure, particularly for workers in some occupations (smelting, electroplating, metallurgical processes). The ISE method is the most common method for measuring fluoride in environmental samples. It is a convenient, sensitive, and reliable method, but does not detect bound fluorides. Several sample preparation techniques are available for the necessary step of isolating the free fluoride ion (Dabeka and McKenzie 1981; Eyde 1982; Kakabadse et al. 1971; Lopez and Navia 1988). These methods are usually inconvenient and yield low recoveries, along with a potential risk of contamination. Improved collection techniques for fluoride would be useful for increasing the accuracy and reliability of analyses.

6.3.2 On-going Studies

No on-going studies regarding techniques for measuring and determining fluoride in biological and environmental samples were located.

7. REGULATIONS AND ADVISORIES

Hydrogen fluoride is on the list of chemicals appearing in "Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986" (EPA 1987). Fluorine, sodium fluoride, and the class of chemicals known as fluorides do not appear on that list.

No international regulations pertaining to fluorides were found. The national and state regulations and guidelines regarding fluorine, hydrogen fluoride, and fluorides in air, water, and other media are summarized in Table 7-1.

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to Fluorine, Hydrogen Fluoride, or Fluoride

Agency	Description	Information	References
NATIONAL			
Regulations:			
a. Air:			
OSHA	PEL TWA (8 hours)		OSHA 1989
	Fluoride (as F)	2.5 mg/m^3	
	Fluoride as dust	2.5 mg/m^3	
	Hydrogen fluoride	3.0 ppm	
	Fluorine	0.1 ppm [0.2 mg/m^3]	
b. Water:			
EPA ODW	MCL (fluoride)	4.0 mg/L	EPA 1985b (40 CFR 141.62)
	SMCL (fluoride)	2.0 mg/L	EPA 1979 (40 CFR 143.3)
FDA	Bottled water; quality standard		FDA 1977 (21 CFR 103)
	Imported[a]	1.4 mg/L	
	Domestic[b]		
	(Corresponding to the range of annual average maximum air temperatures 53.8°-90.5°C)		
	Where no fluoride is added to water	2.2-1.4 mg/L	
	Where fluoride is added to water	1.5-0.8 mg/L	
c. Food:			
EPA	Tolerances and exemptions from tolerances for pesticide chemicals in or on raw agricultural commodities		EPA 1971 (40 CFR 180.145)
	Fluorine compounds; tolerances for residues of cryolite and synthetic cryolite (sodium aluminum fluoride) on several raw agricultural commodities	7 ppm	
FDA	Tolerances for pesticides in food administered by EPA	No data	FDA (21 CFR 193.450)
d. Other:			
EPA OERR	CERCLA reportable quantity		EPA 1986 (40 CFR 117.3)
	Fluorine	10 pounds (4.54 kg)	
	Hydrogen fluoride	100 pounds (45.4 kg)	
	Sodium fluoride	1,000 pounds (454 kg)	
	Extremely hazardous substance TPQ		TPCDB 1989
	Fluorine	500 pounds	

7. REGULATIONS AND ADVISORIES

TABLE 7-1 (Continued)

Agency	Description	Information	References
NATIONAL (Continued)			
EPA OSW	Designation of hazardous substances		EPA 1978 (40 CFR
	Hydrogen fluoride	Yes	116.4)
	Sodium fluoride	Yes	
RCRA	Fluorine designated as hazardous substance	Yes	EPA (40 CFR 302.4)
Guidelines:			
a. Air:			
ACGIH	TLV TWA (fluoride)	2.5 mg/m^3	ACGIH 1990
	Ceiling (hydrogen fluoride-- as fluoride)	3 ppm	
	TLV (fluorine)	1 ppm	
	TLV-STEL (fluorine)	2 ppm	
	Biological exposure indices		ACGIH 1990
	In urine		
	Prior to shift	3mg/g	
	End of shift	10mg/g creatinine	
NIOSH			NIOSH 1990b
	Fluoride:		
	REL TWA	2.5 mg/m^3	
	IDLH	500 mg/m^3	
	Hydrogen Fluoride:		
	REL TWA	3 ppm [2.5 mg/m^3]	
	IDLH	30 ppm	
	Fluorine:		
	REL TWA	0.1 ppm [0.2 mg/m^3]	
	IDLH	25 ppm	
NAS	PEL (for hydrogen fluoride)		NAS 1971a
	10 minutes	8 mg/m^3 (10 ppm)	
	30 and 60 minutes	4 mg/m^3 (5 ppm)	
	STPL (for hydrogen fluoride)		NAS 1971a
	10-30 and 60 minutes	3 mg/m^3 (4ppm)	
	5 hour/day, 3-4 days/month	1 mg/m^3	
b. Water:			
EPA ODW	MCLG (fluoride)	4.0 mg/L	EPA 1985a (40 CFR 141.51)
c. Other:			
EPA	RfD (oral) for soluble fluorides	6x10^{-2} mg/kg/day	IRIS 1992
OSHA	Meets criteria for proposed OSHA medical records rule	Yes	OSHA 1982

7. REGULATIONS AND ADVISORIES

TABLE 7-1 (Continued)

Agency	Description	Information	References
STATE			
Regulations and Guidelines:			
a. Air:	Average acceptable ambient air concentrations for fluorides		NATICH 1989
Iowa	(24 hour)	2.85 $\mu g/m^3$	
Kentucky	(monthly)	80.00 ppm	
Massachusetts	(24 hour)	34.00 $\mu g/m^3$	
Montana[c]	(Grazing season)	35.00 ppm	
North Carolina	(1 hour)	0.25 mg/m^3	
	(24 hour)	0.0160 mg/m^3	
North Dakota	(8 hour)	0.0250 mg/m^3	
Virginia	(24 hour)	40.00 $\mu g/m^3$	
	Average acceptable ambient air concentrations for fluorine		NATICH 1989
Connecticut	(8 hour)	4.00 $\mu g/m^3$	
Florida-Tampa	(8 hour)	0.0200 mg/m^3	
North Carolina	Under consideration		
North Dakota	(1 hour)	0.0400 mg/m^3	
	(8 hour)	0.0200 mg/m^3	
Nevada	(8 hour)	0.0480 mg/m^3	
New York	(1 year)	6.700 $\mu g/m^3$	
Virginia	(24 hour)	30.00 $\mu g/m^3$	
	Average acceptable ambient air concentrations for hydrogen fluoride		NATICH 1989
Connecticut	(8 hour)	50.00 $\mu g/m^3$	
Kentucky	(24 hour)	1.00 ppm	
Massachusetts	(24 hour)	3.400 $\mu g/m^3$	
North Carolina	(15 minutes)	0.2500 mg/m^3	
	(24 hour)	0.0250 mg/m^3	
North Dakota	(1 hour)	0.0250 mg/m^3	
Nevada	(8 hour)	0.0600 mg/m^3	
New York	(1 year)	8.300 $\mu g/m^3$	
Rhode Island	(1 hour)	30.00 $\mu g/m^3$	
South Carolina	(24 hour)	25.00 $\mu g/m^3$	
South Dakota	(8 hour)	50.00 $\mu g/m^3$	
Virginia	(24 hour)	20.00 $\mu g/m^3$	
b. Water:	Drinking water quality standards and guidelines		FSTRAC 1989
Arizona	(Fluoride at 20°C)	1800 $\mu g/L$	
Maine	(Fluoride)	2400 $\mu g/L$	

7. REGULATIONS AND ADVISORIES

TABLE 7-1 (Continued)

Agency	Description	Information	References
	Maximum contaminant levels for fluorides		CELDS 1989
Arkansas	(Not specified)	2.4 mg/L	
Colorado	(Not specified)	4.0 mg/L	
Connecticut	(For drinking waters)	2.0 mg/L	
Florida	(Not specified)	4.0 mg/L	
	(Secondary MCL)	2.0 mg/L	
Florida	(For drinking waters)	1.5 mg/L	
Idaho	(Fluorides up to 12.0°C)	2.4 mg/L	
	(12.1°–14.6°C)	2.2 mg/L	
	(14.7°–17.6°C)	2.0 mg/L	
	(17.7°–21.4°C)	1.8 mg/L	
	(21.5°–26.1°C)	1.6 mg/L	
	(26.3°–32.5°C)	1.4 mg/L	
Illinois[d]	(Maximum allowable concentration)	1.8–2.0 mg/L	
	(Not specified)	1.4 mg/L	
	(Secondary contact, and for aquatic life)	15.0 mg/L	
	(Effluent levels, surface and groundwater)	15.0 mg/L	
Indiana	(Recreational water uses)	1.0 mg/L	
	(For Lake Michigan, Inner, Gary, and Burns Harbors, monthly average)	1.0 mg/L	
Iowa	(Not specified)	4.0 mg/L	
	(For class C waters)	2.0 mg/L	
Kansas	(For drinking waters)	1.8 mg/L	
Maine	(Not specified)	2.4 mg/L	
Massachussetts	(Minimum criteria for groundwaters)	2.4 mg/L	
	(Primary effluent limits for groundwaters)	2.4 mg/L	
Minnesota	(For groundwater and drinking water)	2.2 mg/L	
		1.5 mg/L	
Mississippi	(For drinking waters)	1.2 mg/L	
Missouri	(Effluent limitations for subsurface waters)	4.0 mg/L 2 mg/L	
Nebraska	(Groundwater protection standard)	4.0 mg/L	
	(For drinking waters)	1.8 mg/L	
Nevada	(For groundwater domestic water)	1.4–2.4 mg/L	
New Hampshire	(For drinking water)	2.4 mg/L	
New Mexico	(For groundwater and human health)	1.6 mg/L	
New York	(For drinking waters)	2.2 mg/L	
	(For groundwaters—class GA)	1.5 mg/L	
	(Effluent standards)	3.0 mg/L	
North Carolina	(For drinking waters)	1.5 mg/L	
	(For community water systems)	4.0 mg/L	
North Dakota	(Not specified)	2.4 mg/L	

7. REGULATIONS AND ADVISORIES

TABLE 7-1 (Continued)

Agency	Description	Information	References
Ohio	(Not specified)	1.0 mg/L	
	(For public water supply, maximum level)	1.8 mg/L	
	(For agricultural use, maximum level)	2.0 mg/L	
	(For Lake Erie water quality)	1.2 mg/L	
Oklahoma	(Not specified)	4.0 mg/L	
	(Secondary standards)	2.0 mg/L	
	(For raw water, fluoride at 90°F)	1.6 mg/L	
	(Maximum effluent concentrations)	1.0 mg/L	
Puerto Rico	(Coastal waters limit)	1300 μg/L	
	(Surface waters limit)	700 μg/L	
Rhode Island	(For drinking waters)	2.0 mg/L	
South Carolina	(Not specified)	1.6 mg/L	
South Dakota	(Not specified)	4 mg/L	
	(Criteria for domestic water)	2.4 mg/L	
Tennessee[d]	(For community water systems)	2.0 mg/L	
	(For industrial wastewater treatment plants daily maximum concentration of soluble fluorides)	20.0 mg/L	
Utah	(Not specified)	1.4-2.4 mg/L	
Vermont	(Potable groundwaters)	2.2 mg/L	
Virginia[d]	(Primary MCL)	1.8 mg/L	
Washington	(Primary contamination)	4.0 mg/L	
	(Secondary contamination)	2.0 mg/L	
Wisconsin	(For drinking water)	2.2 mg/L	
Wyoming	(Groundwater, domestic water)	1.4-2.4 mg/L	

[a]The standard for imported bottled water is not specific for fluoride-treated and non-fluoride-treated water.

[b]The range in average maximum air temperatures corresponds respectively to the range in domestic bottled water standards values presented, with the lower air temperatures corresponding to the higher standard values.

[c]Montana has adopted the listed acceptable air concentration for fluorides in order to protect grazing cattle from fluorosis. Therefore, this value is averaged over the grazing season which starts in the spring.

[d]Public water systems, which artificially fluoridate the water, should maintain the fluoride level between 0.8 and 1.3 mg/L.

ACGIH = American Conference of Governmental Industrial Hygienists; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IDLH = Immediately Dangerous to Life or Health Level; MCL = Maximum Contaminant Level; MCLG = Maximum Contaminant Level Goal; NAS = National Academy of Sciences; NIOSH = National Institute for Occupational Safety and Health; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Wastes; PEL (for OSHA) = Permissible Exposure Limit; PEL (for NAS) = Public Emergency Limits; RCRA = Resource Conservation and Recovery Act; REL = Recommended exposure limit; RfD = Reference dose; SMCL = Secondary Maximum Contaminant Level; STPL = Short-Term Public Limits; TLV = Threshold Limit Value; TPQ = Threshold Planning Quantity; TWA = Time-Weighted Average

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9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{oc}) -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) -- The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL) -- The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen -- A chemical capable of inducing cancer.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

9. GLOSSARY

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

In vivo -- Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC$_{LO}$) -- The lowest concentration of a chemical in air which has been reported to have cause death m humans or animals.

Lethal Concentration$_{(50)}$ (LC$_{50}$) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD$_{LO}$) -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD$_{50}$) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT$_{50}$) -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) -- The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations -- Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level -- An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow}) -- The equilibrium ratio of the concentrations of a chemical in n-octanoland water, in dilute solution.

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

q_1* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually $\mu g/L$ for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 3 11 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

9. GLOSSARY

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen -- A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD$_{50}$) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in nontechnical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or substance release. If the Public Health Statement were removed from the rest of the document. it would still communicate to the lay public essential information about the substance.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1.2-2. and 2-3) and figures (2-1 and 2-2) are used to summarize health effects by duration of exposure and endpoint and to illustrate graphically levels of exposure associated with those effects. AU entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed- Adverse-Effect Levels (LOAELs) for Less Serious and Serious health effects, or Cancer Effect Levels (CELs). In addition, these tables and figures illustrate differences in response by species.Minimal Risk Levels (MRLs) to humans for noncancer end points. and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10.000 to 1 in 10.000.000. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text.

The legends presented below demonstrate the application of these tables and figures. A representative example of LSE Table 2- 1 and Figure 2-l are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND
See LSE Table 2-1

(1). <u>Route of Exposure</u> One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2. and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-l) and oral (LSE Figure 2-2) routes.

(2). <u>Exposure Duration</u> Three exposure periods: acute (14 days or less): intermediate (15 to 364 days): and chronic (365 days or more) are presented within each route of exposure. In this example, an inhalation study of intermediate duration exposure is reported.

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(3). <u>Health Effect</u> The major categories of health effects included in LSE tables and figures are death. systemic. Immunological, neurological, developmental, reproductive and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects can be further defined in the "System" column of the LSE table.

(4). <u>Key to Figure</u> Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to define a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in Figure 2-l).

(5). <u>Species</u> the test species, whether animal or human, are identified in this column.

(6). <u>Exposure Frequency/Duration</u> The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to [substance x] via inhalation for 13 weeks, 5 days per week, for 6 hours per day.

(7). <u>System</u> This column further defines the systemic effects. These systems include: respiratory, cardiovascular. gastrointestinal, hematological. musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated in this study.

(8). <u>NOAEL</u> A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9). <u>LOAEL</u> A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest exposure level used in the study LOAEL that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The "Less Serious" respiratory effect reported in key number 18 (hyperplasia) occurred at a LOAEL of 10 ppm.

(10). <u>Reference</u> The complete reference citation is given in Chapter 8 of the profile.

(11). <u>CEL</u> A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiological studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses which did not cause a measurable increase in cancer.

(12). <u>Footnotes</u> Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

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LEGEND

See LSE Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables.
Figures help the reader quickly compare health effects according to
exposure levels for particular exposure duration.

(13).   Exposure Duration The same exposure periods appear as in the LSE table. In
            this example, health effects observed within the intermediate and chronic
            exposure periods are illustrated.

(14).   Health Effect These are the categories of health effects for which reliable
            quantitative data exist. The same health effects appear in the LSE table.

(15).   Levels of Exposure Exposure levels for each health effect in the LSE tables
            are graphically displayed in the LSE figures. Exposure levels are reported on
            the log scale "y"axis. Inhalation exposure is reported in mg/m^3 or ppm and
            oral exposure is reported in mg/kg/day.

(16).   NOAEL In this example, 18r NOAEL is the critical end point for which an
            intermediate inhalation exposure MRL is based. As you can see from the LSE
            figure key, the open-circle symbol indicates a NOAEL for the test species
            (rat). The key number 18 corresponds to the entry in the LSE table. The
            dashed descending arrow indicates the extrapolation from the exposure level
            of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote
            "b" in the LSE table).

(17).   CEL Key number 38r is one of three studies for which Cancer Effect Levels
            (CELs) were derived. The diamond symbol refers to a CEL for the test species
            (rat). The number 38 corresponds to the entry in the LSE table.

(18).   Estimated Upper-Bound Human Cancer Risk Levels This is the range associated
            with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in
            10.000.000. These risk levels are derived from EPA's Human Health As.sessment
            Group's upper-bound estimates of the slope of the cancer dose response curve
            at low dose levels (q_1*).

(19).   Key to LSE Figure The Key explains the abbreviations and symbols used in the
            figure

1 ──────────────────────────→ TABLE 2-1. Levels of Significant Exposure to [Chemical x] - Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	

2 ──→ **INTERMEDIATE EXPOSURE**

3 ──→ Systemic   [5]   [6]   [7]   [8]   [9]   [10]

4 ──→ 18   Rat   13 wk   Resp   3[b]   10 (hyperplasia)   Nitschke et al.

                5d/wk   1981

                6hr/d

CHRONIC EXPOSURE

   Cancer   [11]

   38   Rat   18 mo   20 (CEL, multiple   Wong et al. 1982

                5d/wk   organs)

                7hr/d

   39   Rat   89-104 wk   10 (CEL, lung tumors,   NTP 1982
                5d/wk   nasal tumors)
                6hr/d

   40   Mouse   79-103 wk   10 (CEL, lung tumors,   NTP 1982
                5d/wk   hemangiosarcomas)
                6hr/d

[a] The number corresponds to entries in Figure 2-1.

12 ──→ [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)
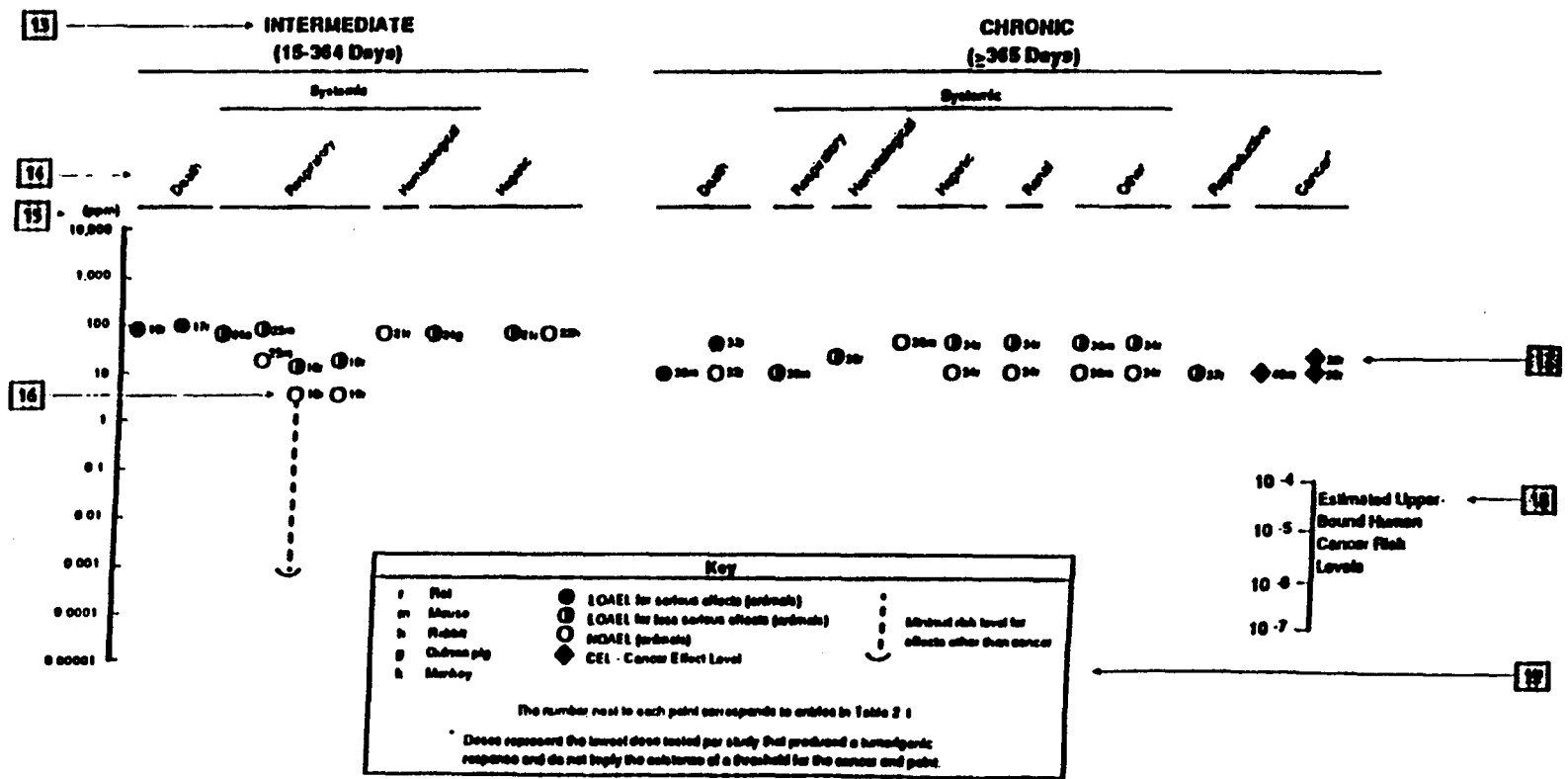
FIGURE 2-1. Levels of Significant Exposure to [Chemical X]-Inhalation

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Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicological, epidemiological, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1.   What effects are known to occur in humans?

2.   What effects observed in animals are likely to be of concern to humans?

3.   What exposure conditions are likely to be of concern to humans. especially round hazardous waste sites?

The section discusses health effects by end point. Human data are presented first. then animal data. Both are organized by route of exposure (inhalation, oral, and dermal) and by duration (acute. intermediate. and chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate. using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Marls for noncancer end points if derived, and the end points from which they were derived are indicated and discussed in the appropriate section(s).

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the identification of Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information was available, MRLs were derived. MRLs are specific for route (inhalation or oral) and duration (acute, intermediate, or chronic) of exposure. Ideally, MRLs can be derived from all six exposure scenarios (e.g.. InhaIation - acute, -intermediate, -chronic; oral - acute, -intermediate. - chronic). These MRLs are not meant to support regulatory action, but to aquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a substance emission, given the concentration of a contaminant in air or the estimated daily dose received via food or water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users shouid be familiar with the toxicological information on which the number is based. Section 2.4,"Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.6, "Interactions with Other Chemicals" and 2.7, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology used by the Environmental Protection Agency (EPA) (Barnes and Dourson, 1988: EPA 1989a) to derive reference doses (RfDs) for lifetime exposure.

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To derive an MRL, ATSDR generally selects the end point which. in its best judgement. represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential effects (e.g., systemic, neurological and developmental). In order to compare NOAELs and LOAELs for specific end points, all inhalation exposure levels are adjusted for 24hr exposures and all intermittent exposures for inhalation and or,al routes of intermediate and chronic duration are adjusted for continous exposure (i.e., 7 days/week). If the information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. The NOAEL is the most suitable end point for deriving an MRL. When a NOAEL is not available, a Less Serious LOAEL can be used to derive an MRL, and an uncertainty factor (UF) of 10 is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of 10 each are used for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncentainty factors are multiplied together. The product is then divided into the adjusted inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MLR are provided in the footnotes of the LSE Tables.

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
f_1	first generation
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
HPLC	high performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
Koc	octanol-soil partition coefficient
Kow	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration low
LC_{50}	lethal concentration 50 percent kill
LD_{Lo}	lethal dose low
LD_{50}	lethal dose 50 percent kill

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LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeters
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectroscopy
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
nm	nanometer
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportional mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short-term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxic Release Inventory
TWA	time-weighted average
U.S.	United States

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UF	uncertainty factor
WHO	World Health Organization
>	greater than
$\geq$	greater than or equal to
=	equal to
<	less than
$\leq$	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram

APPENDIX C

PEER REVIEW

A peer review panel was assembled for fluorine, hydrogen fluoride and fluoride. The panel consisted of the following members: Dr. Ingeborg Harding-Barlow, private consultant, Palo Alto, California; Dr. Thomas Hinesly, Professor of Soil Ecology, Department of Agronomy, University of Illinois, Urbana, Illinois; and Dr. Caroline Kramer, Assistant Professor, Department of Pharmacology and Toxicology, Medical College of Virginia, Richmond, Virginia. These experts collectively have knowledge of the physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans of fluorine, hydrogen fluoride, and fluoride. All reviewers were selected in conformity with the conditions for peer review specified in the Comprehensive Environmental Response, Compensation, and Liability Act of 1986, Section 104.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.