DRAFT
TOXICOLOGICAL PROFILE FOR FLUORINE, HYDROGEN FLUORIDE, AND FLUORIDES

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (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 succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is 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.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that 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 are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance 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 that present a significant risk to human health of acute, subacute, and chronic health effects; and

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

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. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Comments should be sent to:

Agency for Toxic Substances and Disease Registry
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Background Information

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential

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This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Jeffrey P. Koplan, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by *type of health effect* (death, systemic, immunologic, reproductive), by *route of exposure*, and by *length of exposure* (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6	**How Can (Chemical X) Affect Children?**
Section 1.7	**How Can Families Reduce the Risk of Exposure to (Chemical X)?**
Section 3.7	**Children's Susceptibility**
Section 6.6	**Exposures of Children**

Other Sections of Interest:

Section 3.8	**Biomarkers of Exposure and Effect**
Section 3.11	**Methods for Reducing Toxic Effects**

ATSDR Information Center

Phone: 1-888-42-ATSDR or (404) 498-0110 ***Fax:*** (404) 498-0057
E-mail: atsdric@cdc.gov ***Internet:*** http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity;* and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. *Contact:* NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. *Contact:* NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

*The National Institute of Environmental Health Sciences (*NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. *Contact:* NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. *Contact:* AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. *Contact:* ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR/CDC INTERNAL REVIEWS:

1. 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 end points.

2. 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.

3. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

PEER REVIEW

A peer review panel was assembled for fluorine, hydrogen fluoride and fluorides. The panel consisted of the following members:

1. Dr. Arthur Gregory, private consultant, Sterling, Virginia;

2. Dr. Ingeborg Harding-Barlow, private consultant, Palo Alto, California;

3. Dr. Thomas Hinesly, Professor of Soil Ecology, Department of Agronomy, University of Illinois, Urbana, Illinois; and,

4. Dr. Caroline Holsapple, Assistant Professor, Department of Pharmacology and Toxicology, Medical College of Virginia, Richmond, Virginia.

These experts collectively have knowledge of fluorine, hydrogen fluoride, and fluorides' physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

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.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about fluorine, hydrogen fluoride, and fluorides, and the effects of exposure presented in the toxicological profile. These profiles were specifically prepared by ATSDR for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List (Superfund sites) and are intended to describe the effects of exposure from chemicals at these sites.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Fluorine, hydrogen fluoride, or fluorides have been found in at least 177 of the 1,585 current or former NPL sites. However, the total number of NPL sites evaluated for these substances is not known. As more sites are evaluated, the sites at which fluorides are found may increase. This information is important because exposure to these substances may harm you and because these sites may be sources of exposure.

When a substance 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. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to fluorine, hydrogen fluoride, or fluorides, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with them. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT ARE FLUORINE, HYDROGEN FLUORIDE, AND FLUORIDES?

Fluorides are properly defined as binary compounds or salts of fluorine and another element. Examples of fluorides include sodium fluoride and calcium fluoride. Both are white solids. Sodium fluoride readily dissolves in water, but calcium fluoride does not. Sodium fluoride is often added to drinking water supplies and to a variety of dental products, including toothpastes and mouth rinses to prevent dental cavities. The widespread use of fluoride has been a major factor in the overall decline in recent decades in tooth decay. Calcium fluoride is the compound in the common minerals fluorite and fluorspar. Fluorspar is the mineral from which hydrogen fluoride is produced. It is also used in the production of glass and enamel and in the steel industry. In this profile, we will often use the term "fluoride" to include substances that contain the element fluorine. The reason for this is that we generally measure the amount of fluorine in a substance rather than the amount of a particular fluorine compound.

Fluorine is a naturally occurring, widely distributed element and a member of the halogen family, which includes chlorine, bromine, and iodine. However, the elemental form of fluorine, a pale yellow-green, irritating gas with a sharp odor, is so chemically reactive that it rarely occurs naturally in the elemental state. Fluorine occurs in ionic forms, or combined with other chemicals in minerals like fluorspar, fluorapatite, and cryolite, and other compounds. (Ions are atoms, collections of atoms, or molecules containing a positive or negative electric charge.) Fluorine gas reacts with most organic and inorganic substances; with metals, it forms fluorides and with water, it forms hydrofluoric acid. Fluorine gas is primarily used to make certain chemical compounds, the most important of which is uranium hexafluoride, used in separating isotopes of uranium for use in nuclear reactors and nuclear weapons.

Hydrogen fluoride is a colorless, corrosive gas or liquid (it boils at 19.5 EC) that is made up of a hydrogen atom and a fluorine atom. It fumes strongly, readily dissolves in water, and both the liquid and vapor will cause severe burns upon contact. The dissolved form is called hydrofluoric acid. It is known for its ability to etch glass. Commercially, hydrogen fluoride is the most important fluorine compound. Its largest use is in the manufacture of fluorocarbons, which are used as refrigerants, solvents, and aerosols.

For more information on the chemical properties of fluorine, hydrogen fluoride, and fluorides, and their production and use, see Chapters 4 and 5.

1.2 WHAT HAPPENS TO FLUORINE, HYDROGEN FLUORIDE, AND FLUORIDES WHEN THEY ENTER THE ENVIRONMENT?

Fluorides occur naturally in the earth's crust where they are found in rocks, coal, clay, and soil. They are released into the air in wind-blown soil. Hydrogen fluoride is released to the air from fluoride-containing substances, including coal, minerals, and clays, when they are heated to high temperatures. This may occur in coal-fired power plants; aluminum smelters; phosphate fertilizer plants; glass, brick, and tile works; and plastics factories. These facilities may also release fluorides attached to particles. The biggest natural source of hydrogen fluoride and other fluorides released to the air is volcanic eruptions.

Fluorine cannot be destroyed in the environment; it can only change its form. Fluorides released into the atmosphere from volcanoes, power plants, and other high temperature processes are usually hydrogen fluoride gas or attached to very small particles. Fluorides contained in wind-blown soil are generally found in larger particles. These particles settle to the ground or are washed out of the air by rain. Fluorides that are attached to very small particles may stay in the air for many days. Hydrogen fluoride gas will be absorbed by rain and into clouds and fog to form aqueous hydrofluoric acid, which will fall to the ground mainly in precipitation. The fluorides released into air will eventually fall on land or water.

In water, fluorides associate with various elements present in the water, mainly with aluminum in freshwater and calcium and magnesium in seawater, and settle into the sediment where they are strongly attached to sediment particles. When deposited on land, fluorides are strongly retained by soil, forming strong associations with soil components. Leaching removes only a small amount of fluorides from soils. Fluorides may be taken up from soil and accumulate in plants, or they may be deposited on the upper parts of the plants in dust. The amount of fluoride taken up by plants depends on the type of plant, the nature of the soil, and the amount and form of fluoride in the soil. Tea plants are known to accumulate fluoride in their leaves. Animals that eat fluoride-containing plants may accumulate fluoride. However, the fluoride accumulates primarily in the bones or shell rather than in edible meat.

For more information about what happens to fluorides in the environment, see Chapter 6.

1.3 HOW MIGHT I BE EXPOSED TO FLUORINE, HYDROGEN FLUORIDE, AND FLUORIDES?

Fluoride is a natural component of the earth's crust and soil. Small amounts of fluorides are present in water, air, plants, and animals. You may be exposed to small amounts of fluoride by breathing air, drinking water, and eating food. In particular, fluorides are frequently added to drinking water supplies at approximately 1 ppm and to toothpaste and mouth rinses to prevent dental decay. Analytical methods used by scientists to determine the levels of fluoride in the environment generally do not determine the specific form of fluoride present. Therefore, we do not always know the form of fluoride that a person may be exposed to. Similarly, we do not know what forms of fluoride are present at hazardous waste sites. Some forms of fluoride may be insoluble or so tightly attached to particles or embedded in minerals that they are not taken up by plants or animals.

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 per cubic meter ($\mu g/m^3$) of air. Rural areas have even lower levels. The amount of fluoride that you breathe in a day is much less than what you consume in food and water. You may breathe in higher levels of fluoride in areas near coal-fired power plants or fluoride-related industries (e.g., aluminum smelters, phosphorus fertilizer plants) or near hazardous waste sites.

Levels of fluorides in surface water average about 0.2 parts of fluoride per million parts of water (ppm). Levels of fluorides in well water generally range from 0.02 to 1.5 ppm, but often exceed 1.5 ppm in parts of the southwest United States. Many communities fluoridate their water supplies; the recommended level of fluoride is around 1 ppm. In the United States, approximately 15,000 water systems serving about 144 million people are fluoridated in the optimal range of 0.7–1.2 ppm, either occurring naturally or through adjustment. Persons living in non-fluoridated areas may receive water exposure through beverages and foods processed in fluoridated areas. You will be exposed to fluorides in the water that you drink or in beverages prepared with fluoridated water.

The concentration of fluorides in soils is usually between 200 and 300 ppm. However, levels may be higher in areas containing fluoride-containing mineral deposits. Higher levels may also occur where phosphate fertilizers are used, where coal-fired power plants or fluoride-releasing industries are located, or in the vicinity of hazardous waste sites. You may be exposed to fluorides through dermal contact with these soils.

You may also be exposed to fluorides in your diet. While food generally contains low levels of fluoride, food grown in areas where soils have high amounts of fluorides or where phosphate fertilizers are used may have higher levels of fluorides. Tea and some seafoods have been found to have high levels of fluorides. The average daily fluoride intake by adults from food and water is estimated to be 1 milligram (mg) if you live in a community with <0.7 ppm in your water, and about 2.7 mg if you have fluoridated water. You can contact your local water system to determine the level of fluoride in your drinking water or refer to the annual Consumer Confidence Report furnished by your water system operators. You may also be exposed to fluoride in dental products, such as toothpastes, fluoride gels, and fluoride rinses. If you swallow these products, you will be exposed to fluoride. Swallowing toothpaste can account for a large percentage of the fluoride to which a child <8 years of age might be exposed. Dental products used in the home such as toothpastes, rinses, and topically applied gels contain high concentrations of fluoride (range 230–5,000 ppm) and are not intended to be ingested. If you swallow these products, you will be exposed to higher levels of fluoride. The Food and Drug Administration requires that toothpaste tubes be labeled with instructions to minimize ingestion of fluoride by children including the use of a “pea-sized” amount of paste and parental supervision of brushing.

You may also be exposed to higher levels of fluoride if you work in industries where fluoride-containing substances are used, most notably in the electronics industry where hydrogen fluoride may be used to etch glass in TV picture tubes or to clean silicon chips and in aluminum and phosphate fertilizer plants. Exposure will primarily result from breathing in hydrogen fluoride or fluoride-containing dust. Exposure will be reduced if exhaust systems or protective masks are used in the workplace.

For more information on how you can be exposed to fluorine, hydrogen fluoride, or fluorides, see Chapter 6.

1.4 HOW CAN FLUORINE, HYDROGEN FLUORIDE, 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. Exposure to fluorine gas is uncommon, except in industrial settings.

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 bloodstream 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 bloodstream 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. Factors 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 24 hours unless large amounts (20 mg or more, which is the amount in 20 or more liters of optimally fluoridated water) are ingested. 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.

1.5 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 (e.g., flucytosine, an antifungal) and some cancers (e.g., fluorouracil, an antimetabolite).

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 decay in all age groups. 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. In 2000, the PHS published the first ever Surgeon General's Report on Oral Health in America. The report emphasizes that community water fluoridation is an effective, safe, and ideal public health measure, and benefits individuals of all ages and socioeconomic strata. The fluoride at levels in drinking water reduces the incidence of dental caries and slows or reverses the progression of existing lesions. Fluoride has been a major factor in the overall decline in recent decades in the prevalence and severity of dental caries in the United States.

However, exposure to higher levels of fluoride may 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. 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 may have a greater risk of breaking a bone if they take fluoride pills containing over 30 mg of fluoride per day (a high dose). Some studies have shown that fluorides in drinking water may increase the risk of old women breaking a bone, but other studies have not found this effect. If you eat large amounts of sodium fluoride, it can cause stomachaches, vomiting, and diarrhea. Extremely large amounts can cause death by damaging your stomach and affecting your heart.

Reproductive effects, such as decreased fertility and sperm and testes damage, have been seen in laboratory animals at high doses. Some studies have not found any reproductive effects in laboratory animals. One study found birth defects in children living in areas with very high levels of fluoride in the drinking water. No studies have addressed whether low levels of fluoride will cause birth defects in humans. Birth defects have not been found in most studies of 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. Most studies have 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 studies had problems that limited their usefulness in showing whether fluoride can cause cancer in humans. The International Agency for Research on Cancer (IARC) has determined that the carcinogenicity of fluoride to humans is not classifiable.

For more information on the health effects of fluorine, hydrogen fluoride, and fluorides, see Chapter 3.

1.6 HOW CAN FLUORINE, HYDROGEN FLUORIDE, AND FLUORIDES AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans.

When used appropriately, fluoride is both safe and effective in preventing and controlling dental caries. Drinking or eating excessive 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. Dental fluorosis develops only when the teeth are forming in the jaw and before they erupt into the mouth (age <6 years). After the teeth have developed and erupted, they cannot become fluorosed. Most enamel fluorosis seen today is of the mildest form, in which 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 stains. Cosmetically objectionable enamel fluorosis can occur when young children ingest higher than optimal amounts of fluoride, from any source, while tooth enamel is forming. 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.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO FLUORINE, HYDROGEN FLUORIDE, AND FLUORIDES?

If your doctor finds that you have been exposed to significant amounts of fluorine, hydrogen fluoride, and fluorides, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate.

It is unlikely that the general population would be exposed to fluorine gas or hydrogen fluoride. Because fluorides are found naturally in the environment, we cannot avoid being exposed to them. Some areas of the United States, such as the Southwest, naturally have high levels of fluorides in well water. There has been an increase in the cosmetic condition of tooth enamel fluorosis in children in both fluoridated and non-fluoridated communities. Ask your health department whether your area has high levels of fluorides in the drinking water. If you live in such an area, you should use bottled drinking water and consult your dentist for guidance on the need for appropriate alternative fluoride supplements.

These areas may also contain high levels of fluorides in soil. A few hazardous waste sites may contain high levels of fluorides in soil. By limiting your contact with such soil (for example, reducing recreational activities that raise dust, you would reduce your family's exposure to fluoride. Some children eat a lot of dirt. You should prevent your children from eating dirt. You should discourage your children from putting their hands or objects in their mouths or engaging in other hand-to-mouth activity. Make sure they wash their hands frequently and before eating.

If you work in a phosphate fertilizer plant or other industry that uses minerals high in fluorides. It is sometimes possible to carry fluorides home from work on your clothing, skin, hair, tools, or other objects removed from the workplace. You may contaminate your car, home, or other locations outside work where children might be exposed to fluoride-containing dust. Your

occupational health and safety officer at work can and should tell you whether the chemicals that you work with are likely to be carried home on your clothes, body, or tools as well as whether you should be showering and changing clothes before you leave work, storing your street clothes in a separate area of the workplace, or laundering your work clothes at home separately from other clothes.

Children may be exposed to high levels of fluorides if they swallow dental products containing fluoridated toothpaste, gels, or rinses. Swallowing toothpaste can account for a large percentage of the fluoride to which a small child might be exposed. You should teach your children not to swallow these products. For children under age 8, parents should supervise brushing and place, at most, a small pea size dab of toothpaste on the brush.

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

Urine samples can be analyzed to find out if you have been exposed to fluorides. The fluoride level in the sample is compared with 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 cannot 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.

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

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals; then they are adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for fluorine, hydrogen fluoride, and fluorides include the following:

Fluorine, hydrogen fluoride, and sodium fluoride have been named hazardous substances by the EPA. The federal government has set regulatory standards and guidelines to protect workers from the possible health effects of fluorine, hydrogen fluoride, and fluorides in air. OSHA has set a legally enforceable limit of 0.2 milligrams per cubic meter (mg/m^3) for fluorine, 2.0 mg/m^3 for hydrogen fluoride, and 2.5 mg/m^3 for fluoride in workroom air to protect workers during an 8-hour shift over a 40-hour work week. NIOSH recommends air levels of 0.2 mg/m^3 for fluorine, 2.5 mg/m^3 for hydrogen fluoride, and 2.5 mg/m^3 for sodium fluoride in workroom air to protect workers during an 8-hour shift over a 40-hour work week.

The federal government has also set regulatory standards and guidelines to protect the public from the possible health effects of fluoride in drinking water. EPA decided that the maximum

amount of fluoride allowed in drinking water is 4.0 milligrams per liter (mg/L). For the prevention of dental decay, the PHS has, since 1962, recommended that public water supplies contain fluoride at concentrations between 0.7 and 1.2 mg/L.

PHS scientists representing the National Institutes of Health, the Centers for Disease Control and Prevention, the Food and Drug Administration, the Agency for Toxic Substances and Disease Registry, and other government agencies conducted an extensive examination of the worldwide biomedical literature on the public health risks and benefits of fluoride in 1991. The PHS report stated that fluoride in the drinking water substantially reduces tooth decay.

For more information on recommendations regarding exposure to fluorine, hydrogen fluoride, and fluorides, see Chapter 8.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or

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

* Information line and technical assistance

Phone: 1-888-42-ATSDR (1-888-422-8737)
Fax: 1-404-498-0057

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

* To order toxicological profiles, contact

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO FLUORINE, HYDROGEN FLUORIDE, AND FLUORIDES IN THE UNITED STATES

Fluorine is the most electronegative and reactive of all elements. It is a pale yellow gas that is used in rocket fuels and in making glass, enamel, and bricks. Fluoride is the ionic form of fluorine. Hydrogen fluoride is a colorless gas that readily dissolves in water to form hydrofluoric acid. Anhydrous hydrogen fluoride is used in the production of most fluorine-containing chemicals and in the production of refrigerants, herbicides, pharmaceuticals, high octane gasoline, aluminum, plastics, electrical components, and fluorescent light bulbs. Aqueous hydrofluoric acid is used in stainless steel pickling, glass etching, and metal coatings. Volcanoes are the major natural source of hydrogen fluoride. The major anthropogenic sources of hydrogen fluoride is the combustion of coal, aluminum production plants, and phosphate fertilizer plants. The general population is exposed to very low levels of hydrogen fluoride. Populations living near industrial sources of hydrogen fluoride, including coal burning facilities, as well as workers in fluoride processing industries, may be exposed to higher levels of hydrogen fluoride in the air. Additionally, vegetables and fruits grown near these sources may contain higher levels of fluoride, particularly from fluoride-containing dust settling on the plants.

Fluoride salts, generically referred to as fluorides, are naturally occurring components of rocks and soil. They enter the atmosphere through volcanic emissions, resuspension of soil by wind, and runoff from weathering of fluoride-containing rocks and soil. Sodium fluoride is a white solid that is readily soluble in water. One of the principal uses of sodium fluoride is the fluoridation of public water for the prevention of dental caries. The population is generally exposed to low levels (~1 ppm) of fluoride through consumption of drinking water, food, and dentifrices. Numerous studies support the effectiveness of water fluoridation in preventing coronal and root caries in children and adults. Individuals who consume a large quantity of tea may also be exposed to higher levels of fluoride since tea plants accumulate fluoride. Industrial uses include: flux for deoxidizing rimmed steel and in the manufacture of vitreous enamels, pickling of stainless steel, wood preservative compounds, casein glues, and coated papers. Sodium fluoride has been used as an insecticide, rodenticide, and fungicide. Populations living near industrial sources of fluoride may be exposed to airborne fluoride.

2.2 SUMMARY OF HEALTH EFFECTS

The following section lists health effects caused by exposure to fluorine, hydrogen fluoride, and fluoride. Readers should keep in mind that adverse health effects generally occur at high exposure levels.

Fluorine. Limited data exist on the toxicity of fluorine; the two possible routes of exposure to fluorine are inhalation or dermal contact with the gas. Fluorine gas is extremely irritating; human and animal data suggest that 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 been observed.

Hydrogen Fluoride. Hydrogen fluoride is highly corrosive and like fluorine, the primary effects are tissue damage resulting from direct contact. Acute inhalation exposure can result in bronchiolar ulceration, pulmonary hemorrhage and edema, and death. Gastrointestinal irritation has also been observed in humans exposed to low levels of hydrogen fluoride. Direct contact of hydrogen fluoride/hydrofluoric acid with the eyes or skin can produce skin burns, “burning sensation”, and lacrimation. In addition to these direct contact effects, exposure to hydrogen fluoride can result in skeletal and cardiac effects. Skeletal fluorosis has been observed in workers exposed to hydrogen fluoride and fluoride dusts. Exposure to very high levels of hydrogen fluoride/hydrofluoric acid can result in severe cardiovascular effects, which are attributed to a combination of hypocalcemia and hyperkalemia; cardiac arrhythmias have been seen in humans following hydrofluoric acid splashes in the face region; and myocardial necrosis and congestion were observed in rabbits. Hepatic (fatty degeneration and necrosis) and renal effects (tubular degeneration and necrosis) have also been observed in animal studies.

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. Because of these multiple exposures and the problems inherent in all occupational studies in identifying appropriate reference 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. The International Agency for Research on Cancer has determined that the carcinogenicity of fluoride to humans is not classifiable.

Fluoride. During the past 50 years, numerous studies have provided strong evidence that water fluoridation (at approximately 1 ppm) results in a notable reduction in coronal and root surface caries in children and adults. Furthermore, communities that no longer fluoridate their water have experienced an

increase in caries (DHHS 2000). However, at higher levels of exposure, fluoride might cause adverse health effects. The main health concern regarding fluoride is likely to be from excessive 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. Excessive exposure to fluoride in children under 6 years old can result in mottling of their permanent teeth. 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; <1% may have brown spots. Mild dental fluorosis is considered a cosmetic effect; it is not necessarily a precursor to skeletal fluorosis, but may be a clinical indicator of exposure of children to excess 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. Some recent studies suggest that elderly women and men in communities with fluoridated water may have an elevated risk of hip fractures, but other studies have not found this effect. Long-term, high level exposure can lead to skeletal fluorosis.

Additional systemic effects that have been observed in humans and/or animals include symptoms of gastrointestinal irritation (nausea, vomiting, gastric pain), severe cardiac effects (e.g., tetany, decreased myocardial contractility, cardiovascular collapse, ventricular fibrillation) at or near lethal doses, and parenchymal degeneration in the liver. Reproductive effects have been observed in humans and animals. An ecological study found a significant association between fluoride levels in municipal drinking water and decreases in fertility rates. In animal studies, alterations in reproductive hormone levels, histology of the testes, spermatogenesis, and male fertility have been observed. In addition, while studies in laboratory animals (rats and rabbits) have not found developmental effects, developmental effects have been seen in wild and domestic animals (cattle and mink).

Numerous ecological studies have examined the possible association between fluoridated water and cancer. The weight of the evidence indicates that fluoridation of water does not increase the risk of developing cancer. These studies were not designed to detect small increases in cancer occurrences; the most sensitive studies required increases of 10–20%. A 2-year study in rats found a weak, equivocal fluoride-related increase in the occurrence of osteosarcomas in male rats, and no evidence of carcinogenicity in female rats or male or female mice.

In response to public health concerns raised by equivocal findings of carcinogenicity in male rats, 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."

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."

The 2000 Surgeon General's Report (DHHS 2000) on Oral Health reaffirms the benefits of fluoride, when used at recommended levels, in reducing dental caries in the United States. The Surgeon General's Report concludes:

> "Given the modest cost of less than 1 dollar per person per year to fluoridate water systems serving most people, community water fluoridation is recommended as a very effective and cost-effective method of preventing coronal and root caries in children and adults."

Respiratory, Gastrointestinal, Dermal, and Ocular Effects. Fluorine, hydrogen fluoride, and hydrofluoric acid are extremely irritating chemicals and can cause tissue damage after direct contact. Inhalation exposure to fluorine has been observed to cause respiratory tract irritation in people, and dyspnea and lung congestion in animals. Pulmonary and nasal irritation have also been reported following repeated exposures for about 30 days. However, human and animal data suggest that preexposure to lower levels can reduce the respiratory effects.

Acute lethal inhalation exposure of humans to hydrofluoric acid has produced pulmonary edema. Acute inhalation exposure to hydrofluoric acid has produced nasal irritation, respiratory distress, pulmonary congestion, and intraalveolar edema in rats, rabbits, and guinea pigs. Similarly, intermediate-duration inhalation exposure caused pulmonary hemorrhage and signs of inflammation. The respiratory effects of hydrofluoric acid are attributed to its highly corrosive properties. Chronic exposure to hydrogen fluoride and cryolite dust has resulted in impaired lung function in workers.

Gastrointestinal effects have been observed following inhalation and oral exposure to fluorides. Populations living near a smelter emitting hydrogen fluoride or exposed during an accidental release of hydrogen fluoride have reported gastrointestinal effects, including nausea, gastrointestinal distress, and vomiting. Although no studies examined the gastrointestinal tract following oral exposure to hydrofluoric acid, it is likely that ingestion would result in severe gastrointestinal effects due to its caustic properties.

Gastrointestinal effects have also been observed following both acute and chronic oral exposure to excessive fluoride; the most commonly reported effects are 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. Vomiting, nausea, and diarrhea are the most commonly reported gastrointestinal effects of individuals ingesting <1 mg/kg fluoride. Endoscopic examination of individuals consuming high levels of sodium fluoride revealed minute hemorrhages and erosions in the stomach. Marked stomach irritation (ulcers, necrosis) has been observed in rats exposed to fairly high levels of sodium fluoride, but not after chronic exposure to lower doses, suggesting that the concentration of sodium fluoride in the stomach may strongly influence its gastrointestinal toxicity.

Dermal and ocular effects have occurred in humans exposed to hydrofluoric acid dermally and to atmospheric fluorine or 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., length of exposure, strength of the acid solution, percentage of the body exposed, and treatment utilized). Animal data support the human data and indicate that hydrofluoric acid produces severe skin and ocular damage, which, if severe enough, is not reversible.

Skeletal Effects. Human and animal data clearly indicate that fluoride accumulates in the teeth and skeleton. Numerous studies have shown that the increase in fluoride levels in teeth results in a decreased occurrence of dental caries and the topical effect of frequent exposure to low-dose fluoride that protects the teeth from demineralization and helps to remineralize already damaged enamel. Levels of up to about 1 ppm in drinking water have been associated with a decreased number of dental cavities. Drinking water fluoride levels that reduce the incidence of dental caries can sometimes result in dental fluorosis. At higher fluoride concentrations, changes in tooth color and surface irregularities are visible. Dental fluorosis only occurs in children during the development of their deciduous and/or permanent teeth. Mild dental fluorosis is considered a cosmetic effect not causing functional damage to the teeth. Fluoride causes dental fluorosis by impairing the work of ameloblast cells. High fluoride levels can increase the susceptibility to dental caries resulting from an increase in porosity and hypoplasia of the teeth. Dental fluorosis has also been observed in animal studies.

In bone, fluoride replaces the hydroxyl ion in hydroxyapatite to form fluorapatite, thus changing the physicochemical properties of the bone. Ingestion (and inhalation) of large doses of fluoride for an extended period of time can result in thickened bones and exostoses (skeletal fluorosis). 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. Reported cases are found almost exclusively in developing countries, particularly India, and are often associated with malnutrition. It is generally stated that a dose of 20–80 mg/day (equivalent to 10–40 ppm in the water, for a person who ingests 2 L/day) is necessary for the development of crippling skeletal fluorosis, 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.

A large number of epidemiology studies have attempted to examine the relationship between fluoride in drinking water and the risk of bone fracture. The results of these predominantly ecological studies are inconsistent. Studies have found increases and decreases in hip fracture rates among older women living in areas with fluoride in the drinking water, as compared to women living in areas with very low levels of fluoride in the drinking water (<0.3 ppm). Other studies have not found an effect of fluoride on fracture risk. A relationship between fluoride in drinking water and bone fractures cannot be established from these studies. A number of other studies have examined the efficacy of using fluoride to treat osteoporosis because fluoride exposure results in increased bone density. In studies using high levels of fluoride (34 mg/day), an increased risk of nonvertebral fractures has been found. The risk of vertebral fractures was not affected. These studies also found increases in lumbar spinal and femoral head and trochanter bone mineral density and decreases in radium bone mineral density. Animal studies have shown that the increase in bone density was negatively associated with bone strength, suggesting that the new bone was of inferior quality.

2.3 MINIMAL RISK LEVELS

Inhalation MRLs

Fluorine

- An acute-duration inhalation MRL of 0.01 ppm fluorine was derived for fluorine.

Irritation appears to be the primary effect following acute inhalation exposure to fluorine. The observed effects include eye, skin, and nasal irritation in humans intermittently exposed to $50 ppm for 0.5–3 minutes and dyspnea and lung congestion in rats and mice exposed to 47–175 ppm fluorine for 5–60 minutes. The threshold for the respiratory effects appears to be duration-related. Necrosis was also observed in the liver parenchymal tissue and in the renal tubules of rodents acutely exposed to fluorine. In general, the liver and kidney effects occurred at higher concentrations than the respiratory effects.

The Keplinger and Suissa human study was selected as the basis of an acute-duration inhalation MRL for fluorine. This study reported slight eye and skin irritation (considered a dermal effect) in five volunteers exposed to 23 ppm for 3–5-minute periods every 15 minutes for 2–3 hours; nasal irritation was reported at concentrations of 67 ppm fluorine (3-minute exposure) and higher. The severity of the irritation was concentration-related, and irritation was not reported at 10 ppm for 3, 5, or 15 minutes. The NOAEL of 10 ppm for the 15-minute exposure and an uncertainty factor of 10 to account for intrahuman variability were used to derive an acute-duration inhalation MRL of 0.01 ppm fluorine.

Longer-duration exposure studies are limited to lethality studies and an occupational exposure study in which the workers and the controls were exposed to uranium hexafluoride and hydrogen fluoride. These data are inadequate for the derivation of intermediate-duration and chronic-duration inhalation MRLs for fluorine.

Hydrogen Fluoride.

- An acute-duration inhalation MRL of 0.03 ppm fluoride was derived for hydrogen fluoride.

The respiratory tract appears to be the primary target of hydrogen fluoride toxicity. There are limited data on the acute toxicity of hydrogen fluoride in humans. One human subject reported nasal irritation following exposure to 3.22 ppm fluoride as hydrogen fluoride 6 hours/day for 10 days. Several animal studies report respiratory effects in rats. Mild nasal irritation was reported in rats exposed to 120 ppm fluoride as hydrogen fluoride for 60 minutes; the LOAELs for nasal irritation were higher for shorter

durations. Respiratory distress was observed in rats exposed to 50% of the LC_{50} value for 5, 15, 30, or 60 minutes (2,310, 1,339, 1,308, and 465 ppm fluoride, respectively). Midtracheal necrosis was reported in rats exposed to 902 or 1,509 ppm fluoride as hydrogen fluoride for 2 or 10 minutes using a mouth breathing model with a tracheal cannula. These effects were not observed when the tracheal cannula was not used. A 60-minute exposure study was selected as the basis of an acute-duration inhalation MRL for hydrogen fluoride. In this study, general discomfort, pawing at the nose and tearing from the eyes were observed during exposure to 120 ppm fluoride as hydrogen fluoride. At 98 ppm, the study authors noted that there was occasional pawing at the nose; this concentration was considered a NOAEL. A $NOAEL_{HEC}$ was calculated by multiplying the NOAEL by the RDGR and adjusting for less than 24-hour exposure. The $NOAEL_{HEC}$ was divided by an uncertainty factor of 30 (3 for interspecies extrapolation using dosimetric adjustments and 10 for intrahuman variability) to yield an acute-duration inhalation MRL of 0.03 ppm fluoride as hydrogen fluoride.

- An intermediate-duration inhalation MRL of 0.02 ppm fluoride was derived for hydrogen fluoride.

There are limited data on the long term toxicity of hydrogen fluoride. Slight nasal irritation was reported by volunteers exposed to an average concentration of 2.98 ppm fluoride, 6 hours/day for 15–50 days. In rats, rabbits, and dogs, pulmonary hemorrhages were observed after exposure to 31 ppm fluoride for 6 hours/day, 6 days/week for 5 weeks. In the study selected as the basis of an intermediate-duration inhalation MRL for hydrogen fluoride, five volunteers were exposed to average hydrogen fluoride concentrations of 0.85–7.7 ppm fluoride; the mean of the average concentrations was 2.98 ppm fluoride. A duration-adjusted LOAEL of 0.75 ppm fluoride was calculated by adjusting the mean concentration for intermittent exposure (an assumption was made that the subjects were exposed daily to hydrogen fluoride). This duration-adjusted LOAEL was divided by an uncertainty factor of 30 (3 to account for the use of a LOAEL for slight irritation and 10 for intrahuman variability) to derive an MRL of 0.02 ppm fluoride for hydrogen fluoride.

No chronic-duration studies were located for hydrogen fluoride; thus, a chronic-duration inhalation MRL was not derived.

Fluoride

- No inhalation MRLs were derived for fluoride.

Several occupational exposure studies examined fluoride toxicity in aluminum potroom workers. Interpretation of these studies is limited by co-exposure to hydrogen fluoride and other chemicals

including aluminum. No animal studies examined the toxicity of inhaled fluorides. Thus, inhalation MRLs were not derived for this chemical.

Oral MRLs

Hydrogen Fluoride/Hydrofluoric Acid

- No oral MRLs were derived for hydrogen fluoride/hydrofluoric acid

Only lethality studies were identified for hydrogen fluoride/hydrofluoric acid, precluding derivation of oral MRLs for this chemical.

Fluoride

- A chronic-duration oral MRL of 0.06 mg fluoride/kg/day was derived for fluoride.

There are limited data on the acute toxicity of fluoride in humans and animals. The only nonlethal adverse effect that was identified was a decrease in modulus of elasticity in the bones of weanling rats exposed to 9.5 mg fluoride/kg/day as sodium fluoride in drinking water for 2 weeks. The remaining nonlethality studies examined reproductive and developmental end points and did not find report adverse effects. Because the available studies examined a limited number of end points (skeletal, reproductive, developmental), identification of the critical effect cannot be made with confidence. Additionally, the Guggenheim et al. study only tested one dose level; thus, a dose-response relationship can not be established for the observed skeletal effects.

Several studies have examined the toxicity of sodium fluoride following intermediate-duration exposure in laboratory animals. These studies have identified a number of potentially sensitive targets of fluoride toxicity. The lowest identified LOAELs are 0.5 mg fluoride/kg/day for thyroid effects in rats exposed to sodium fluoride in drinking water for 2 months and 0.80 mg fluoride/kg/day for increased bone formation in mice exposed to sodium fluoride in drinking water for 4 weeks. Neither study identified a NOAEL. Derivation of an intermediate-duration MRL from either study would result in an MRL that is lower than chronic-duration oral MRL.

A number of human studies have investigated the toxicity, particularly potential skeletal toxicity, of fluoride. The vast majority of these studies were ecological studies examining the possible relationship between fluoride in drinking water and the occurrence of hip fractures. These studies, as well as retrospective cohort studies, have found decreases, increases, and no effect on hip fracture occurrence in

communities consuming fluoridated water. Limitations in the study designs of many of these studies preclude using these data to establish a causal relationship between fluoride and risk of hip fractures. In addition to these epidemiology studies, several human experimental studies have examined the effect of fluoride administration for the treatment of osteoporosis. One study found significant increases in lumbar spine and femoral head and trochanter bone mineral density, decreases in radius bone mineral density, no effect on vertebral fracture rate, and increases in nonvertebral fracture rate among postmenopausal women with osteoporosis ingesting a capsule containing 34 mg fluoride/day as sodium fluoride for 4–6 years. Another study did not find any effect on bone mineral density or vertebral or nonvertebral fracture rates among postmenopausal women with spinal osteoporosis ingesting 34 mg fluoride/day as sodium fluoride. A meta-analysis of these data, as well as other clinical studies, found a significant correlation between exposure to high levels of fluoride and an increased relative risk of nonvertebral fractures. The LOAEL of 34 mg fluoride/day (0.56 mg fluoride/kg/day) was selected as the basis of a chronic-duration oral MRL for fluoride. The MRL of 0.06 mg fluoride/kg/day was derived by dividing the LOAEL by an uncertainty factor of 10 to account for the use of a LOAEL in a sensitive subpopulation.

3. HEALTH EFFECTS

3.1 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 on the toxicology of fluorine, hydrogen fluoride, and fluorides. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

Fluorine is a gaseous element that occurs only in very low concentrations in the environment in the absence of anthropogenic sources (see Chapter 6 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 cations 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 term 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 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 that 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 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, food, and fluoride-containing dental products. 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.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others 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, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), 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 no-observed-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. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining 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 Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others 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 (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of fluorine, hydrogen fluoride, and fluorides are indicated in Table 3-3 and Figure 3-3. Because cancer effects could occur at lower exposure levels, Figure 3-3 also shows a range for the upper boundary of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 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 been 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, because 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 3.2.3.

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.

3.2.1.1 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 rats for a given duration are generally at least 3.5 times higher than 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} values of hydrogen fluoride in Crl:CD®BR and Wistar-derived rats were 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} values for exposures of 5, 15, 30, and 60 minutes were 700, 390, 270, and 185 ppm, 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.

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 preexposure 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 preexposure regimen (Keplinger 1969). For example, 4 weeks of exposure to 50 ppm for 30 minutes once/week increased the survival time following a 30-minute challenge with 400 ppm from a maximum 18–48 hours. Small increases in the LC_{50} were observed when mice were preexposed 4 times in 7 days to 25 ppm 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 0.5, 2, 5, or 18 ppm fluorine were conducted for up to 178 hours over 35 days (Stokinger 1949). The exposure regimen was not stated, but appears to be 6 hours/day, 6 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 and dogs exposed to 5 ppm and mice exposed to 18 ppm died, while only half of the rats and guinea pigs exposed to 18 ppm died. Most animals exposed to 2 ppm survived.

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 <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 (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 rats, and rats are more sensitive than guinea pigs. The 15-minute LC_{50} values for hydrogen fluoride were 4,327 ppm fluoride for guinea pigs and 2,555 ppm fluoride for Wistar-derived rats (Rosenholtz et al. 1963). The 60-minute LC_{50} values for hydrogen fluoride were 325 ppm fluoride in ICR-derived mice (Wohlslagel et al. 1976), 1,325 ppm fluoride in Sprague-Dawley-derived rats (Wohlslagel et al. 1976), and 1,242 ppm fluoride in Wistar-derived rats (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 6,620 ppm, while the 60-minute LC_{50} was 1,610 ppm. 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 8.2 or 31 ppm fluoride as hydrogen fluoride for 6 hours/day, 6 days/week for 5 weeks (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 31 ppm died, but no guinea pigs, rabbits, or dogs exposed at this level died. No animal of any species died following exposure to 8.2 ppm. In an experiment where five rabbits, three guinea pigs, and two Rhesus monkeys were exposed to 18 ppm 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 of 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 3-1 and plotted in Figure 3-1. The LC_{50} values for each species and duration category of exposure to hydrogen fluoride are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.1.2 Systemic Effects

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

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. Preexisting 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 3-1 and plotted in Figure 3-1. 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 3-2 and plotted in Figure 3-2.

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 3.2.3) because it is caused by direct contact with the gases.

Fluorine. Limited data are available regarding respiratory effects of fluorine on humans. Five volunteers (19–50 years of age; gender not specified) 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 10 ppm was not irritating to the respiratory tract for at least 15 minutes. Slight nasal irritation was reported following a 3-minute exposure to 50 ppm, and exposure to 100 ppm for 0.5 or 1 minute was very irritating to the nose. Intermittent inhalation (3–5 minute exposure every 15 minutes for 2–3 hours) of 23 ppm did not cause respiratory difficulty.

Table 3-1. Levels of Significant Exposure to Fluorine - Inhalation

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
ACUTE EXPOSURE							
Death							
1	Rat (Osborne-Mendel)	1d 5-60min/d				700 (5-minute LC_{50})	Keplinger and Suissa 1968 fluorine
						390 (15-minute LC_{50})	
						270 (30-minute LC_{50})	
						185 (60-minute LC_{50})	
2	Mouse (Swiss-Webster)	1d 15-60min/d				600 (5-minute LC_{50})	Keplinger and Suissa 1968 fluorine
						375 (15-minute LC_{50})	
						225 (30-minute LC_{50})	
						150 (60-minute LC_{50})	
3	Gn Pig (New England)	1d 15-60min/d				395 (15-minute LC_{50})	Keplinger and Suissa 1968 fluorine
						170 (60-minute LC_{50})	
4	Rabbit (New Zealand)	1d 5-30min/d				820 (5-minute LC_{50})	Keplinger and Suissa 1968 fluorine
						270 (30-minute LC_{50})	
Systemic							
5	Human	1d 1min/d	Resp		67 (nasal irritation)		Keplinger and Suissa 1968 fluorine
6	Human	1d 3min/d	Resp	10	50 (slight nasal irritation)		Keplinger and Suissa 1968 fluorine

Table 3-1. Levels of Significant Exposure to Fluorine - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
7	Human	1d 5min/d	Resp	10			Keplinger and Suissa 1968 fluorine
8	Human	1d 3-5min every 15 min for 2-3 hr	Resp	23			Keplinger and Suissa 1968 fluorine
9	Human	1d 15 min	Resp	10[b]			Keplinger and Suissa 1968 fluorine
10	Human	1d 0.5min/d	Resp		100 (nasal irritation)		Keplinger and Suissa 1968 fluorine
11	Rat (Osborne-Mendel)	1d 5min/d	Resp	88	175 (dyspnea; mild lung congestion)	350 (irritation)	Keplinger and Suissa 1968 fluorine
12	Rat (Osborne-Mendel)	1d 15min/d	Resp	49	98 (very mild lung congestion)	195 (irritation)	Keplinger and Suissa 1968 fluorine
13	Rat (Osborne-Mendel)	1d 30min/d	Resp	35	70 (very mild lung congestion)	140 (nasal irritation)	Keplinger and Suissa 1968 fluorine
14	Rat (Osborne-Mendel)	1d 60min/d	Resp	28	47 (very mild lung congestion)	93 (nasal irritation)	Keplinger and Suissa 1968 fluorine

Table 3-1. Levels of Significant Exposure to Fluorine - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)	Reference Chemical Form
15	Mouse (Swiss-Webster)	1d 5min/d	Resp	79	174	(dyspnea; mild lung congestion, slight alveolar necrosis)		Keplinger and Suissa 1968 fluorine
			Hepatic	174	195	(necrosis and cloudy swelling)		
			Renal	79	114	(necrosis)		
16	Mouse (Swiss-Webster)	1d 15min/d	Resp	65	87 188	(very mild lung congestion) (irritation)		Keplinger and Suissa 1968 fluorine
17	Mouse (Swiss-Webster)	1d 15min/d	Resp	65	82	(alveolar necrosis and hemorrhage)		Keplinger and Suissa 1968 fluorine
			Hepatic	128	144	(coagulation, necrosis, and cloudy swelling)		
			Renal	65	82	(coagulation, necrosis)		
18	Mouse (Swiss-Webster)	1d 30min/d	Resp	51	82	(alveolar necrosis and hemorrhage)		Keplinger and Suissa 1968 fluorine
			Hepatic	82	116	(coagulation, necrosis, and cloudy swelling)		
			Renal	51	82	(coagulation, necrosis)		
19	Mouse (Swiss-Webster)	1d 30min/d	Resp	32 67	67 113	(very mild lung congestion) (irritation)		Keplinger and Suissa 1968 fluorine
20	Mouse (Swiss-Webster)	1d 60min/d	Resp	30 75	50 150	(very mild lung congestion) (nasal irritation)		Keplinger and Suissa 1968 fluorine

Table 3-1. Levels of Significant Exposure to Fluorine - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
21	Mouse (Swiss-Webster)	1d 60min/d	Resp	30	50 (alveolar necrosis and hemorrhage)		Keplinger and Suissa 1968 fluorine
			Hepatic	55	80 (necrosis,and cloudy swelling)		
			Renal	50	55 (necrosis)		
22	Gn Pig (New England)	1d 15min/d	Resp	70	100 (very mild lung congestion) 198 (irritation)		Keplinger and Suissa 1968 fluorine
23	Gn Pig (New England)	1d 60min/d	Resp	73	135 (mild lung congestion, irritation, dyspnea)		Keplinger and Suissa 1968 fluorine
24	Dog (NS)	1d 15min/d	Resp	39	93 (slight lung congestion)		Keplinger and Suissa 1968 fluorine
25	Dog (NS)	1d 60min/d	Resp	68	93 (irritation, cough, slight dynspnea, lung hemorrhage)		Keplinger and Suissa 1968 fluorine
26	Rabbit (New Zealand)	1d 5min/d	Resp	79	134 (slight dyspnea) 410 (irritation)		Keplinger and Suissa 1968 fluorine
27	Rabbit (New Zealand)	1d 30min/d	Resp	32	71 (very mild lung congestion) 135 (irritation)		Keplinger and Suissa 1968 fluorine

INTERMEDIATE EXPOSURE

Table 3-1. Levels of Significant Exposure to Fluorine - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form
Death									
28	Rat (NS)	5 wks 6d/wk 6hr/d					18	(24/48 deaths)	Stokinger 1949 fluorine
29	Dog (NS)	5 wks 6d/wk 6hr/d					5	(100% mortality)	Stokinger 1949 fluorine
30	Rabbit (NS)	5 wks 6d/wk 6hr/d					5	(100% mortality)	Stokinger 1949 fluorine
Systemic									
31	Rat (NS)	5 wks 6d/wk 6hr/d	Resp	5	18	(severe pulmonary irritation)			Stokinger 1949 fluorine
			Bd Wt				18	(weight loss)	
32	Dog (NS)	5 wks 6d/wk 6hr/d	Resp	0.5	2	(pulmonary hemorrhage and edema)			Stokinger 1949 fluorine
			Hepatic	5	18	(liver congestion)			
33	Rabbit (NS)	5 wks 6d/wk 6hr/d	Resp	0.5	2	(mild bronchial inflammation)	18	(hemorrhage in the lungs)	Stokinger 1949 fluorine
			Hepatic	2	5	(hyperemia of the liver)			

Table 3-1. Levels of Significant Exposure to Fluorine - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
Reproductive							
34	Rat (NS)	5 wks 6d/wk 6hr/d		5		18 (testicular degeneration)	Stokinger 1949 fluorine

[a]The number corresponds to entries in Figure 3-1.
[b]Used to derive an acute inhalation minimal risk level of 0.01 ppm; concentration adjusted for intermittent exposure (0.25hours/24hours) and divided by an uncertainty factor of 10 for human variability.

d = day(s); Gn Pig = Guinea pig; LC_{50} = lethal concentration, 50% kill; LOAEL; lowest-observed-adverse-effect-level; min = minute(s); NOAEL = no-observed-adverse-effect level; ppm = parts per million; Resp = respiratory

Figure 3-1. Levels of Significant Exposure to Fluorine - Inhalation

Acute (≤14 days)

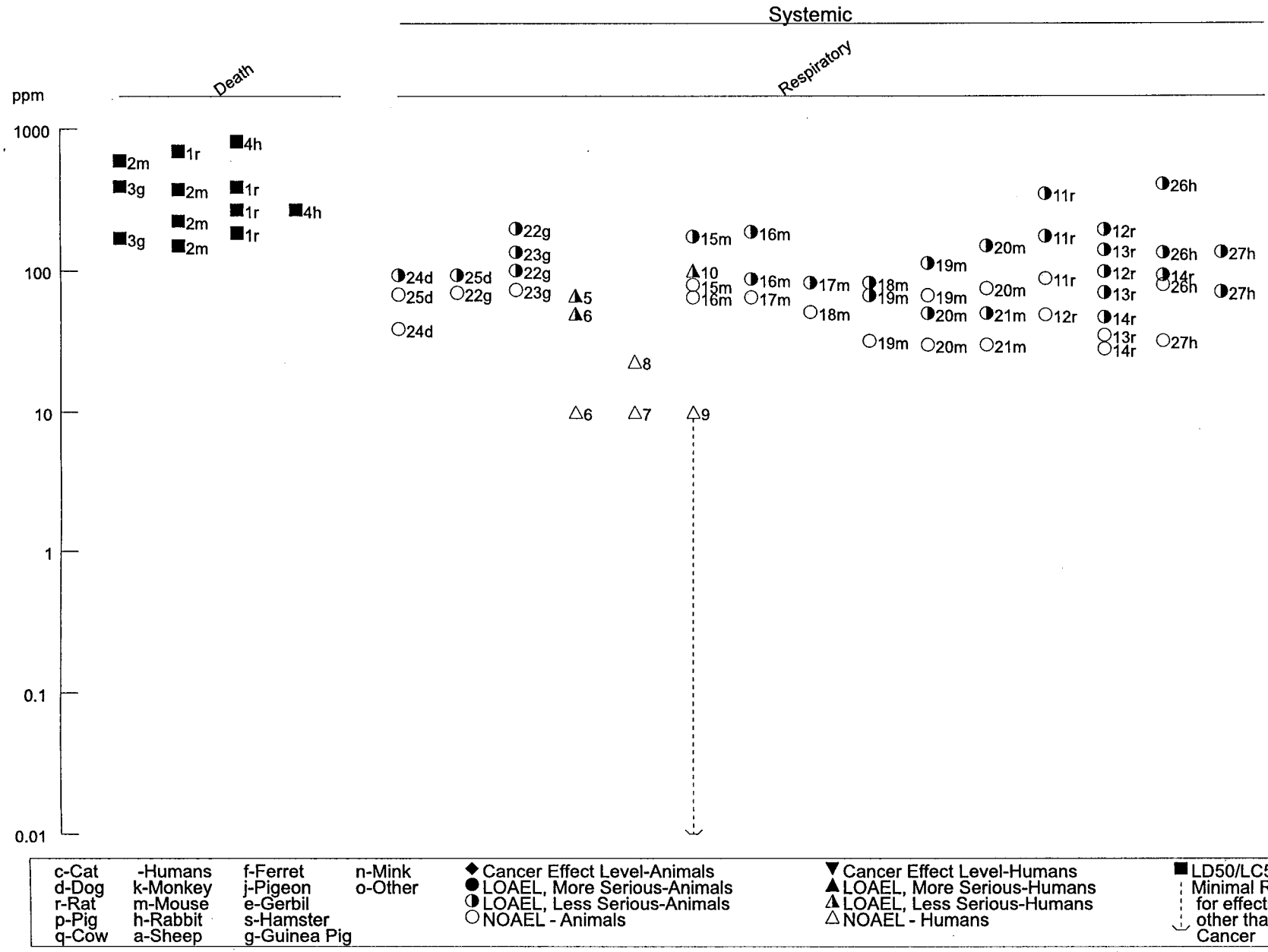
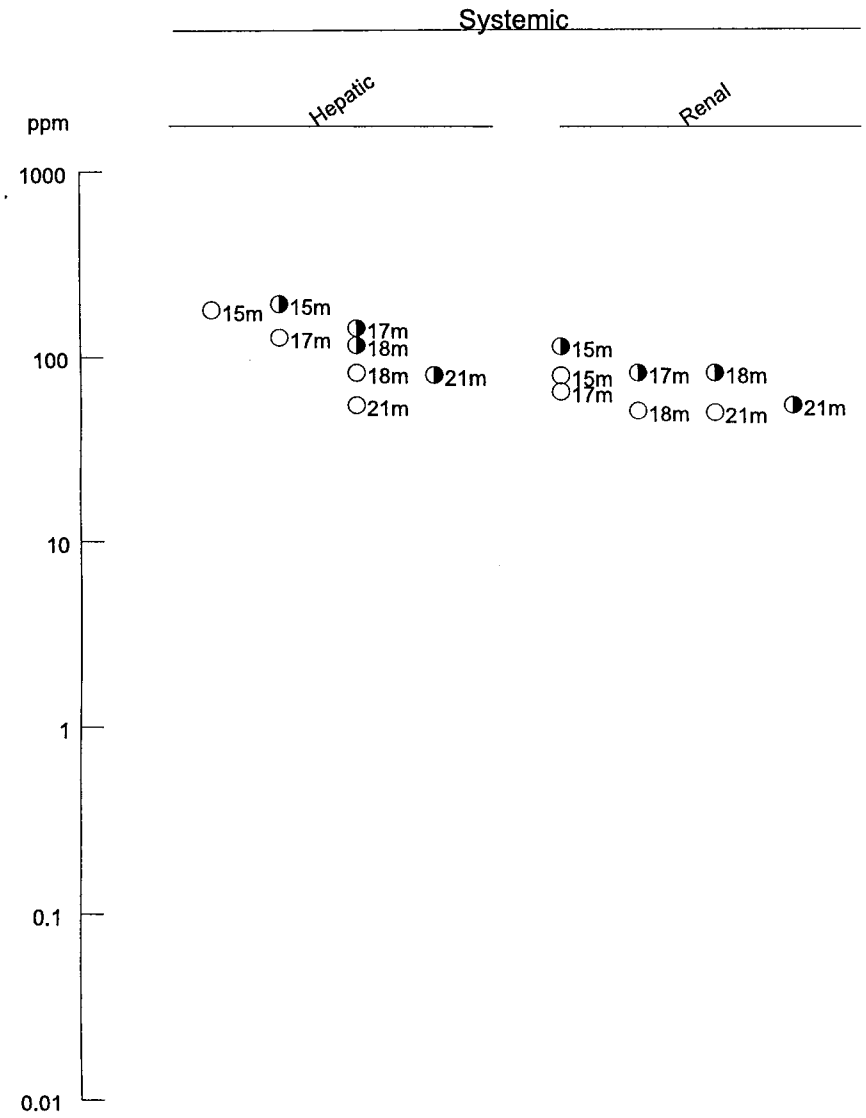


Figure 3-1. Levels of Significant Exposure to Fluorine - Inhalation (*continued*)

Acute (≤14 days)



c-Cat -Humans f-Ferret n-Mink
d-Dog k-Monkey j-Pigeon o-Other
r-Rat m-Mouse e-Gerbil
p-Pig h-Rabbit s-Hamster
q-Cow a-Sheep g-Guinea Pig

◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◮ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

Figure 3-1. Levels of Significant Exposure to Fluorine - Inhalation (*continued*)

Intermediate (15-364 days)

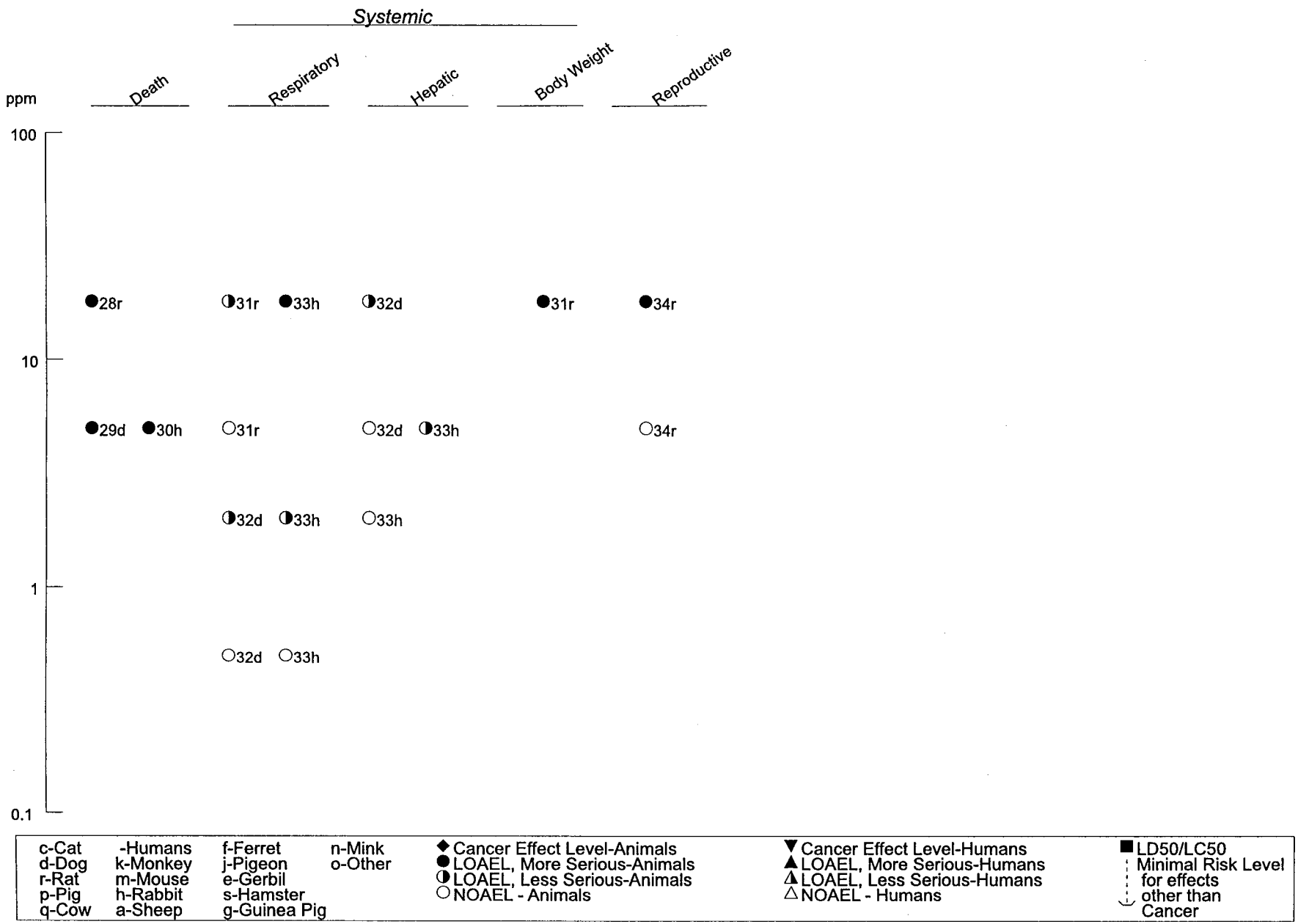


Table 3-2. Levels of Significant Exposure to Hydrogen Fluoride - Inhalation

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)		Reference Chemical Form
ACUTE EXPOSURE								
Death								
1	Rat	1 d 5-60 min/d				14,600	(5-minute LC_{50})	Haskell Laboratory 1988 hydrogen fluoride
						6620	(15-minute LC_{50})	
						2890	(30-minute LC_{50})	
						1610	(60-minute LC_{50})	
2	Rat (Wistar)	1 d 5-60 min/day				4722	(5-minute LC_{50})	Rosenholtz et al. 1963 hydrogen fluoride
						2555	(15-minute LC_{50})	
						1940	(30-minute LC_{50})	
						1242	(60-minute LC_{50})	
3	Rat	1 d 60 min/d				1325	(60-minuteLC_{50})	Wohlslagel et al. 1976 hydrogen fluoride
4	Mouse	1 d 60min/d				325	(60-minute LC_{50})	Wohlslagel et al. 1976 hydrogen fluoride
5	Gn Pig (Hartley)	1 d 5-60 min/d				4327	(15-minute LC_{50})	Rosenholtz et al. 1963 hydrogen fluoride

Table 3-2. Levels of Significant Exposure to Hydrogen Fluoride - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form
Systemic									
6	Rat (Sprague-Dawley)	2 min	Resp	563	1509	(mucosal necrosis in mid trachea)			Dalbey et al. 1998a, b hydrogen fluoride
			Hemato	4643	8190	(incr RBC, hemoglobin, and hematocrit levels)			
			Hepatic	563	1509	(incr asparate aminotransferase activity)			
7	Rat (Sprague-Dawley)	10 min	Resp	257	902	(minimal midtracheal necrosis)			Dalbey et al. 1998a, b hydrogen fluoride
			Hemato		1676	(incr hemoglobin and hematocrit levels)			
			Hepatic	1676					
8	Rat	1 d 5 min/d	Resp		712	(mild nasal irritation)	2310	(temporary respiratory distress and nasal discharge)	Rosenholtz et al. 1963 hydrogen fluoride
9	Rat	1 d 60min/d	Resp	98[b]	120	(mild nasal irritation)	465	(temporary respiratory distress and nasal discharge)	Rosenholtz et al. 1963 hydrogen fluoride
10	Rat	1 d 15min/d	Resp	292	357	(mild nasal irritation)	1339	(temporary respiratory distress and nasal discharge)	Rosenholtz et al. 1963 hydrogen fluoride

Table 3-2. Levels of Significant Exposure to Hydrogen Fluoride - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form
11	Rat (Fischer- 344)	30 min	Resp				1235	(fibrinonecrotic rhinitis in nose breathing rats; tracheal and bronchial necrosis in mouth breathing rats)	Stavert et al. 1991 hydrogen fluoride
			Bd Wt		1235	(10% body weight reduction)			
INTERMEDIATE EXPOSURE									
Death									
12	Rat (NS)	5 wks 6d/wk 6hr/d					31	(death in 29/29)	Stokinger 1949 hydrogen fluoride
13	Mouse (NS)	5 wks 6d/wk 6hr/d					31	(death in 18/18)	Stokinger 1949 hydrogen fluoride
Systemic									
14	Human	15-50 d 6 hr/d	Resp		2.98[c]	(slight nasal irritation)			Largent 1960 hydrogen fluoride
15	Rat (NS)	5 wks 6hr/d	Resp	8.2	31	(pulmonary hemorrhage)			Stokinger 1949 hydrogen fluoride
			Hemato	31					
			Renal	8.2	31	(cortical necrosis)			
16	Dog (NS)	5 wks 6d/wk 6hr/d	Resp		31	(pulmonary hemorrhage)			Stokinger 1949 hydrogen fluoride
			Hemato	31					

Table 3-2. Levels of Significant Exposure to Hydrogen Fluoride - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
17	Rabbit (NS)	5 wks 6d/wk 6hr/d	Resp	8.2	31 (pulmonary hemorrhage)		Stokinger 1949 hydrogen fluoride
			Hemato	31			
Neurological							
18	Rat (albino)	5mo 24hr/d		0.01	0.03 (disturbances in conditioned reflexes; lengthened latent periods)		Sadilova et al. 1965 hydrogen fluoride

[a]The number corresponds to entries in Figure 3-2.
[b]Used to derive an acute-duration inhalation minimal risk level (MRL) of 0.03 ppm; the concentration was adjusted for differences between the rat and human ratio of extrathoracic surface area to minute volume [(0.43 m^3/day/15 cm^2)/(20 m^3/day / 200 cm^2)] and for less than 24 hour exposure (1 hour/24 hours) and divided by an uncertainty factor of 30 (3 for interspecies extrapolation using dosimetric adjustments and 10 for human variability).
[c]Used to derive an intermediate inhalation minimum risk level (MRL) of 0.02 ppm; concentration adjusted for intermittent exposure (6hours/24hours) and divided by an uncertainty factor of 30 (3 for use of a LOAEL of a minimally adverse effect and 10 for human variability).
Bd = body weight; d = day(s); Hemato = hematological; hr = hour(s); incr = increase; LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; min =

Figure 3-2. Levels of Significant Exposure to Hydrogen Fluoride - Inhalation

Acute (≤14 days)

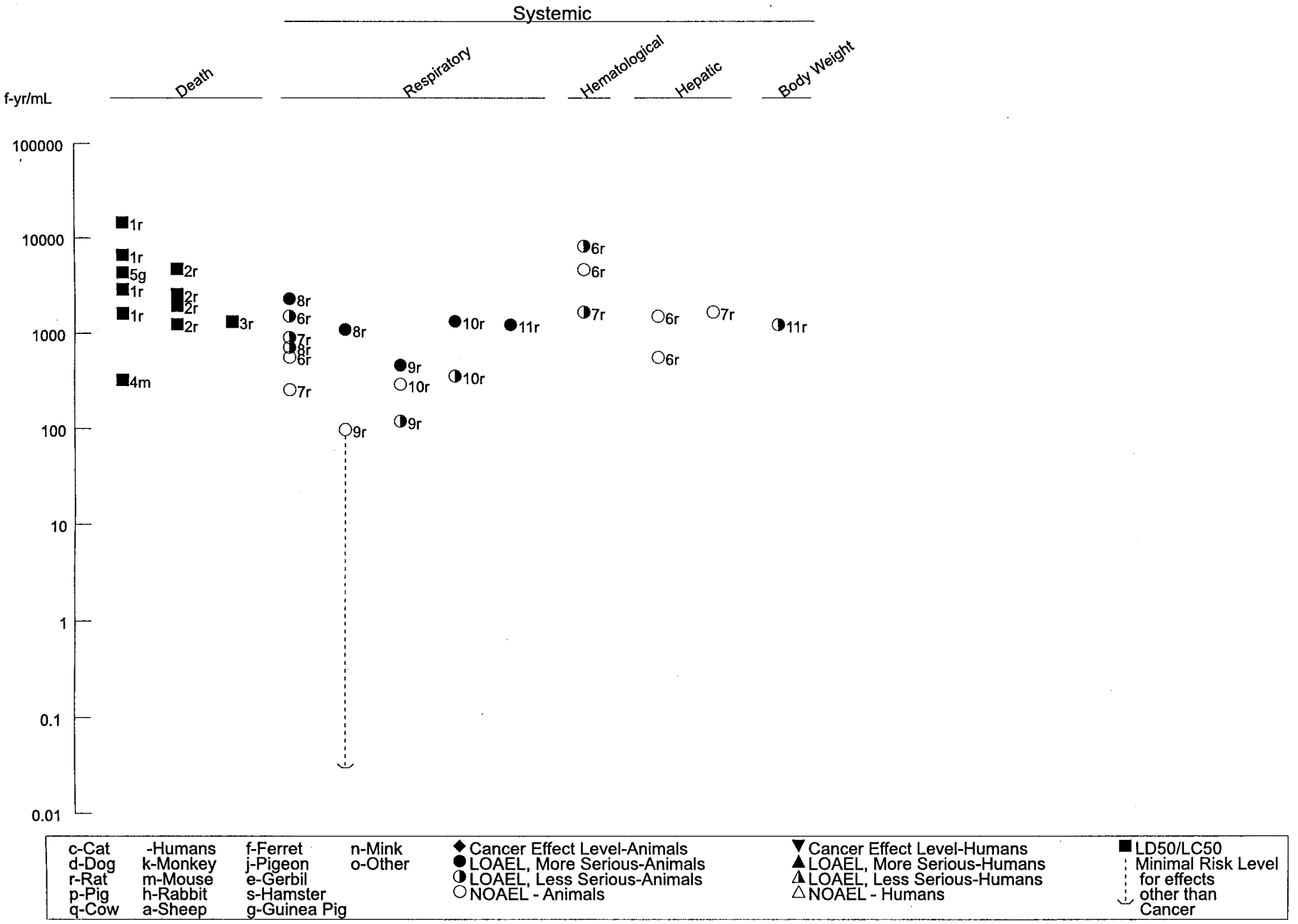
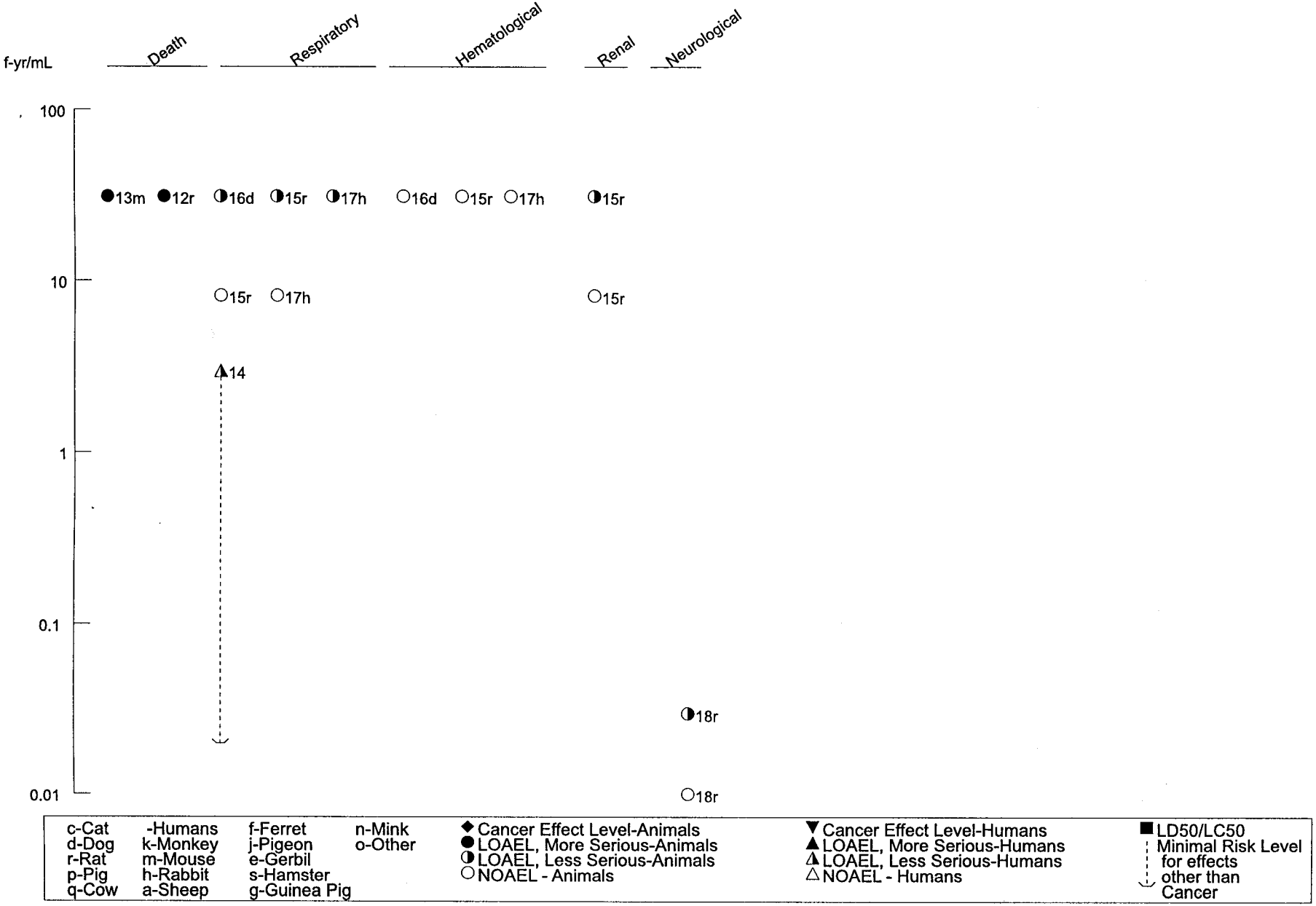


Figure 3-2. Levels of Significant Exposure to Hydrogen Fluoride - Inhalation (*continued*)

Intermediate (15-364 days)



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 0.9 ppm, and the maximum measured value was 24 ppm. 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 3.2.1.1 and later in this section (Keplinger 1969).

Diffuse lung congestion has been reported in rats, mice, guinea pigs, dogs, and rabbits exposed to fluorine for 5–60 minutes (Keplinger and Suissa 1968). The severity was concentrated-related. The adverse effect levels for each exposure duration did not appear to vary across species. The ranges of adverse effect levels for each exposure duration were 174–175 ppm for 5 minutes, 87–100 ppm for 15 minutes, 67–71 ppm for 30 minutes, and 47–135 ppm for 60 minutes. Other respiratory effects that were observed in these animals included dyspnea, irritation, and alveolar necrosis.

In 5-week exposure studies conducted by Stokinger (1949), pulmonary hemorrhage, edema, and bronchial inflammation were reported. These studies found species differences in sensitivity to fluorine-induced respiratory effects. Exposure to 2 ppm, 6 hours/day, 6 days/week for 5 weeks resulted in no effects in rats, pulmonary hemorrhage and edema in dogs, and mild bronchial inflammation in rabbits; respiratory effects (severe pulmonary irritation) were observed in rats exposed to 18 ppm.

Swiss-Webster mice that were preexposed once to 30 ppm fluorine for 60 minutes, and were then exposed to 118–410 ppm 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 (410 ppm), exposure 4 hours prior to the challenge reduced the lung pathology from the most severe rating to a rating of normal–mild. Preexposure also reduced the increased lung weight otherwise seen following fluorine exposure. However, a similar preexposure regimen only resulted in slight increases in the LC_{50}, as discussed in Section 3.2.1.1.

Hydrogen Fluoride. Acute inhalation of 122 ppm fluoride as 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.

A number of residents of Texas City, Texas, reported respiratory symptoms following the accidental release of hydrogen fluoride. It was estimated that most of the hydrogen fluoride was released in the first 2 hours after the accident, and evacuation of residents within 0.5 miles of the facility began within 20 minutes of the accident. Many of the 939 people who went to the emergency room within 24 hours of the accident reported signs of respiratory irritation: throat burning (21.0%), shortness of breath (19.4%), sore throat (17.5%), and cough (16.4%) (Wing et al. 1991). Forced expiratory volume in 1 second (FEV_1) was <80% of predicted values in 42.3% of the 130 individuals who underwent pulmonary function testing. In another study of the Texas City residents, health effects within 1 month of the accident and 2 years after the accident were assessed in 1,994 residents who were asked to complete health questionnaires (Dayal et al. 1992). A large number of highly exposed residents reported severe symptoms of breathing problems (e.g., coughing, difficulty breathing, shortness of breath), throat problems (e.g., difficulty swallowing, burning irritation, phlegm, voice changes), and nose problems (e.g., sneezing, runny nose, problems smelling food); the prevalence of severe symptoms were 60.2, 51.9, and 40.7 for breathing, throat, and nose problems, respectively, within the first month of the accident. High prevalence of these effects were still reported 2 years after the accident; 38.5, 22.1, and 26.5 for severe breathing, throat, and nose problems, respectively. The prevalence of severe breathing, throat, and nose problems in the nonexposed population were 11.3, 6.2, and 6.4, respectively, within 1 month of the accident and 8.2, 3.3, and 4.1, respectively, 2 years after the accident. The prevalences of the breathing problems were higher in a subgroup of the high exposure group that had pre-existing respiratory problems or smoked more than two packs of cigarettes per day.

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 intra-alveolar 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.

A series of experiments by Dalbey et al. (1998a, 1998b) examined the acute toxicity of nonlethal concentrations of hydrogen fluoride in rats following a 2- or 10-minute exposure. In most of the experiments, a mouth-breathing model with a tracheal cannular was used to maximize delivery of hydrogen fluoride to the lower respiratory tract. A number of respiratory tract effects were found in the mouth-breathing rats, including alterations in bronchioalveolar lavage (BAL) parameters (increased total protein, myeloperoxidase, lactate dehydrogenase, β-glucuronidase, and glucose-6-phosphate dehydrogenase), impaired lung function (decreased total lung capacity, vital capacity, peak expiratory flow, forced expiratory flow at 50 and 25% of the forced vital capacity, forced expiratory volume at 0.1 second, forced vital capacity, and diffusing capacity and increased pulmonary resistance), and histological damage (necrosis and acute inflammation in trachea and acute alveolitis and perivascular/

peribronchial edema and inflammation in the lung). Rats exposed for 2 minutes manifested histological damage and BAL parameter alterations at 1,509 ppm fluoride, and impaired lung function at 4,643 ppm. No adverse respiratory effects were observed at 563 ppm fluoride. In the rats exposed for 10 minutes, histopathological alterations (necrosis of the trachea only) and BAL parameters (polymorphonuclear leukocytes and myeloperoxidase levels only) were observed at 903 ppm fluoride ; impaired respiratory function was observed at 1,676 ppm fluoride. No adverse effects were observed at 257 ppm fluoride. The respiratory effects were consistently more severe in the rats exposed for 2 minutes as compared to 10 minutes, when exposure was expressed as the product of concentration x time. In other experiments, rats were exposed for 60 minutes to hydrogen fluoride. No adverse respiratory effects were observed at 19 or 46 ppm. Respiratory effects observed in nose-breathing rats were limited to the nose. Necrosis and acute inflammation of the ventral meatus, nasal septum, and nasoturbinates were observed in rats exposed to 6,072 ppm for 2 minutes and 1,586 ppm for 10 minutes. A dramatic decrease in breathing frequency was also observed in the nose-breathing rats; within the first minute of exposure, breathing frequency was 32–35% of the preexposure levels. The decrease in breathing frequency, which is a component of reflex apnea, is a response to sensory irritation.

Similar results were observed in rats exposed to 1,235 ppm fluoride for 30 minutes. Moderate to severe fibronecrotic rhinitis and large fibrin thrombi in the submucosa and hemorrhage were observed in the nasal cavity of nose-breathing rats; no nasal lesions were observed in similarly exposed rats fitted with a tracheal cannula to simulate mouth-breathing. Epithelial, submucusal, and cartilage necrosis in the trachea, trace levels of neutrophils in the alveoli, and necrosis of the bronchi were observed in the mouth-breathing rats, but not in the nose-breathing rats, suggesting that the toxicity of hydrogen fluoride occurs at the point of entry. Reflex apnea, as evidenced by a marked decrease in breathing frequency, was observed in the nose-breathing rats. Based on differences in minute ventilation rates, the study authors estimated that the mouth-breathing rats inhaled 27% more hydrogen fluoride than the nose-breathing rats.

Pulmonary hemorrhage was noted in dogs, rabbits, and rats exposed to 31 ppm fluoride as hydrogen fluoride for 6 hours/day, 6 days/week for 5 weeks (Stokinger 1949). At 8.2 ppm fluoride, no effect was seen in rats or rabbits, and localized hemorrhages were seen in only 1/5 dogs.

Pulmonary hemorrhage, alveolar inflammation, and hyperplasia of the bronchial epithelium were observed in guinea pigs that died due to exposure to 18 ppm fluoride as hydrogen fluoride 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. Because 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 26 ppm fluoride as anhydrous hydrogen fluoride for an 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 levels of gastrointestinal complaints were 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 nonindustrial 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).

Similar gastrointestinal effects (diarrhea, nausea, and vomiting) were reported by Texas residents exposed to an accidental 2-hour release of hydrogen fluoride (Dayal et al. 1992). During the first month after the accident, 38.5% of the highly exposed residents reported severe gastrointestinal effects; 15.5% of the residents still reported severe gastrointestinal effects 2 years after the accident. The occurrence of severe gastrointestinal effects among nonexposed residents was 4.5 and 2.7%, respectively, for these time periods.

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 in Osborne-Mendel rats exposed to 142 ppm for 60 minutes or 329 ppm for 15 minutes or in dogs exposed to 109 ppm for 60 minutes or 93 ppm for 15 minutes (Keplinger and Suissa 1968). These concentrations were higher than the corresponding LC_{50} values. Blood counts were monitored for 21 days postexposure. Similarly, Stokinger (1949) saw no effect on hematological parameters in dogs, rabbits, or rats following repeated exposures at concentrations up to lethal levels (31 ppm). 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 18 ppm fluoride for 6 hours/day, 6 days/week, for 5 weeks showed no clear changes (Stokinger 1949).

Five rabbits and two Rhesus monkeys were exposed to 18 ppm fluoride as 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 on leucocyte levels in either species. These experiments used only a few animals from each species, and the exposure measurement technology was not very precise.

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 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 18 ppm fluorine for approximately 6 hours/day, 6 days/week for 5 weeks 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 2 ppm fluorine.

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 osteo-arthritis 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.

Duration- and concentration-related increases in tooth and bone fluoride levels were reported in the rat following exposure to 8.2 or 31 ppm fluoride as hydrogen fluoride for 6 hours/day, 6 days/week for

5 weeks (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, because 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 >10 years. No effects, however, were seen in workers exposed for <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, 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. 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 to be 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 of 195, 144, 116, or 80 ppm fluoride for 5, 15, 30, or 60 minutes, respectively. Damage became apparent 7–14 days after exposure. Liver congestion was reported in dogs, but not in other species subjected to repeated exposures to a lethal concentration of fluorine (18 ppm 6 hours/day, 6 days/week for 5 weeks) (Stokinger 1949).

Hydrogen Fluoride. Ten animals (five rabbits, three guinea pigs, and two Rhesus monkeys) were exposed via inhalation to 18 ppm fluoride as hydrogen fluoride 6–7 hours/day for 50 days (Machle and Kitzmiller 1935). 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 following exposure to 114 ppm for 5 minutes, 82 ppm for 15 or 30 minutes, or 55 ppm for 60 minutes (Keplinger and Suissa 1968). 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 EC (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 31 ppm fluoride as hydrogen fluoride for 6 hours/day, 6 days/week for 5 weeks, but not in rats exposed to 8.2 ppm fluoride (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 durations were tested, but the levels at which exposure-related effects were seen were not reported. Rabbits (n=4) exposed via inhalation to 18 ppm fluoride as hydrogen fluoride 6–7 hours/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, the testing method used in this study is considered to be 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 #5.68 mg/L (Dinman et al. 1976c) and #9.6 mg/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 inhalation 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 relevance 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.

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

Dermal Effects. Dermal effects (irritation of the skin) have been observed in humans following exposure to airborne fluoride. Because the effects are believed to be due to irritation caused by direct dermal contact with these gases, they are discussed under Dermal Exposure (see Section 3.2.3).

Ocular Effects. As with dermal effects, ocular effects such as lacrimation and reddened conjunctiva have been reported in humans and animals exposed to airborne fluorine and hydrogen fluoride. These effects are discussed under Dermal Exposure (see Section 3.2.3) because they are due to direct contact rather than from absorbed fluoride.

Body Weight Effects.

Fluorine. Decreased weight gain was observed in rats, guinea pigs, and rabbits exposed to 18 ppm fluorine for about 6 hours/day, 6 days/week for 5 weeks (Stokinger 1949). While a decreased weight gain in the high-exposure group compared to the low-exposure groups is clear, no control animals were used and the lowest exposure level that would result in a significant change was not established.

Hydrogen Fluoride. Pronounced weight loss shortly before death was observed in rats exposed to a lethal level of hydrogen fluoride (31 ppm fluoride for 6 hours/day, 6 days/week for 5 weeks). 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 and the lowest exposure level that would result in a significant change was not established. Animals surviving a lethal exposure exhibited a body weight loss of 10–15% for up to a week after exposure (Rosenholtz et al. 1963; Stavert et al. 1991).

3.2.1.3 Immunological and Lymphoreticular Effects

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

3.2.1.4 Neurological Effects

Fluorine. No studies were located regarding neurological effects in humans of fluorine following inhalation exposure. Dogs exposed to 5 or 18 ppm for 6 hours/day, 6 days/week for up to 35 days had seizures 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 ppm fluoride (Sadilova et al. 1965). While the threshold level was determined to be 0.03 ppm, 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 0.03 or 0.1 ppm fluoride as 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 ppm. A concentration of 0.01 ppm 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 1-month recovery period in the animals exposed to 0.1 ppm. Animals exposed to 0.03 ppm recovered completely.

All reliable LOAEL values for neurological effects of exposure to hydrogen fluoride in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.1.5 Reproductive Effects

Fluorine. Rats exposed to 18 ppm fluorine, 6 hours/day, 6 days/week for 5 weeks 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.

Hydrogen Fluoride. All four dogs exposed to 18 ppm fluoride as hydrogen fluoride for 6 hours/day, 6 days/week for 5 weeks developed degenerative testicular changes and ulceration of the scrotum (Stokinger 1949). This effect was not seen at 8.2 ppm, 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.

3.2.1.6 Developmental Effects

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

3.2.1.7 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 3.5]) (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 been 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 or concurrent exposure to tars and polycyclic aromatic hydrocarbons. Similarly, fluorspar miners had

increased lung cancer rates, but they were also 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 rates was statistically significant. Increases in incidence of hematopoietic cancers and respiratory disease were also reported by Milham (1979). Because of the confounding factors mentioned above, and because 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 occurrence and exposure to fluoride among individuals 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.

3.2.2 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 on oral exposure refer to 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. 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 Institute of Medicine has derived adequate intake values ranging from 0.01 to 4 mg/day to reduce the occurrence of dental caries. Adequate intake values broken down by age group are 0–6 months, 0.01 mg/day; 7–12 months, 0.5 mg/day; 1–3 years, 0.7 mg/day; 4–8 years, 1 mg/day; 9–13, 2 mg/day; 14–18 years, 3 mg/day; 19 years and older, 4 mg/day (males) and 3 mg/day (females); pregnancy, 3 mg/day; and lactation, 3 mg/day (IOM 1997). The World Health Organization (WHO) also lists fluorine as essential for animal life, without providing supporting data (WHO 1973).

As discussed in Section 3.2.2.6, 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 #8.8 ppm 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.

3.2.2.1 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 that 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 probable 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.

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 and 200–359 g were 52 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-year-old 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 3-3 and plotted in Figure 3-3.

3.2.2.2 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 dermal or 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 3-3 and plotted in Figure 3-3.

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

Congestion, the presence of edema fluid, and desquamation of respiratory epithelium were observed in the lungs of rabbits exposed to 4.5 or 9 mg fluoride/kg/day as sodium fluoride in the diet for 6 months (Purohit et al. 1999). Inflammatory cell infiltrates, congestion, and desquamated epithelium were also observed in the large bronchi and trachea of rabbits fed 9 mg fluoride/kg/day. Necrosis of the lung parenchyma was also observed in two high-dose rabbits that died before the end of the study.

Table 3-3. Levels of Significant Exposure to Fluoride - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Human	1d 1x/d (C)				16 (1 child)	Eichler et al. 1982 sodium fluoride
2	Rat (Sprague-Dawley)	1 d 1x/d (GW)				54 (LD_{50} for 80 g rats)	DeLopez et al. 1976 sodium fluoride
						52 (LD_{50} for 150 g rats)	
						31[b] (LD_{50} for 250 g rats)	
3	Rat (Rochester)	1 d 1x/d (GW)				51.6 (LD_{50})	Lim et al. 1978 sodium fluoride
4	Rat (Sprague-Dawley)	1 d 1x/d (GW)				101.3 (LD_{50})	Skare et al. 1986 sodium fluoride
5	Mouse (Swiss)	1 d 1x/d				44.3 (LD_{50})	Lim et al. 1978 sodium fluoride
	Systemic						
6	Rat	2wk (W)	Musc/skel		9.5 (decreased modulus of elasticity)		Guggenheim et al. 1976 sodium fluoride

Table 3-3. Levels of Significant Exposure to Fluoride - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
	Reproductive						
7	Mouse	5d 1x/d (G)		32			Li et al. 1987a sodium fluoride
	Developmental						
8	Rat (Sprague-Dawley)	Gd 6-15 daily (W)		12.26			Heindel et al. 1996 sodium fluoride
9	Rabbit (New Zealand)	Gd 6-19 daily (W)		13.21			Heindel et al. 1996 sodium fluoride

Table 3-3. Levels of Significant Exposure to Fluoride - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	INTERMEDIATE EXPOSURE						
	Death						
10	Mouse (B6C3F1)	6 mo daily (W)				67 (increased mortality)	NTP 1990 sodium fluoride
11	Mouse	6mo ad lib (W)				300[c] M (mortality) 600 F (mortality)	NTP 1990 sodium fluoride
	Systemic						
12	Rat	2 mo 7d/wk 24hr/d (W)	Endocr		0.5 (decreased thyroxine levels; increased T3-resin uptake ratio)		Bobek et al. 1976 sodium fluoride
13	Rat (Sprague-Dawley)	7d/wk 24hr/d (W)	Musc/skel		10.5 (decr mineral content and incr proline in tooth enamel matrix)		DenBesten and Crenshaw 1984 sodium fluoride
14	Rat (Wistar)	5 wk (W)	Musc/skel	13	19 (histological fluorosis; decr bone growth)		Harrison et al. 1984 sodium fluoride
15	Rat (Fischer- 344)	6 mo daily (W)	Gastro		7 (hyperplasia of glandular stomach)		NTP 1990 sodium fluoride
			Hepatic	20			
			Renal	20			

Table 3-3. Levels of Significant Exposure to Fluoride - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
16	Rat	30d (W)	Musc/skel		14 (delayed healing of broken bones)		Uslu 1983 sodium fluoride
17	Mouse	280 d daily (W)	Hepatic		0.95 (pale, granular hepatocytes with fatty vacuoles)		Greenberg 1982a sodium fluoride
18	Mouse	280d (W)	Renal		1.9 (nephron degeneration)		Greenberg 1986 sodium fluoride
19	Mouse	4 wk 7d/wk daily (W)	Musc/skel		0.80 (incr bone formation rate; slight decr bone calcium)		Marie and Hott 1986 sodium fluoride
20	Mouse (B6C3F1)	6 mo daily (W)	Cardio			67 (multifocal mineralization and degeneration of the myocardium)	NTP 1990 sodium fluoride
			Musc/skel		5.6 M (increased osteoid in femur and tibia)		
			Hepatic		67 (megaolocytosis and syncytial alteration)		
			Renal			67 (multifocal nephrosis)	
			Bd Wt		67 (20% decr bw gain)		
21	Mouse	35 d 1x/d (GW)	Hemato		5.2 (decr RBC and hemoglobin, incr WBC)		Pillai et al. 1988 sodium fluoride
			Bd Wt		5.2 (decr body weight)		
22	Rabbit (NS)	6 mo daily (F)	Resp		4.5 (congestion, edema fluid, desquamation of respiratory epithelium in lungs)		Purohit et al. 1999 sodium fluoride

Table 3-3. Levels of Significant Exposure to Fluoride - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
Neurological							
23	Rat (Sprague-Dawley)	6 wk daily (W)			6 F (altered spontaneous behavior)		Mullenix et al. 1995 sodium fluoride
24	Rat (Sprague-Dawley)	6 wk daily (W)		5.5 F	7.5 F (altered spontaneous behavior)		Mullenix et al. 1995 sodium fluoride
25	Rat (Wistar)	60 d daily (GW)			9 (decr spontaneous activity)		Paul et al. 1998 sodium fluoride
Reproductive							
26	Rat (CD)	60 d 7d/wk (F)			2.3 (decr seminiferous tubule diameter)	4.5 (50% reduction in fertility, decr in percentage of seminiferous tubules containing spermatozoa and decr testosterone levels)	Araibi et al. 1989 sodium fluoride
27	Rat (NS)	daily 30 d (GW)				2.3 (decreased fertility and sperm counts)	Chinoy et al. 1992 sodium fluoride
28	Rat (Charles Foster)	30 or 50 days d (F)				4.5 (decreased sperm motility and count)	Chinoy et al. 1995 sodium fluoride
29	Rat (Wistar)	daily 6 wk (W)		21			Krasowska and Wlostowski 1992 sodium fluoride

Table 3-3. Levels of Significant Exposure to Fluoride - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
30	Rat (Wistar)	daily 16 wk (W)			7.5 (seminiferous tubule atrophy)		Krasowska and Wlostowski 1992 sodium fluoride
31	Rat	3 mo 7d/wk (F)		23			Marks et al. 1984 sodium fluoride
32	Rat Charles Foster	daily 50 d (GW)			4.5 (decr testosterone levels and Leydig cell diameter)		Narayana and Chinoy 1994 sodium fluoride
33	Rat (Sprague-Dawley)	daily (W)		16			Sprando et al. 1997 sodium fluoride
34	Rat (Sprague-Dawley)	daily (W)		16			Sprando et al. 1998 sodium fluoride
35	Mouse (Swiss)	30 d daily (F)				4.5 (decr sperm motility and count and infertility)	Chinoy and Sequeira 1992 sodium fluoride
36	Mouse (Swiss-Webster)	25 wks (W)		9.5		19 (nearly complete infertility)	Messer et al. 1973 sodium fluoride
37	Mouse	35 d 1x/d (GW)		5.2			Pillai et al. 1988 sodium fluoride

Table 3-3. Levels of Significant Exposure to Fluoride - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
38	Gn Pig (NS)	30 d daily (GW)				4.5 (decr sperm motility and viability)	Chinoy et al. 1997 sodium fluoride
	Developmental						
39	Rat (CD)	Gd 1-20 daily (W)		11.2	11.4 (incr in average number of fetuses per litter with 3+ skeletal variations)		Collins et al. 1995 sodium fluoride
40	Rat (Sprague-Dawley)	28 wk 7d/wk 24hr/d (W)		21			Ream et al. 1983 sodium fluoride

Table 3-3. Levels of Significant Exposure to Fluoride - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	CHRONIC EXPOSURE						
	Systemic						
41	Human	4 yr (C)	Musc/skel		0.56[d] (increased fracture rate)		Riggs et al. 1990 sodium fluoride
42	Rat (Fischer- 344)	103 wk (W)	Resp	3.9			NTP 1990 sodium fluoride
			Cardio	3.9			
			Gastro	3.9			
			Hemato	3.9			
			Musc/skel	2.5	4.3 (osteoscleosis)		
			Hepatic	3.9			
			Renal	3.9			
			Bd Wt	3.9			
43	Mouse (B6C3F1)	103 wk (W)	Resp	7.6			NTP 1990 sodium fluoride
			Cardio	7.6			
			Gastro	7.6			
			Hemato	7.6			
			Musc/skel	4.3 M	7.6 M (dentine dysplasia)		
			Hepatic	7.6			
			Renal	7.6			
			Bd Wt	7.6			
44	Rabbit	24 mo 1x/d (GW)	Gastro		5 (roughened duodena mucosa)		Susheela and Das 1988 sodium fluoride

Table 3-3. Levels of Significant Exposure to Fluoride - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
45	Rabbit	7-12 mo 1x/d (G)	Hemato		4.52 (decr leukocyte and hemoglobin levels)		Susheela and Jain 1983 sodium fluoride
46	Mink	382 d 24hr/d (F)	Musc/skel		5 (mottled and brittle kit teeth)	9.1 (sagittal crests deformed, 3/6 adults)	Aulerich et al. 1987 sodium fluoride
	Immunological/Lymphoreticular						
47	Rabbit (albino)	18 mo 1x/d (G)			4.5 (decr primary and secondary antibody titers)		Jain and Susheela 1987 sodium fluoride
	Reproductive						
48	Mouse	3 gen (F)		13			Tao and Suttie 1976 sodium fluoride
49	Rabbit (NS)	daily 18 mo (GW)				4.5 M (structural damage of the spermatid and epididymal spermatozoa)	Kumar and Susheela 1994 sodium fluoride
50	Rabbit (NS)	daily 20 or 23 mo (GW)				4.5 M (structural damage of the spermatid and epididymal spermatozoa)	Kumar and Susheela 1995 sodium fluoride
51	Rabbit (NS)	daily 18 or 29 mo (GW)				4.5 (complete cessation of spermatogenesis)	Susheela and Kumar 1991 sodium fluoride
52	Rabbit (New Zealand)	daily 18 or 23 mo (GW)			4.5 (Leydig cell damage)		Susheela and Kumar 1997 sodium fluoride

Table 3-3. Levels of Significant Exposure to Fluoride - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
53	Mink	382 d daily (F)		9.1			Aulerich et al. 1987 sodium fluoride
	Cancer						
54	Rat (Fischer- 344)	103 wk (W)				2.4 M (osteosarcoma of bone)	NTP 1990 sodium fluoride

[a]The number corresponds to entries in Figure 3-3.
[b]Only this dose level, the most sensitive dose level, is plotted in Figure 3-3.
[c]Differences in levels of health effects and cancer effects between males and females are not indicated in Figure 3-3. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[d]Used to derive a chronic oral minimal risk level (MRL) of 0.06 mg/kg/day; dose divided by an uncertainty factor of 10 for use of a LOAEL identified in a sensitive subpopulation.

ad lib = ad libitum; Bd Wt = body weight; (C) = capsule); d = day(s); decr = decrease; Endocr = endocrine; (F) = feed; F = female(s); (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; gen = generation(s); (GW) = gavage in water; Hemato = hematological; hr = hour(s); incr = increase; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = males; mg/kg/day = milligram per kilogram per day; mo = month(s); Musc/skel = muscular/skeletal; NOAEL = no-observed-adverse-effect level; RBC = red blood cell(s); Resp = respiratory; T3 = triiodothyronine; (W) = water; WBC = white blood cell(s); wk = week(s); x = time

Figure 3-3. Levels of Significant Exposure to Fluoride - Oral

Acute (≤14 days)

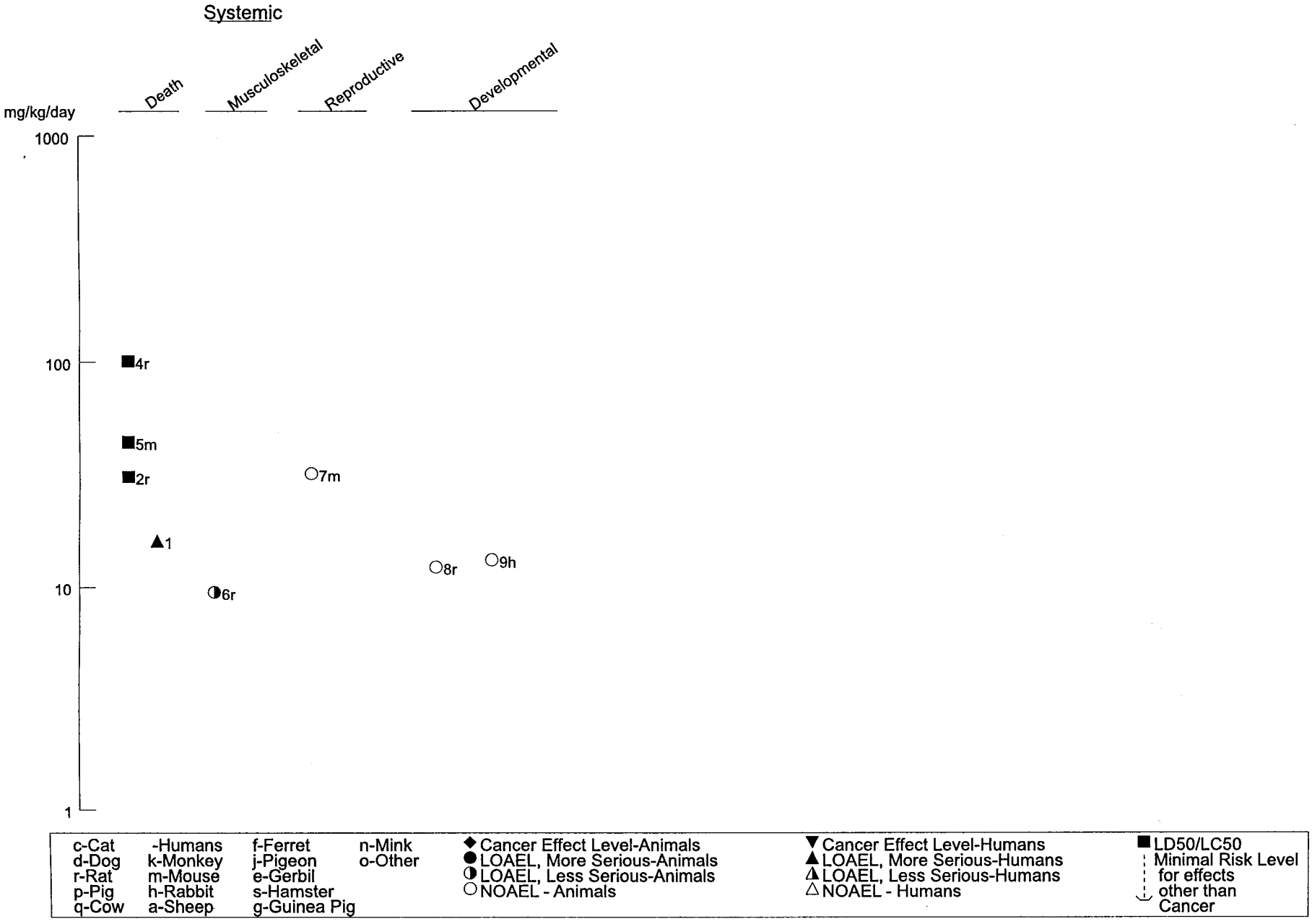


Figure 3-3. Levels of Significant Exposure to Fluoride - Oral (*continued*)

Intermediate (15-364 days)

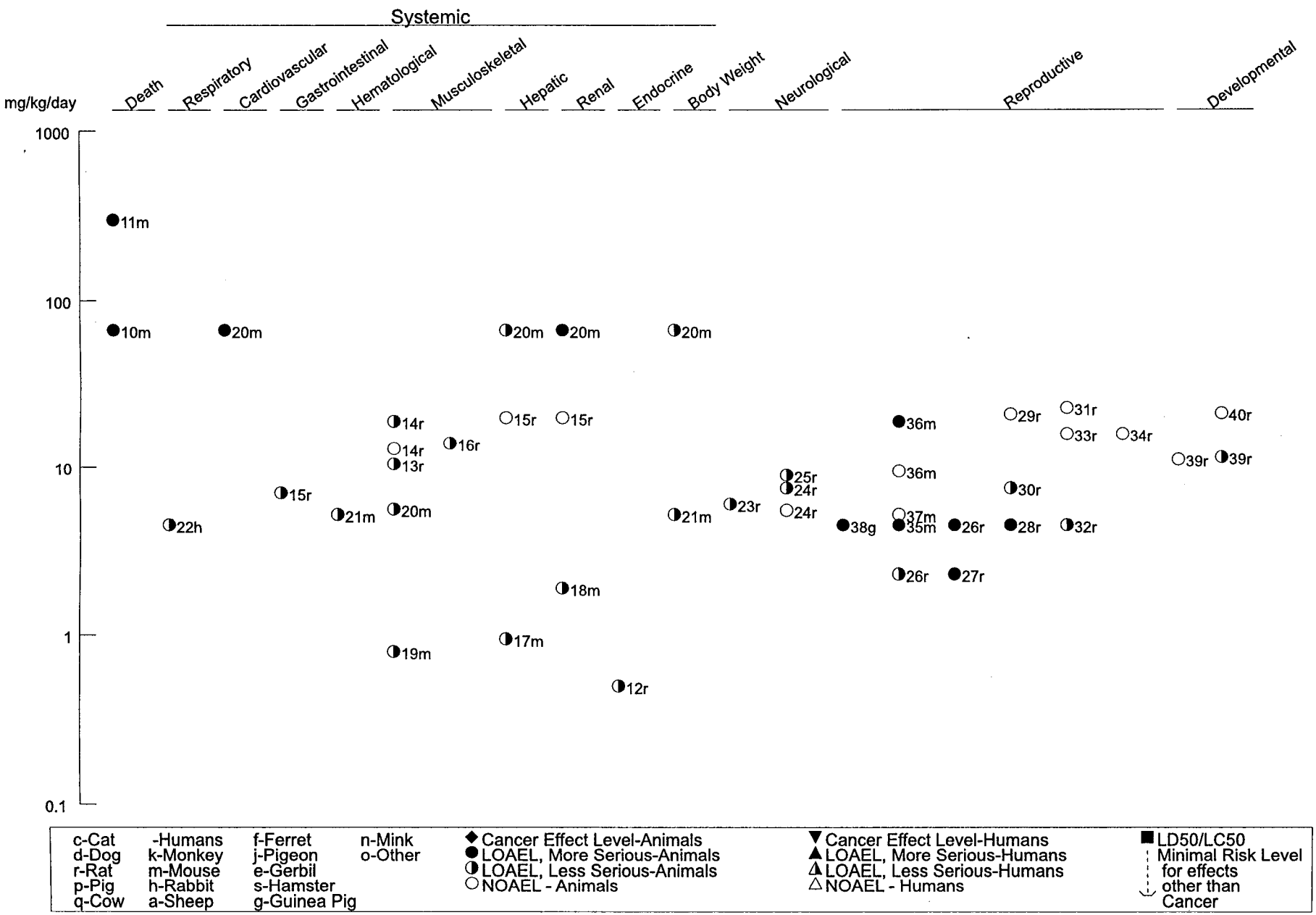
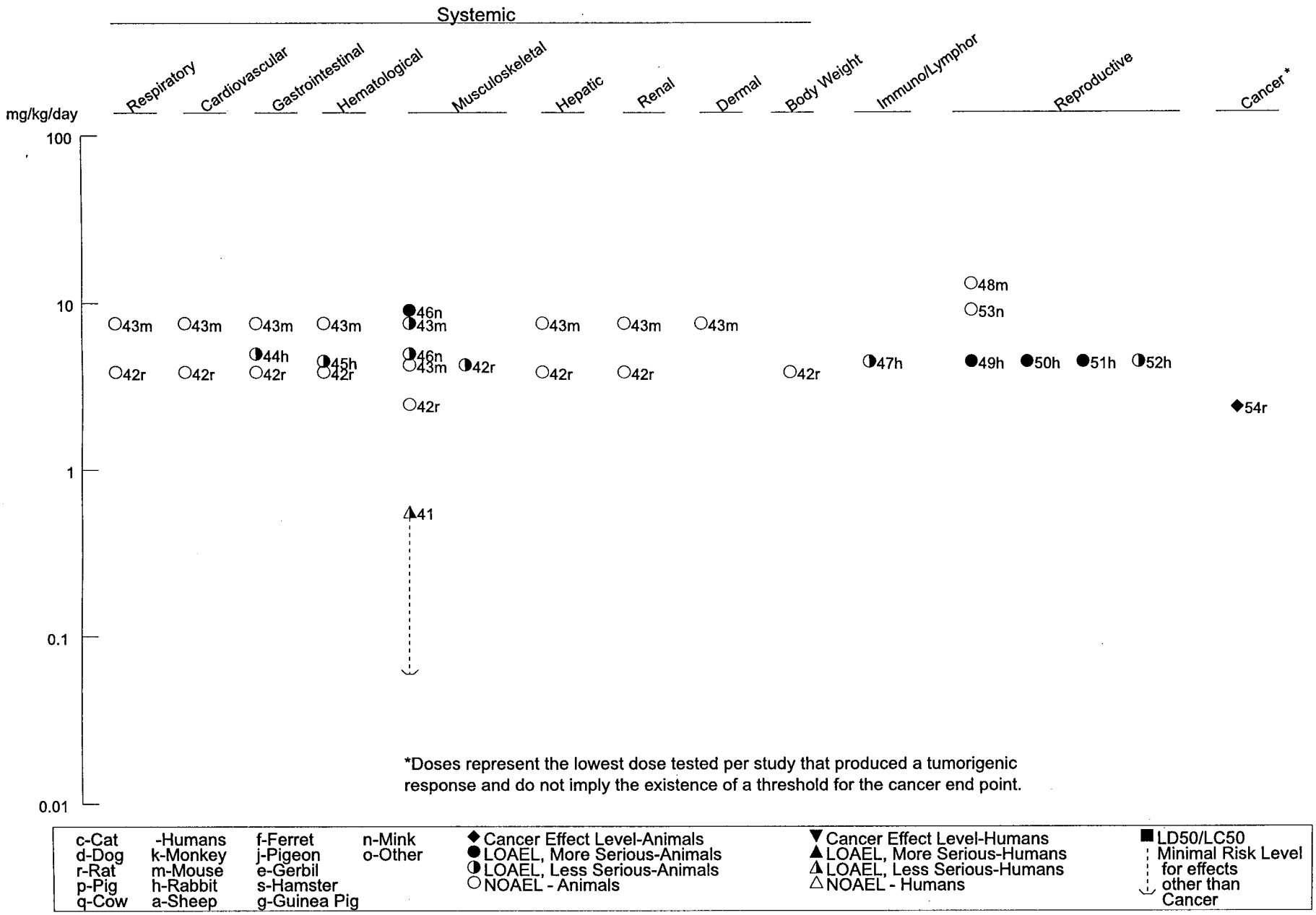


Figure 3-3. Levels of Significant Exposure to Fluoride - Oral (*continued*)

Chronic (≥365 days)



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, 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 $1 ppm (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 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 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. Additional studies have suggested a role for fluoride in reducing cardiovascular disease. In a study of four towns in Finland, Luoma (1980) found that incidence of cardiovascular disease correlated negatively with water fluoride concentration. Taves (1978) likewise found that standard mortality ratios decreased to a greater extent in fluoridated cities from 1950 to 1970 as compared to non-fluoridated control cities. Both studies, however, relied on population-summary information for disease rates. A mechanism for this potential reduction in cardiovascular disease could be the ability of fluoride to inhibit the calcification of soft tissue such as the aorta, as demonstrated in *in vitro* studies (Taves and Neuman 1964; Zipkin et al. 1970).

About half of the male and female B6C3F_1 mice that died as a result of exposure to 67–71 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 1–5 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 <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 were taken from 12 healthy volunteers either after no treatment (control) or 2 hours after drinking 20 mL of a solution containing 20 mg fluoride (1,000 ppm) 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, which allowed 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 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 3-3 or plotted in Figure 3-3.

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 nonulcer dyspepsia patients at an outpatient clinic in India and 10 volunteers without gastrointestinal problems from the surgical clinic (Susheela et al. 1992). While none of the drinking water supplies of the controls had fluoride levels >1 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 >0.1 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 <2 years of exposure were included; 18 workers had been exposed for >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 that 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 28.5 mg fluoride/kg in the form of sodium fluoride 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.

Thickening of the mucosa of the glandular stomach and punctate hemorrhages were seen in F344/N rats given 20 mg fluoride/kg/day as sodium fluoride in drinking water for 26 weeks (NTP 1990). Similar, but less severe, alterations were seen in some rats that received 7 mg fluoride/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 67–71 mg fluoride/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 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 (6,000 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) when ingested in excess amounts during tooth development (1–8 years of age). 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 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 dentition could 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 both the prevalence and the severity of dental fluorosis were 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 <1 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 increased from 0.0 to 0.9%. While there were some differences between the studies in the 1940s and those in the 1980s, 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 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 increased 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 <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.

Fluoride results in thickened bones and exostoses (skeletal fluorosis) when ingested in large doses for an extended period of time. 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 6, 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 to

40 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 to 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 were evident, and the subjects were asymptomatic.

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 L 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 was from eating soil, 4.2 mg/day from tea, and 1.4 mg/day 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 were 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 fluoride in human bone are generally determined by biopsy of the iliac crest bone, and are generally reported as ppm of bone ash. Average 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). 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 5 years may have been a confounding factor.

Numerous studies have examined the possible relationship between exposure to fluoride in drinking water and the risk of bone fractures. Many of these studies are ecological studies that examined communities with high level of fluoride in the water or fluoridated water (Arnala et al. 1984; Cooper et al. 1990, 1991; Danielson et al. 1992; Jacobsen et al. 1990; Kröger et al. 1994; Madans et al. 1983; Simonen and Laittenen 1985; Sowers et al. 1986); a few prospective (Cauley et al. 1995; Phipps et al. 2000) or retrospective (Kurttio et al. 1999) studies have also examined this possible association. These studies have found conflicting results, with studies finding a lower or higher incidence of hip fractures or no differences in hip fracture between humans exposed to fluoride in drinking water.

Several studies have found decreases in hip fracture incidences in communities with fluoride in the drinking water, suggesting that there may be a beneficial effect. Simonen and Laittinen (1985) examined male and female residents older than 50 years living in two cities in Finland with either trace amounts of fluoride in the water or with 1 ppm fluoride in the water. The occurrence of femoral neck fractures was lower in the men 50–80 years old and women >70 years old living in the area with fluoridated water, as compared to the low fluoride community. No difference in femoral neck fracture was observed in women 50–69 years of age. Madans et al. (1983) examined the association between fluoride in drinking water and risk of hip fractures using hip fracture data from the National Health Interview Surveys of 1973–1977 and Centers for Disease Control and Prevention (CDC) data on the percent of a population in each U.S. count served with water having a natural or adjusted fluoride content of at least 0.7 ppm in 1973. Female residents over 45 years of age living in areas with lower fluoride levels in the drinking water had 9% more hip fractures than women living in high fluoride areas; however, the difference was not statistically significant. In a prospective study of older women, Phipps et al. (2000) examined the possible relationship between living in an area with fluoridated water and the risk of fractures. Higher bone mineral density of the lumber spine and femoral neck and trochanter and lower bone mineral density of the radius were observed in women continuously living in an area with fluoridated water, as compared to residents in a non-fluoridated water area. Fewer spine, hip, and humerus fractures were also observed in this group. However, a higher incidence of wrist fractures were also observed in the continuous exposure group. Cauley et al. (1995) examined a subset of this population, and found no effect on age-adjusted axial and appendicular bone mineral density and no effect on the risk of vertebral or nonvertebral fractures.

In contrast to the results of these studies, other studies have found an increase in the incidence of hip fractures in communities with fluoride in the drinking water. Sowers et al. (1986) examined female residents living in three communities in northwest Iowa with either high fluoride (4 mg/L)-low calcium (14–19 mg/L), low fluoride (1 mg/L)-high calcium (336–390 mg/L), or low fluoride (1 mg/L)-low calcium (62–71 mg/L) levels in the drinking water. The subjects had lived in the communities for at least 5 years and did not have wrist or forearm fractures in the previous 2 years. Among women 55–80 years old living in the high fluoride community, bone mass of the radius was significantly lower and a higher incidence of hip fractures was observed, as compared to the other groups. No effect was seen in younger women (20–35 years old). A geographical correlational study of 541,985 white women hospitalized for hip fractures found a weak association (regression coefficient=0.001, 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 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 $45 years) to account for differences in the precision of the county-specific rates, a significant positive correlation between water fluoride levels and hip fracture rates was found ($r=0.41$, $p=0.009$). The correlation existed for both women ($r=0.39$, $p=0.014$) and men ($r=0.42$, $p=0.007$) (Cooper et al. 1991). Kurttio et al. (1999) studied over 144,000 residents living in rural areas of Finland from 1967–1980. When all age groups were considered together, no relationship between fluoride levels in drinking water and the risk of hip fractures was found. However, among women aged 50–64 years with higher fluoride levels, an increase in the risk of hip fractures was found. No consistent relationships were found in men or in older women. The study authors suggested that other risk factors for hip fracture may be more important than fluoride exposure in determining risk of hip fractures in older women. An 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 age-adjusted 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 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 $80 years 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.

Other studies have not found a relationship between fluoride in drinking water and hip fracture prevalence. No significant differences in the incidence or type of upper femoral fracture were observed when groups of subjects living in communities with low fluoride (<0.3 ppm), fluoridated (1.0–1.2 ppm),

or high fluoride (>1.5 ppm) drinking water (Arnala et al. 1986). An increase in the fluoride content of bone and an increase in the volumetric density of the osteod were observed in the residents in the high fluoride area, as compared to the low fluoride area. Kröger et al. (1994) found no effect on self-reported fractures among a group of older Finnish residents (mean age of approximately 53 years) living in an area with fluoridated water (1.0–1.2 mg/L), as compared to residents living in an area with low fluoride levels in the drinking water (<0.3 ppm). Increases in spine and femoral neck bone mineral density were observed in the fluoridated water group.

Because of the increased levels of bone mineral density observed in many studies of residents exposed to fluoride in drinking water, fluoride has been used as a treatment for osteoporosis. A number of studies have examined the efficacy of this treatment. 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 (0.56 mg fluoride/kg/day) (Riggs et al. 1990). Both groups received 1,500 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 4 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. In a follow-up to this study, Riggs et al. (1994) examined 50 of the women in the fluoride treatment group after an additional2 years of treatment with 34 mg fluoride/day as sodium fluoride. The lumbar spine, femoral neck, and femoral trochanter bone mineral density continued to increase and the bone mineral density of the radium continued to decrease during years 4–6 of treatment. The vertebral fracture rate decreased during years 4–6 as compared to years 0–4. The nonvertebral fracture rate also decreased during the last 2 years, but the rate for the full 6-year period was still 3 times higher than the rate in the placebo control group. In addition to extending the study for an additional 2 years, Riggs et al. (1994) also re-examined the data from the previous study. Vertebral fracture rate was influenced by several factors. Vertebral fracture rate decreased with increasing lumbar spine bone mineral density except in the cases where the higher bone mineral density was associated with a rapid rate of increase in the lumbar spine bone mineral density or a large increase from baseline serum fluoride level.

In a similar study by Kleerekoper et al. (1991), the anti-fracture efficacy of 34 mg fluoride/day as sodium fluoride was examined in 46 postmenopausal women (mean age of 66.2 years) with spinal osteoporosis.

A daily dose of 1,500 mg calcium was also administered to this group as well as a placebo control group of 38 postmenopausal women with spinal osteoporosis (mean age of 67.9 years). No significant differences in bone mineral density of the forearm, vertebral fractures, or peripheral fractures were found. A significant increase in painful lower extremity syndrome was observed in the fluoride group. It should be noted that Riggs et al. (1990, 1994) considered the lower extremity syndrome to be incomplete fractures and the incidence of incomplete fractures was added to the complete fracture incidence to calculate nonvertebral fracture incidence.

Haguenauer et al. (2000) performed a meta-analysis to examine the effects of fluoride on the treatment and prevention of post-menopausal osteoporosis using the data from the Riggs et al. (1990, 1994), Kleerekoper et al. (1991), and 10 other studies. The meta-analysis showed a significant increase in bone mineral density in the lumbar spine and hip and a decrease in bone mineral density in the forearm after 2 or 4 years of fluoride treatment. When the data from all studies was used, fluoride treatment for 2 or 4 years did not affect the relative risk of vertebral fractures. However, in studies in which the subjects were exposed to low levels of fluoride or a slow-release formulation for 4 years, a significant decrease in vertebral fracture relative risk was seen. An increase in the relative risk of nonvertebral fracture was observed when data from all studies were used; no effect was seen in studies using low levels of fluoride (<30 mg/day) or slow-release fluoride.

Evidence from animal experiments supports the association of high levels of fluoride and adverse effects on bone. The femurs of weanling male rats of a Wistar-derived strain that were given $9.5 mg 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 preeruptive 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. Turner et al. (1992) found a

biphasic relationship between bone strength and bone fluoride content in rats. At lower fluoride intakes, increased bone strength was observed; the maximum bone strength was achieved at 1,000–1,500 ppm fluoride in the bone. At fluoride concentrations higher than 1,000 ppm, bone strength started to decrease.

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.

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 33–36 or 67–71 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 71 mg/kg/day dose level. No liver effects were seen in a parallel experiment with F344/N rats at doses up to 20 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 67–71 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 67 mg/kg/day that died, the single male that died after exposure to 33 mg/kg/day, and two of the four females in the high dose group that died. No kidney histopathology was observed in surviving mice or in rats exposed to 20 mg fluoride/kg/day and higher (NTP 1990).

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 $B6C3F_1$ 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).

Endocrine Effects. Significant increases in serum thyroxine levels were observed in residents of North Gujarat, India with high levels of fluoride in the drinking water (range of 1.0–6.53 mg/L; mean of 2.70 mg/L) (Michael et al. 1996). No significant changes in serum triiodothyronine or thyroid stimulating hormone levels were found. Increases in serum epinephrine and norepinephrine levels were also observed. It is unclear if nutritional deficiencies played a contributing role to the observed endocrine 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.

Body Weight Effects. 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 $B6C3F_1$ 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 $B6C3F_1$ 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.

3.2.2.3 Immunological and Lymphoreticular 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.

3.2.2.4 Neurological Effects

Fluoride has been shown to interfere with glycolysis. (See Section 3.4 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). As discussed in the Developmental Effects section, decreases in intelligence were reported in children living in areas of China with high levels of fluoride in the drinking water, as compared to matched groups of children living in areas with low levels of fluoride in the drinking water (Li et al. 1995a; Lu et al. 2000), but these studies are weak inasmuch as they do not address important confounding factors.

There are limited animal data on the neurotoxicity of fluoride. Significant decreases in spontaneous motor activity was observed in rats exposed via gavage to 9 mg fluoride/kg/day as sodium fluoride in saline for 60 days (Paul et al. 1998). No alterations in motor coordination, as assessed with the rotarod test, were found. A decrease in blood cholinesterase activity was also observed in these rats. Another study (Mullenix et al. 1995) found alterations in spontaneous behavior in female rats exposed to 7.5 mg fluoride/kg/day as sodium fluoride in drinking water for 6 weeks beginning at 3 weeks of age and in female rats exposed to 6.0 mg fluoride/kg/day as sodium fluoride in drinking water for 6 weeks beginning at 13 weeks of age. The study authors noted that the observed effects were consistent with hyperactivity and cognitive deficits. Another study found increases in the frequency of neuronal abnormalities in the neocortex and a bilateral accumulation of β-amyloid in the thalamus of rats exposed to 0.11 mg fluoride/kg/day as sodium fluoride in drinking water (Varner et al. 1998). This study did not assess neurofunction; thus, it is difficult to assesses the toxicological significance of these effects.

3.2.2.5 Reproductive Effects

There are limited data on the potential of fluoride to induce reproductive effects in humans following oral exposure. A meta-analysis found a statistically significant association between decreasing total fertility rate and increasing fluoride levels in municipal drinking water (Freni 1994). Annual county birth data (obtained from the National Center for Health Statistics) for over 525,000 women aged 10–49 years living in areas with high fluoride levels in community drinking water were compared to a control population approximately 985,000 women) living in adjacent counties with low fluoride drinking water levels. The fluoride-exposed population lived in counties reporting a fluoride level of 3 ppm or higher in at least one system. The weighted mean fluoride concentration (county mean fluoride level weighted by the 1980 size of the population served by the water system) was 1.51 ppm (approximately 0.04 mg fluoride/kg/day), and 10.40% of the population was served by water systems with at least 3 ppm fluoride. The mean weighted mean fluoride concentration in the control population was 1.08 ppm (approximately 0.03 mg fluoride/kg/day). However, this meta-analysis relied on a comparison of two quite disparate data sets, inasmuch as the fluoridation population often did not correlate well with the population for whom health statistics was available. Furthermore, other studies have not found a similar correlation. Another study found significantly decreased serum testosterone levels in 30 men diagnosed with skeletal fluorosis and in 16 men related to men with fluorosis and living in the same house as the patient (Susheela and Jethanandani 1996). The mean drinking water fluoride levels were 3.9 ppm (approximately 0.11 mg fluoride/kg/day), 4.5 ppm (0.13 mg fluoride/kg/day), and 0.5 ppm (0.014 mg fluoride/kg/day) in the patients with skeletal fluorosis, related men, and a control group of 26 men living in areas with low endemic fluoride levels. No correlations between serum testosterone and urinary fluoride levels or serum testosterone and serum fluoride levels were found. One limitation of this study is that the control men were younger (28.7 years) than the men with skeletal fluorosis (39.6 years) and the related men (38.7 years). In addition, the groups are small and potentially confounding factors are not well addressed.

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 1,000,000 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 1,700,00 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 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 have examined the effect of fluoride on reproductive hormone levels, histology of the testes, spermatogenesis, and fertility. No alterations in mean serum levels of testosterone, luteinizing hormone, or follicle stimulating hormone were found in male rats exposed to 16 mg fluoride/kg/day as sodium fluoride in drinking water for 14 weeks or in their male offsprings exposed during gestation, lactation, and for 14 weeks after weaning (Sprando et al. 1997). In contrast, significant decreases in serum testosterone levels were observed in rats receiving daily gavage doses of 4.5 mg fluoride/kg/day as sodium fluoride for 50 days (Narayana and Chinoy 1994) and in rats exposed for 60 days to 4.5 mg fluoride/kg/day as sodium fluoride in the diet (Araibi et al. 1989).

No alterations in Sertoli cells or in the seminiferous tubules were observed in the male offspring of rats exposed during gestation, lactation, and for 14 weeks post weaning to 16 mg fluoride/kg/day as sodium fluoride in drinking water (Sprando et al. 1998). However, other studies have reported testicular damage, which appears to be directly related to the length of exposure. No histological alterations were observed in the testes of rats exposed to 21 mg fluoride/kg/day as sodium fluoride for 6 weeks (Krasowska and Wlostowski 1992). However, after 16 weeks of exposure, seminiferous tubule atrophy was observed at 7.5 mg fluoride/kg/day and higher (Krasowska and Wlostowski 1992). A decrease in the mean diameter of the seminiferous tubules was observed in rats exposed to 2.3 or 4.5 mg fluoride/kg/day as sodium fluoride in the diet for 60 days (Araibi et al. 1989); thickening of the peritubular membrane of the seminiferous tubules was also observed at 4.5 mg fluoride/kg/day. Consistent with the decreases in serum testosterone levels, significant decreases in Leydig cell diameter were observed in rats (Narayana and Chinoy 1994) and rabbits (Susheela and Kumar 1991) receiving 4.5 mg fluoride/kg/day via gavage as sodium fluoride in water for 50 days or 18–23 months, respectively.

Although some studies have not found significant alterations in spermatogenesis or sperm morphology, a number of studies have reported adverse effects. No alterations in sperm head abnormalities (Li et al. 1987a) or sperm morphology (Dunipace et al. 1989) were observed in $B6C3F_1$ mice administered sodium fluoride by gavage at doses up to 32 mg fluoride/kg/day for 5 days and killed 30 days later or in $B6C3F_1$ mice administered 23 mg fluoride/kg/day as sodium fluoride in water. In CD rats administered 4.5 mg fluoride/kg/day as sodium fluoride in the diet for 60 days, a significant decrease in the percentage of seminiferous tubules containing spermatozoa was observed (Araibi et al. 1989). Damage to the spermatid and epididymal spermatozoa were observed in rabbits administered by gavage 4.5 mg fluoride/kg/day as sodium fluoride in water for at least 18 months (Kumar and Susheela 1994, 1995), and complete cessation of spermatogenesis was observed after 29 months of exposure (Susheela and Kumar 1991). A number of studies have found significant alterations in cauda epididymal and vas deferens sperm. Decreased sperm counts, sperm motility, and sperm viability (the ratio of live to dead sperm) have been observed in rats exposed to 2.3 mg fluoride/kg/day and higher (Chinoy et al. 1992, 1995) and mice (Chinoy and Sequeira 1992) and guinea pigs (Chinoy et al. 1997) exposed to 4.5 mg fluoride/kg/day and

higher. When exposed male rats were mated with unexposed males, decreased fertility was observed at 2.3 mg fluoride/kg/day as sodium fluoride and higher (Chinoy and Sequeira 1992; Chinoy et al. 1992). The alterations in sperm and the infertility were reversible 30–60 days after termination of a 30-day exposure period (Chinoy and Sequeira 1992).

Adverse reproductive effects have also been observed in females. Nearly complete infertility was observed in female Swiss-Webster mice exposed to 19 mg fluoride/kg/day as sodium fluoride in the drinking water for 25 weeks (Messer et al. 1973). However, this effect was not repeated in another study of Webster mice exposed to 13 mg fluoride/kg/day as sodium fluoride in the diet for three generations (Tao and Suttie 1976). The study authors attributed the difference between this study and the Messer et al. (1973) study to the higher iron levels in the Tao and Suttie (1976) study, as anemia was reported by Messer et al. (1973), but not by Tao and Suttie (1976). Decreased estrus rate and increased incidence of missed pregnancies was observed in Sheltie dogs fed dog food with supplemented with rock phosphate at a level of 11.5 mg fluoride/kg/day (Shellenberg et al. 1990). However, these changes were also observed in groups provided with distilled water rather than well water. No adverse effects on reproduction were observed in a two-generation rat study in which male and female Upj TUC(SD)spf rats were fed diets containing 23 mg fluoride/kg/day (Marks et al. 1984). Additional evidence that fluoride adversely affects female reproduction includes decreased lactation in rats exposed to 21 mg fluoride/kg/day in drinking water for 88 days (Yuan et al. 1994) and decreased calving rate (Van Rensburg and de Vos 1966) and decreased milk production (Maylin and Krook 1982) in cows ingesting large amounts of fluoride.

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

3.2.2.6 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). The available human data suggest that fluoride has the potential to be developmentally toxic at doses associated with moderate to severe fluorosis. The human and animal data suggest that the developing fetus is not a sensitive target of fluoride toxicity.

Analysis of birth certificates and hospital records for over 200,000 babies born in an area with fluoridated water and over 1,000,000 babies born in a low fluoride area found no difference in the incidence of birth defects attributable to fluoride (Erickson et al. 1976). Exposure to high levels of fluoride has been described together with an increased incidence of spina bifida (Gupta et al. 1995). The occurrence of spina bifida was examined in a group of 50 children aged 5–12 years living in an area of India with high levels of fluoride in the drinking water (4.5–8.5 ppm) and manifesting either clinical (bone and joint pain,

stiffness, and rigidity), dental, or skeletal fluorosis. An age- and weight-matched group of children living in areas with lower fluoride levels (#1.5 ppm) served as a control group. Spina bifida was found in 22 (44%) of the children in the high fluoride area and in six (12%) children in the control group. This study did not examine the possible role of potentially important nutrients such as folic acid, however, and had other study design flaws.

A study by Li et al. (1995a) examined intelligence in children living in areas with high fluoride levels due to soot from coal burning. A group of 907 children aged 8–13 years were divided into four groups depending on the existence and severity of dental fluorosis; 20–24 children in each age group for each area were examined for intelligence. A significant decrease in IQ was measured in children living in the medium- (mean IQ of 79.7) and severe- (mean of 80.3) fluorosis areas, as compared to the children living in the non- (mean of 89.9) or slight- (mean of 89.7) fluorosis areas. More children with IQs of <70 and 70–79 and fewer children with IQs of 90–109 and 110–119 were found in the medium- and severe-fluorosis areas than in the non- or slight-fluorosis areas. No information on exposure levels were provided; the mean urinary fluoride levels were 1.02, 1.81, 2.01, and 2.69 mg/L in the non-, slight-, medium-, and severe-fluorosis areas, respectively. Numerous potentially confounding variables were not mentioned in this study, however, which raises questions regarding the validity of the study's findings. A study by Lu et al. (2000) also examined exposure to high fluoride levels and decreased intelligence. Sixty children aged 10–12 years living in an area with high fluoride levels in the drinking water (3.15 mg/L) were examined for intelligence. The test results were compared to a group of 58 children with similar social, education, and economic backgrounds who lived in an area with low fluoride levels in water (0.37 mg/L). A significant decrease in IQ was observed in the high fluoride area (mean IQ of 92.27) as compared to the control group (103.05). Additionally, there was a significantly higher number of children from the high exposure area with IQ scores of <70 (retarded) and 70–79 (borderline retarded) than in the control group. A significant inverse relationship between urinary fluoride levels and IQ was also found. Nevertheless, because this study relied on small groups and presented scant discussion of numerous potential confounders, the strength of its conclusions are questionable.

No alterations in the number of live births, sex ratio, fetal body weights, or the occurrence of external, visceral, or skeletal malformations were observed in the offspring of rats and rabbits exposed to doses as high as 12.26 or 13.21 mg fluoride/kg/day, respectively, as sodium fluoride in drinking water consumed on gestational days 6–15 or 6–19, respectively (Heindel et al. 1996). Similarly, no developmental effects were observed in offspring of rats drinking water containing at least 11.2 mg fluoride/kg/day as sodium fluoride on gestational days 1–20 (Collins et al. 1995). An increase in the average number of fetuses per litter with at least three skeletal variations was seen at the highest dose tested (11.4 mg fluoride/kg/day); however, this was associated with decreased maternal water and food consumption and decreased body weight gain.

Bone morphology of weanling Sprague-Dawley rats from dams that 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 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 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.

3.2.2.7 Cancer

Numerous epidemiological studies have examined the issue of a connection between fluoridated water and cancer. The weight of 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 epidemio-

logical 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 3.2.1.7.

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 mid-dose 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 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 or not 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 sex-linked response in bone tumor formation (Litvinov and Soloviev 1973; NCI 1978).

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 preneoplastic 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. Hepato-cholangiocarcinomas, 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 nontreatment-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 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 maximum tolerated dose (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 dose-related 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.

3.2.3 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). Hydrofluoric acid can also rapidly penetrate the skin and cause systemic effects, especially cardiac arrhythmias. If left untreated, death can result.

3.2.3.1 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 <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.

3.2.3.2 Systemic Effects

No studies were located regarding gastrointestinal, hematological, musculoskeletal, endocrine, or body weight 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 3-4. 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 3-5. All reliable LOAEL values for systemic effects in each species and duration category for fluoride are recorded in Table 3-6.

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 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 Effects.

Fluorine. 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.

Hydrogen Fluoride/Hydrofluoric Acid. Dermal exposure to hydrogen fluoride can cause irritation of the skin and mucous membranes. Residents exposed to hydrogen fluoride following an accidental release reported a number of skin effects including itching, burning, and rash; 43.8% of the highly exposed

residents reported severe skin problems, as compared to 5.3% of nonexposed residents (Dayal et al. 1992). Two years after the accident, severe skin problems were reported by 21.9% of the high exposure group compared to 2.7% of the control group. 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.

“Smarting" of exposed skin occurred in humans within 1 minute of exposure to hydrogen fluoride at about 122 ppm fluoride (Machle et al. 1934). This was the highest concentration that two male volunteers could tolerate for >1 minute. Repeated exposures did not reveal any habituation.

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 3.2.3.1.

Exposure to hydrogen fluoride levels approaching the LC_{50} can cause lesions of the face in rats (Haskell Laboratory 1988). Rats exposed to hydrogen fluoride (whole body) at a concentration of approximately 1,395 ppm fluoride 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 8.2 or 31 ppm fluoride as hydrogen fluoride for 6 hours/day, 6 days/week for 5 weeks (Stokinger 1949). The effect was more severe at the higher exposure level. Dogs exposed to 31 ppm fluoride for the same time periods developed inflammation of the scrotal epithelium.

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).

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 1.0%, 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 effects of fluorine exposure for each species and duration category are recorded in Table 3-4. The highest NOAEL and all reliable LOAEL values for dermal effects of hydrogen fluoride exposure for each species and duration category are recorded in Table 3-5. All reliable LOAEL values for dermal effects of fluoride exposure are recorded in Table 3-6.

Ocular Effects.

Fluorine. Volunteers (19–50 years of age) were exposed to 10 ppm fluorine for 15 minutes without discomfort or irritation of the eyes or nose (Keplinger and Suissa 1968). However, repeated exposures to 23 ppm fluorine for 3–5 minutes every 15 minutes over a 2–3-hour period caused slight eye irritation. Exposure was through a face mask that covered the eyes and nose but not the mouth. Eye irritation was also reported following exposure to 50 ppm for 3 minutes and 67 and 78 ppm for 1 minute. Exposure to 100 ppm was very irritating and became uncomfortable after a few seconds. At this concentration, the subjects reported that the eyes burned and felt as though they were covered by a film.

Eye irritation, evidence by pawing of eyes, was observed in rats exposed to 140 or 175 ppm fluorine for 30 or 5 minutes, respectively, and in dogs exposed to 68 or 93 ppm fluorine for 60 or 15 minutes, respectively. 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.

Hydrogen Fluoride/Hydrofluoric Acid. Marked conjunctival irritation 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 >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

Table 3-4. Levels of Significant Exposure to Fluorine - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
ACUTE EXPOSURE						
Systemic						
Human	1d 1min/d	Dermal	67	78 (skin irritation)		Keplinger and Suissa 1968 fluorine
		Ocular		67 (eye irritation)		
Human	1d 3min/d	Ocular	10	50 (eye irritation)		Keplinger and Suissa 1968 fluorine
Human	1d 5min/d	Ocular	10			Keplinger and Suissa 1968 fluorine
Human	1d 3-5min every 15 min for 2-3 hr	Dermal		23 (slight skin irritation)		Keplinger and Suissa 1968 fluorine
		Ocular		23 (slight eye irritation)		
Human	1d 0.5min/d	Ocular		100 (eye irritation)		Keplinger and Suissa 1968 fluorine
Rat (Osborne-Mendel)	1d 60min/d	Ocular	93			Keplinger and Suissa 1968 fluorine
Rat (Osborne-Mendel)	1d 5min/d	Ocular	88	175 (eye irritation)		Keplinger and Suissa 1968 fluorine
Rat (Osborne-Mendel)	1d 15min/d	Ocular	195			Keplinger and Suissa 1968 fluorine

Table 3-4. Levels of Significant Exposure to Fluorine - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
Rat (Osborne-Mendel)	1d 30min/d	Ocular	70	140 (eye irritation)		Keplinger and Suissa 1968 fluorine
Mouse (Swiss-Webster)	1d 5min/d	Ocular	300	467 (eye irritation)		Keplinger and Suissa 1968 fluorine
Mouse (Swiss-Webster)	1d 15min/d	Ocular	188			Keplinger and Suissa 1968 fluorine
Mouse (Swiss-Webster)	1d 30min/d	Ocular	113			Keplinger and Suissa 1968 fluorine
Dog (NS)	1d 15min/d	Ocular	39	93 (eye irritation)		Keplinger and Suissa 1968 fluorine
Dog (NS)	1d 60min/d	Ocular	38	68 (eye irritation)		Keplinger and Suissa 1968 fluorine

d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; min = minute(s); NOAEL = no-observed-adverse-effect level; ppm = parts per million.

Table 3-5. Levels of Significant Exposure to Hydrogen Fluoride - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form
ACUTE EXPOSURE								
Systemic								
Rat	1 d 60min/d	Ocular	98	120	(lacrimation)			Rosenholtz et al. 1963 hydrogen fluoride
Rat	1 d 15min/d	Ocular	292	357	(lacrimation)			Rosenholtz et al. 1963 hydrogen fluoride
Rabbit	1 d 1-4hr/d	Dermal	2% per min			2% per hr	(necrotic lesions)	Derelanko et al. 1985 hydrogen fluoride
INTERMEDIATE EXPOSURE								
Systemic								
Human	15-50 d 6 hr/d	Dermal		2.98	(stinging sensation on skin)			Largent 1960 hydrogen fluoride
		Ocular		2.98	(stinging sensation in eyes)			
Rat (NS)	5 wks 6d/wk 6hr/d	Dermal		8.2	(subcutaneous hemorrhage around the eyes and on the feet)			Stokinger 1949 hydrogen fluoride
Mouse (NS)	5 wks 6d/wk 6hr/d	Dermal		31	(subcutaneous hemorrhage around the eyes and on the feet)			Stokinger 1949 hydrogen fluoride

Table 3-5. Levels of Significant Exposure to Hydrogen Fluoride - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
Reproductive						
Dog (NS)	5 wks 6d/wk 6hr/d		8.2	31 (ulceration of the scrotum)		Stokinger 1949 hydrogen fluoride

d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; min = minute(s); NOAEL = no-observed-adverse-effect level; wk = week(s); ppm = parts per million

Table 3-6. Levels of Significant Exposure to Fluoride - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL				Reference Chemical Form
				Less Serious		Serious		
Rat (Sprague-Dawley)	1 d 24hr/d	Dermal		0.5%	(superficial necrosis, moderate edema, PMN infiltration)	1%	(extensive necrosis, marked edema, degenerating mast cells)	Essman et al. 1981 sodium fluoride

d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; PMN = polymorphnuclear leukocyte

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/day for 10 days, to hydrogen fluoride at concentrations averaging from approximately 2–4 mg/m^3 (Largent 1960). This study is limited by the inadequacy of both the experimental details and the description of effects observed.

Severe symptoms of eye problems were reported by 63.2% of Texas residents exposed to high levels of hydrogen fluoride following an accidental release (Dayal et al. 1992). The most commonly reported eye effects were redness, itching, and burning or irritation. Two years after the accident, 11.5% of the population still reported severe eye problems. In nonexposed residents, the prevalence of severe symptoms within the first month of the accident was 7.4; 2 years later, the prevalence was 4.9.

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 levels approaching the LC_{50} can cause corneal opacity in rats (Haskell Laboratory 1988), while slight ocular irritation was observed in rats exposed to levels as low as 6% of the LC_{50} (Rosenholtz et al. 1963).

McCulley et al. (1983) concluded that the greater severity of hydrofluoric acid eye injuries compared to injuries from other inorganic acids at comparable strengths probably results from the destruction of the corneal epithelium allowing substantial penetration of the fluoride ion into the corneal stroma and underlying structures.

The highest NOAEL values and all reliable LOAEL values for ocular effects of fluorine exposure for each species and duration category are recorded in Table 3-4. The highest NOAEL and all reliable LOAEL values for ocular effects of hydrogen fluoride exposure for each species and duration category are recorded in Table 3-5.

No studies were located regarding the following effects in humans and animals after dermal exposure to fluorine, hydrofluoric acid, or fluoride:

3.2.3.3 Immunological and Lymphoreticular Effects

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

3.3 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 3-7 and 3-8 present the results of more recent assays.

The *in vivo* genotoxicity of fluoride has been tested in humans and animals following inhalation, oral, or parenteral exposure. No alterations in the occurrence of sister chromatid exchange were observed in a population living in areas with high levels of fluoride (4.8 ppm) in the drinking water (Li et al. 1995b). Mixed results have been reported in animal studies examining the clastogenic potential of hydrogen fluoride and sodium fluoride. Increases in the occurrence of chromosome aberrations were found in the bone marrow cells of rats exposed by inhalation to 1.0 mg/m^3 hydrogen fluoride 6 hours/day, 6 days/week for 1 month (Voroshilin et al. 1975) and in mouse bone marrow cells following oral, intraperitoneal, or subcutaneous exposure to sodium fluoride (Pati and Bunya 1987). However, other studies did not find significant alterations in the occurrence of chromosome aberrations in mouse bone marrow cells following oral exposure (Kram et al. 1978; Martin et al. 1979). Additionally, no alterations in sister chromatid exchange occurrence were observed in mouse or Chinese hamster bone marrow cells following oral exposure (Kram et al. 1978; Li et al. 1987b). Intraperitoneal injection of sodium fluoride resulted in an increase in micronuclei in mouse bone marrow cells (Pati and Bhunya 1987); no alterations were observed in rat bone marrow cells following oral exposure (Albanese 1987). Hydrogen fluoride was negative for dominant lethal mutations following inhalation exposure to hydrogen fluoride in C57B1 mice (Voroshilin et al. 1975). A study in *Drosophila melanogaster* in which reproductive parameters were measured as an indicator of genotoxicity, significant reductions in the number of eggs per female and male fertility were observed following inhalation exposure to hydrogen fluoride (Gerdes et al. 1971b). The maximum lethality to adults of one of the two tested strains was 60%; under most of the test conditions, the lethality was #40%.

Table 3-7. Genotoxicity of Fluoride *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Form
Prokaryotic organisms:					
Salmonella typhimurium	Gene mutation	–	–	Martin et al. 1979; NTP 1990; Tong et al. 1988	NaF
Eukaryotic organisms:					
Human lymphocytes	Chromosomal aberrations	No data	+	Albanese 1987	NaF
Human lymphocytes	Chromosomal aberrations	No data	–	Thomson et al. 1985	NaF, KF
Human fibroblasts	Chromosome aberrations	No data	+	Tsutsui et al. 1984c	NaF
Human fibroblasts	Chromosomal aberrations	No data	–	Tsutsui et al. 1995	NaF
Human diploid IMR-90 cells	Chromosomal aberrations	No data	+	Oguro et al. 1995	NaF
Human lymphocytes	Sister chromatid exchange	No data	–	Thomson et al. 1985; Tong et al. 1988	NaF
Human lymphocytes	Sister chromatid exchange	No data	–	Thomson et al. 1985	KF
Human lymphoblasts	Gene mutation	+	+	Caspary et al. 1988	NaF
Human fibroblasts	Unscheduled DNA synthesis	No data	+	Tsutsui et al. 1984c	NaF
Syrian hamster embryo cell	Chromosomal aberrations	No data	+	Tsutsui et al. 1984b	NaF
Syrian hamster embryo cell	Sister chromatid exchange	No data	+	Tsutsui et al. 1984b	NaF
Syrian hamster embryo cell	Unscheduled DNA synthesis	No data	+	Tsutsui et al. 1984b	NaF
Chinese hamster ovary cells	Sister chromatid exchange	No data	–	Li et al. 1987b	NaF
Chinese hamster ovary cells	Sister chromatid exchange	No data	–	Tong et al. 1988	NaF
Chinese hamster ovary cells	Sister chromatid exchange	+	+	NTP 1990	NaF
Chinese hamster ovary cells	Chromosomal aberrations	+	+	Aardema et al. 1989	NaF
Chinese hamster ovary cells	Chromosomal aberrations	–	+	NTP 1990	NaF
Chinese hamster V79 cells	Gene mutation	No data	–	SlameÁová et al. 1992	NaF
Mouse lymphoma cells	Gene mutation	No data	(+)	Cole et al. 1986	NaF

Table 3-7. Genotoxicity of Fluoride *In Vitro (continued)*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Form
Mouse lymphoma cells	Gene mutation	+	+	Caspary et al. 1987, 1988; NTP 1990	NaF
Mouse lymphoma cells	Gene mutation	+	+	Caspary et al. 1987	KF
Rat hepatocytes	DNA repair	No data	–	Tong et al. 1988	NaF
Rat liver epithelium cells	Gene mutation	No data	–	Tong et al. 1988	NaF
Rat vertebral body derived cells	Chromosome aberrations	No data	+	Mihashi and Tsutsui 1996	NaF
Rat bone marrow cells	Chromosome aberrations	No data	(+)	Khalil 1995	NaF, KF
Rat bone marrow cells	Sister chromatid exchange	No data	–	Khalil and Da'dara 1994	NaF, KF

- = negative result; + = positive result; (+) = weakly positive result; DNA = deoxyribonucleic acid; KF = potassium fluoride; NaF = sodium fluoride

Table 3-8. Genotoxicity of Fluoride *In Vivo*

Species (test system)	End point	Results	Reference	Form
Human lymphocytes (oral exposure)	Sister chromatid exchange	–	Li et al. 1995b	NR
Rat bone marrow cells (oral exposure)	Micronuclei	–	Albanese 1987	NaF
Rat bone marrow	Chromosome aberrations	+	Voroshilin et al. 1975	HF
Rat testis cells (oral exposure)	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 cells (oral exposure)	Chromosome aberrations	–	Martin et al. 1979	NaF
Mouse bone marrow cells (oral, intraperitoneal, or subcutaneous exposure)	Chromosome aberrations	+	Pati and Bhunya 1987	NaF
Mouse bone marrow cells (intraperitoneal exposure)	Micronuclei	+	Pati and Bhunya 1987	NaF
Mouse bone marrow cells (oral exposure)	Chromosome aberrations	–	Kram et al. 1978	NaF
Mouse bone marrow cells (oral exposure)	Sister chromatid exchange	–	Kram et al. 1978	NaF
Chinese hamster bone marrow cells (oral exposure)	Sister chromatid exchange	–	Li et al. 1987b	NaF

– = negative result; + = positive result; DNA = deoxyribonucleic acid; HF = hydrogen fluoride; NaF = sodium fluoride; NR = not reported

3.4 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.

3.4.1 Absorption

3.4.1.1 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 to 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 <40 minutes.

Hydrogen Fluoride and Fluoride Dusts. The absorption in humans of inhaled hydrogen fluoride and fluoride dusts was demonstrated by Collings et 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 3.2.1 and 3.2.3.

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.

3.4.1.2 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 hydrogen fluoride molecule by passive absorption (Whitford and Pashley 1984). Since the neutral undissociated 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-absorbed species appeared in the feces. As described below in Section 3.4.4.2, 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 1,320 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 3.11.

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 radio-labeled 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.

3.4.1.3 Dermal 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.

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.

3.4.2 Distribution

3.4.2.1 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-dependent increase 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 postexposure (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).

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.

3.4.2.2 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 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 1–4 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 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.

In a short-term distribution kinetic study in rats, Whitford et al. (1979a) found that soft tissues do not strongly bind fluoride, and that most of these tissues are kinetically homogeneous with plasma. Furthermore, the blood brain barrier is effective in preventing fluoride migration into the central nervous system; brain tissue fluoride concentrations did not exceed 10% of plasma concentrations following intravenous administration. It has also been shown that fecal excretion of fluoride can exceed dietary intake when the diet is supplemented with calcium (Whitford 1994); under these conditions, fluoride balance (the difference between total intake and total excretion) is negative.

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.

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.

3.4.2.3 Dermal Exposure

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

3.4.2.4 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 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.

3.4.3 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 hydroxyfluorapatite. Once absorbed, a portion of the fluoride is deposited in the skeleton, and the remainder is excreted in the urine, feces, sweat, and saliva within 24 hours (Dinman et al. 1976a, 1976b; McClure et al. 1945). Thus, skeletal sequestration and renal excretion are the two 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 decreased 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) (Guminska and Sterkowicz 1975; Najjar 1948; Peters et al. 1964; Slater and Bonner 1952). Although much is known about enzyme inhibition by fluoride, the human health significance remains to be determined. The studies on enzymatic inhibition by fluoride were *in vitro* studies and used fluoride concentrations that were significantly higher than concentrations that would be normally found in human tissues.

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.

3.4.4 Elimination and Excretion

3.4.4.1 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 3.3.1.

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.

3.4.4.2 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. 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 humans, 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, which indicated the excretion of fluoride that was mobilized from bone (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 <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 preexposure rate of about 0.1 mg/hour. In persons not occupationally exposed to fluoride and not using water containing added fluoride, fecal elimination is usually <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 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 mg/kg/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 was 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 hydrogen fluoride (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 1–6-years (Gdalia 1958). These studies indicate that children store more fluoride than adults do, due to high uptake in developing bones.

Sweat is a route of fluoride elimination. In a 1945 study, subjects who ingested 3.7 mg fluoride in 1 day, of which 3 mg was 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.

3.4.4.3 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.

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of

potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste

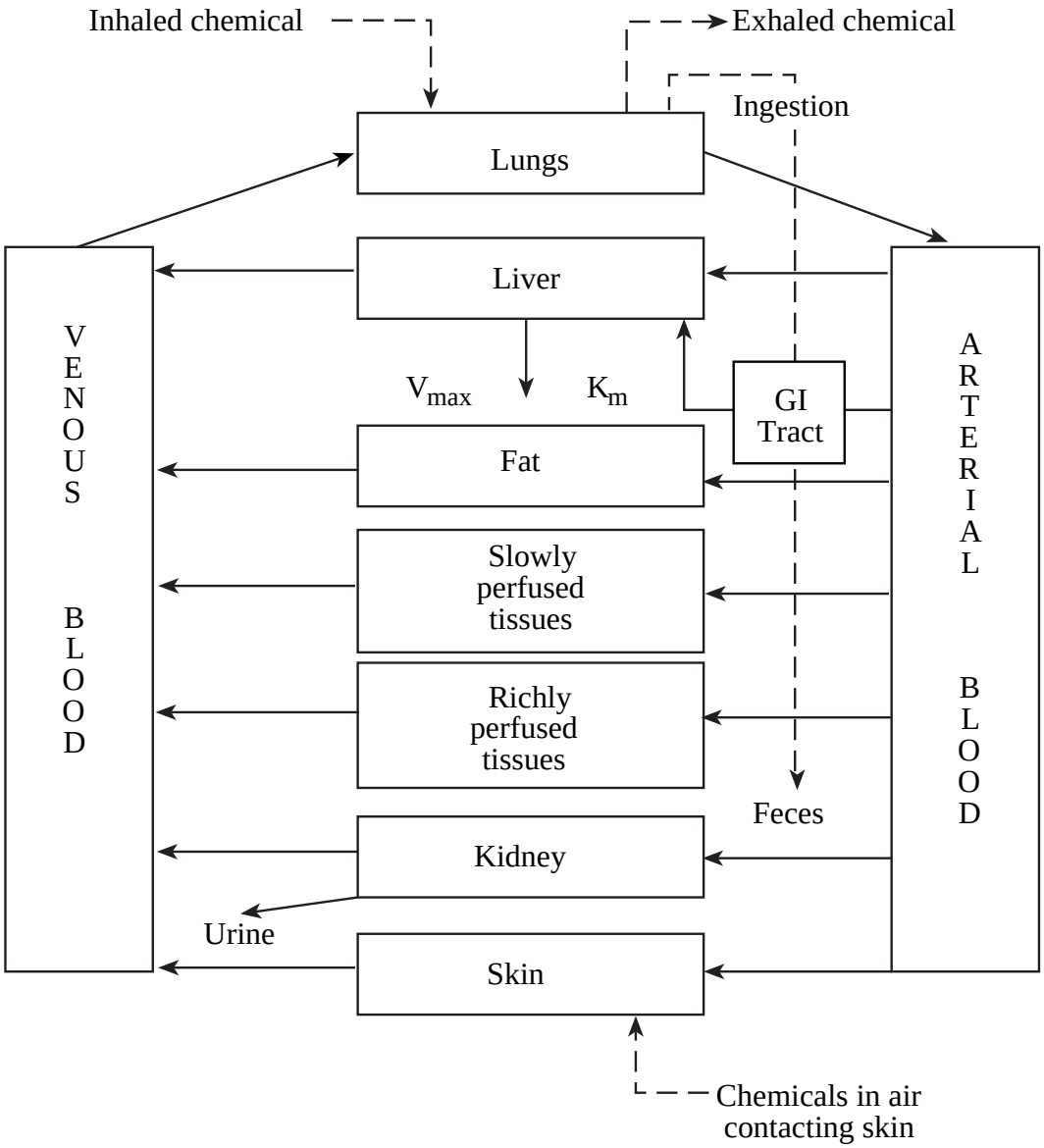
sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-4 shows a conceptualized representation of a PBPK model.

Only one published PBPK model has been identified (Rao et al. 1995); it differs from published compartmental models for fluoride kinetics (Charkes et al. 1978, 1979; Hall et al. 1977) in that the earlier models were data-based and useful only to simulate short-term fluoride kinetics. Because the fluoride ion is characterized by its long residence time in the body, health effects based on long-term fluoride exposure are of concern. In contrast to the earlier models, the Rao et al. PBPK model is amenable to extrapolation across species, routes, and doses, thereby offering an advantage in quantitative risk assessment for fluoride exposure.

In order to assess the complex relationship between extended fluoride exposure, target tissue (bone) dose, and tissue response, a sex-specific PBPK model has been developed to describe the absorption, distribution, and elimination of fluorides in rats and humans (Rao et al. 1995). The PBPK model incorporates age and body weight dependence of the physiological processes that control the uptake of fluoride by bone and the elimination of fluoride by the kidneys. Six compartments (lung, liver, kidney, bone, and slowly- and rapidly-perfused compartments) make up the model. The bone compartment includes two subcompartments: a small, flow-limited, rapidly exchangeable surface bone compartment, and a bulk, virtually nonexchangeable inner bone compartment. The inner bone compartment contains nearly all of the whole body content of fluoride, which, in the longer time frame, may be mobilized through the process of bone modeling and remodeling. This model has been validated by comparing predictions with experimental data gathered in rats and humans after drinking water and dietary ingestion of fluoride.

The PBPK model permits the analysis of the combined effect of ingesting and inhaling fluorides on the target organ, bone. It takes into account the effects of age and growth; in the human model, for instance, the bone and renal clearance rates accounted for 90 and 10%, respectively, during the growth period, compared to about 50% each in adulthood. Estimates of fluoride concentrations in bone are calculated and related to chronic fluoride toxicity. The model incorporates nonlinear binding rates of fluoride to bone, which has been described at high plasma concentrations. The model is thus useful for predicting some of the long-term metabolic features and tissue concentrations of fluoride that may be of value in understanding positive or negative effects of fluoride on human health. In addition, the PBPK model provides a basis for cross-species extrapolation of the effective fluoride dose at the target tissue (bone) in the assessment of risk from different exposure conditions.

Figure 3-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

3.5 MECHANISMS OF ACTION

The following section on the mechanism of fluoride prevention of dental caries is excerpted from the Centers for Disease Control and Prevention's report entitled "Recommendations for using fluoride to prevent and control dental caries in the United States" (DHHS 2001b):

> Dental caries is an infectious, transmissible disease in which bacterial by-products (i.e., acids) dissolve the hard surfaces of teeth. Unchecked, the bacteria can penetrate the dissolved surface, attack the underlying dentin, and reach the soft pulp tissue. Dental caries can result in loss of tooth structure, pain, and tooth loss and can progress to acute systemic infection.
>
> Cariogenic bacteria (i.e., bacteria that cause dental caries) reside in dental plaque, a sticky organic matrix of bacteria, food debris, dead mucosal cells, and salivary components that adheres to tooth enamel. Plaque also contains minerals, primarily calcium and phosphorus, as well as proteins, polysaccharides, carbohydrates, and lipids. Cariogenic bacteria colonize on tooth surfaces and produce polysaccharides that enhance adherence of the plaque to enamel. Left undisturbed, plaque will grow and harbor increasing numbers of cariogenic bacteria. An initial step in the formation of a carious lesion takes place when cariogenic bacteria in dental plaque metabolize a substrate from the diet (e.g., sugars and other fermentable carbohydrates) and the acid produced as a metabolic by-product demineralizes (i.e., begins to dissolve) the adjacent enamel crystal surface. Demineralization involves the loss of calcium, phosphate, and carbonate. These minerals can be captured by surrounding plaque and be available for reuptake by the enamel surface. Fluoride, when present in the mouth, is also retained and concentrated in plaque.
>
> Fluoride works to control early dental caries in several ways. Fluoride concentrated in plaque and saliva inhibits the demineralization of sound enamel and enhances the remineralization (i.e., recovery) of demineralized enamel (Featherstone 1999; Koulourides 1990). As cariogenic bacteria metabolize carbohydrates and produce acid, fluoride is released from dental plaque in response to lowered pH at the tooth-plaque interface (Tatevossian 1990). The released fluoride and the fluoride present in saliva are then taken up, along with calcium and phosphate, by de-mineralized enamel to establish an improved enamel crystal structure. This improved structure is more acid resistant and contains more fluoride and less carbonate (Chow 1990; Ericsson 1977; Featherstone 1999; Kidd et al. 1980; Thylstrup 1990; Thylstrup et al. 1979). Fluoride is more readily taken up by demineralized enamel than by sound enamel (White and Nancollas 1990). Cycles of demineralization and remineralization continue throughout the lifetime of the tooth.
>
> Fluoride also inhibits dental caries by affecting the activity of cariogenic bacteria. As fluoride concentrates in dental plaque, it inhibits the process by which cariogenic bacteria metabolize carbohydrates to produce acid and affects bacterial production of adhesive polysaccharides (Hamilton 1990). In laboratory studies, when a low concentration of fluoride is constantly present, one type of cariogenic bacteria, Streptococcus

mutans, produces less acid (Bowden 1990; Bowden et al. 1982; Marquis 1990; Rosen et al. 1978). Whether this reduced acid production reduces the cariogenicity of these bacteria in humans is unclear (Van Loveren 1990).

Saliva is a major carrier of topical fluoride. The concentration of fluoride in ductal saliva, as it is secreted from salivary glands, is low --- approximately 0.016 parts per million (ppm) in areas where drinking water is fluoridated and 0.006 ppm in nonfluoridated areas (Oliveby et al. 1990). This concentration of fluoride is not likely to affect cariogenic activity. However, drinking fluoridated water, brushing with fluoride toothpaste, or using other fluoride dental products can raise the concentration of fluoride in saliva present in the mouth 100- to 1,000-fold. The concentration returns to previous levels within 1--2 hours but, during this time, saliva serves as an important source of fluoride for concentration in plaque and for tooth remineralization (Rölla and Ekstrand 1996).

Applying fluoride gel or other products containing a high concentration of fluoride to the teeth leaves a temporary layer of calcium fluoride-like material on the enamel surface. The fluoride in this material is released when the pH drops in the mouth in response to acid production and is available to remineralize enamel (LeGeros 1990).

In the earliest days of fluoride research, investigators hypothesized that fluoride affects enamel and inhibits dental caries only when incorporated into developing dental enamel (i.e., preeruptively, before the tooth erupts into the mouth) (Dean et al. 1935; McClure and Likins 1951). Evidence supports this hypothesis (Groeneveld et al. 1990; Marthaler 1979; Murray 1993), but distinguishing a true preeruptive effect after teeth erupt into a mouth where topical fluoride exposure occurs regularly is difficult. However, a high fluoride concentration in sound enamel cannot alone explain the marked reduction in dental caries that fluoride produces (Levine 1976; Margolis and Moreno 1990). The prevalence of dental caries in a population is not inversely related to the concentration of fluoride in enamel (Clarkson et al. 1996), and a higher concentration of enamel fluoride is not necessarily more efficacious in preventing dental caries (Arends and Christoffersen 1990).

The laboratory and epidemiologic research that has led to the better understanding of how fluoride prevents dental caries indicates that fluoride's predominant effect is posteruptive and topical and that the effect depends on fluoride being in the right amount in the right place at the right time. Fluoride works primarily after teeth have erupted, especially when small amounts are maintained constantly in the mouth, specifically in dental plaque and saliva (Clarkson et al. 1996). Thus, adults also benefit from fluoride, rather than only children, as was previously assumed.

A number of mechanisms are involved in the toxicity of fluoride to bone. Fluoride ions are incorporated into bone by substituting for hydroxyl groups in the carbonate-apatite structure to produce hydroxyfluorapatite, thus altering the mineral structure of the bone (Chachra et al. 1999). Unlike hydroxyl ions, fluoride ions reside in the

plane of the calcium ions, resulting in a structure that is electrostatically more stable and structurally more compact (Grynpas 1990). Following administration of fluoride, there is a shift in the mineralization profile towards higher densities and increased hardness (Chachra et al. 1999). However, the structure of the bone (cortical thickness and the trabecular architecture of the femoral head) was largely unchanged in rabbits by fluoride administration. Chachra et al. (1999) suggest that the shift in mineralization could be due to either hypermineralization of older (denser) fractions or to a greater packing density of the hydroxyapatite crystals. Although fluoride administration is associated with an increase in bone mass, *in vivo* and *in vitro* animal studies have found a negative association between fluoride-induced new bone mass and bone strength, suggesting that the quality of the new bone was impaired by the fluoride (Silva and Ulrich 2000; Turner et al. 1997). Because bone strength is thought to derive mainly from the interface between the collagen and the mineral (Catanese and Keavney 1996), alteration in mineralization probably affects strength. The wider crystals, which are formed after fluoride exposure, are presumably not associated with collagen fibrils and thus, do not contribute to mechanical strength. Turner et al. (1997) found that the crystal width was inversely correlated with bending strength of the femur. Thus, although there is an increase in hardness and bone mass and unaltered structure, the mechanical strength of bone is decreased (Cachra et al. 1999).

In addition to the physicochemical effect of fluoride on the bone, at high doses, fluoride can be mitogenic to osteoblasts (Farley et al. 1990; Gruber and Baylink 1991) and inhibitory to osteoclasts. The osteoblasts are still active, although there are fewer plump, cuboidal, highly secretory osteoblasts; whereas fluoride is mitogenic to osteoblastic precursors (Bonjour et al. 1993), it is toxic to individual osteoblasts at the same concentration (Chachra et al. 1999). The effect of fluoride on osteoclasts is not well understood; it appears that fluoride decreases the amount of bone resorbed by osteoclasts (Chachra et al. 1999).

Studies in humans and animals suggest that the effect of fluoride on bone strength is biphasic. In rats administered 1–128 ppm fluoride as sodium fluoride in drinking water for 16 weeks, both increases and decreases in bone strength were found; the maximum femoral bone strength occurred at 16 ppm (Turner et al. 1992). A biphasic relationship between femoral bone strength and bone fluoride content was found. Bone strength increased 18% as the bone fluoride content increased from 100 to 1,216 ppm, and decreased by 31% as the bone fluoride levels increased from 1,216 to 10,000 ppm. It should be noted that the bone fluoride levels in this study, as well as other studies discussed in this section, resulted from high doses of fluoride. Arnala et al. (1986) measured fluoride levels in iliac crest biopsies taken from 18–25 subjects with hip fractures living in areas with low fluoride (<0.3 ppm), high fluoride (>1.5 ppm), or with fluoridated (1.0–1.2 ppm) water. The average fluoride levels in the bone were 450, 3,720, and 1,590 ppm, respectively.

The biphasic nature of bone effects is supported by data from clinical trials in women with postmenopausal osteoporosis (Haguenauer et al. 2000). The meta-analyses of 12 studies found a significant increase in the relative risk of nonvertebral fractures in subjects ingesting high doses of fluoride (>30 mg/day); in subjects administered low fluoride doses or slow-release formulations, there was no effect on nonvertebral fractures.

Similarly, there was no effect on vertebral fracture risk in high fluoride dose subjects, but a decrease in this risk in subjects administered low fluoride doses or slow-release formulations was found.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Colborn and Thomas (1992) and again by Colborn (1993), was also used in 1996 when Congress mandated the Environmental Protection Agency (EPA) to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), which in 1998 completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

Although there is no evidence that fluoride is an endocrine disruptor, there are some data to suggest that fluoride does adversely affect some endocrine glands. An increase in serum thyronine levels, in the absence of changes in triiodothyronine and thyroid stimulating hormone levels, were observed in individuals living in areas of India with high fluoride levels in the drinking water (Michael et al. 1996). In contrast, a decrease in thyroxine levels was observed in rats exposed to fluoride in drinking water for 2 months (Bobek et al. 1976). Significant decreases in serum testosterone have been observed in rats exposed to sodium fluoride for 50–60 days (Araibi et al. 1989; Narayana and Chinoy 1994).

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of

body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

A number of studies have examined the effects of fluoride in children. Due to its cariostatic properties, several agencies (for example, NRC 1999; WHO 1973) advocate fluoride supplementation in children. However, there is a delicate balance between prevention of dental caries and the occurrence of dental fluorosis. Dental fluorosis is characterized by increased porosity of the tooth enamel that may become stained and pitted. In milder forms of dental fluorosis, opaque striations can run horizontally across the surface of the teeth, sometimes becoming confluent giving rise to white opaque patches. The occurrence of mild dental fluorosis is approximately 10–20% in children living in cities with water containing 0.7–1.2 ppm fluoride, which is the recommended range for water fluoride concentration for the prevention of dental caries (DHHS 1991; Heifetz et al. 1988); it is likely that the children were also exposed to other sources of fluoride from manufactured beverages and food. Mild dental fluorosis is considered to be a cosmetic effect and does not appear to affect tooth function. Because dental fluorosis is a response to fluoride exposure during the preeruptive maturation of teeth, only children are susceptible to this effect.

Approximately 99% of the body's fluoride is found in calcified tissues. Chronic exposure to high levels of fluoride results in bone thickening and exostoses (skeletal fluorosis). Because of the dynamic nature of growing bone, it is likely that children will deposit more fluoride in bone than adults consuming an equal amount of fluoride. However, it is not known if children would be more susceptible to skeletal fluorosis than adults.

Developmental effects have been observed in humans and animals exposed to fluoride. In humans, an increased occurrence of spina bifida was found in children living in areas of India with high levels of fluoride in the drinking water (Gupta et al. 1995). However, this study had several deficiencies. For example, it did not address the nutritional status of the mothers. This is important because folic acid deficiency has been implicated in the etiology of spina bifida (Hernandez-Diaz et al. 2001; Honein et al. 2000). In addition, the paper did not provide the fluoride levels in the blood of the mothers, nor radiographic evidence of spina bifida. Studies by Li et al. (1995a) and Lu et al. (2000) concluded that there were decreases in IQ scores in children living in areas of China with high fluoride levels due to soot from coal burning, but it is not known if other contaminants in the soot also contributed to this effect, and the adequacy of the design of these studies is highly questionable. In the Gupta et al. (1995) and Li et al. (1995a) studies, the observed effects occurred in children with dental and/or skeletal fluorosis. In general, developmental effects have not been observed in rat or rabbit oral exposure studies (Collins et al. 1995; Heindel et al. 1996). However, the animal studies did not assess potential neurodevelopmental effects. The available human and animal data suggest that the developing fetus is not a sensitive target of fluoride toxicity.

Fluoride retention appears to be higher in children than adults. Approximately 80% of an absorbed dose of fluoride is retained in young children compared to 50% in adults (Ekstrand et al. 1994a, 1994b). This is supported by the finding that renal fluoride clearance rate and urinary fluoride concentration are markedly lower

in children than adults (Gdalia 1958; Spak et al. 1985). This difference in fluoride retention is due to high fluoride uptake in developing bones. Data on other potential age-related differences in the toxicokinetic properties of fluoride were not located. Only a small proportion of ingested fluoride is transferred from mother to child through breast milk (Ekstrand et al. 1984b; Spak et al. 1982).

Most of the available information on biomarkers, interactions, and methods for reducing toxic effects is from adults and mature animals; no child-specific information was identified, with the exception of biomarker data. It is likely that the available information in adults will also be applicable to children.

3.8 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).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. 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 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 fluorine, hydrogen fluoride, and fluorides are discussed in Section 3.8.1.

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 not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by fluorine, hydrogen fluoride, and fluorides are discussed in Section 3.8.2.

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, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10 "Populations That Are Unusually Susceptible".

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Fluorine, Hydrogen Fluoride, and Fluorides

There is extensive literature regarding fluoride levels in biological tissues such as urine, teeth, bone, and fingernails 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 #1 mg/L when the water supply contains #1 ppm 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 3.2.1.2.

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 (Whitford et al. 1999b), and tooth enamel (McClure and Likins 1951). When using saliva as a biomarker, ductal saliva should be obtained under fasting conditions when measuring body burden (long-term intake) of fluoride (Whitford et al. 1999b). Care must be taken when using plasma fluoride as an indicator of exposure; dosage,

time, and duration must be taken into account (Whitford and Williams 1986). The normal plasma fluoride level is related to daily intake of fluoride (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, postshift urinary levels differ from preshift 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 re-enter 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 (Baud et al. 1978; Boivin et al. 1988). However, this requires a bone biopsy, so bone fluoride levels are most frequently measured after clinical signs appear. As described in Section 3.2.2.2, 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.

Studies of Hungarian (Schamschula et al. 1985) or Brazilian (Whitford et al. 1999a) children have demonstrated a direct relationship between fluoride concentrations in drinking water and fluoride levels in fingernail clippings, suggesting that fluoride in fingernails may be a reliable biomarker of exposure.

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

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 skeletal 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. Only children are 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). It should be noted that dental fluorosis develops during tooth formation, a process that occurs over several years. 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, 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.

Alteration in bone density or derangement of trabecular structure can be detected by radiographs, and can indicate fluoride-induced changes. 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. Exostoses, 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 3.2.2.2, 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.

3.9 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 3.11. No reliable data on interactions that exacerbate negative effects of fluoride were located.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to fluorine, hydrogen fluoride, or fluoride than will most persons exposed to the same level of fluorine, hydrogen fluoride, or fluoride in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of fluorine, hydrogen fluoride, or fluoride, or compromised function of organs affected by fluorine, hydrogen fluoride, or fluoride. Populations who are at greater risk due to their unusually high exposure to fluorine, hydrogen fluoride, or fluoride are discussed in Section 6.7, Populations With Potentially High Exposures.

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. However, these effects would not be expected at typical exposure levels (1 ppm fluoride).

A study by Spencer et al. (1980a) provides suggestive evidence that individuals with chronic renal failure may have increased fluoride retention. In eight patients with chronic renal failure on a low protein, low calcium, and low phosphorus diet, 65% of ingested fluoride was retained, compared to 20% in normal subjects. It is not known if the normal subjects were given the same diet; if the normal subjects were not on the same restrictive diet, then diet may have contributed to the observed difference in fluoride retention. The higher retention of fluoride was primarily due to the significantly decreased fluoride excretion in the renal patients. Urinary fluoride excretion was directly correlated with creatinine clearance. In mild renal failure (creatinine clearance of 50 mL/minute), urinary fluoride levels were in the low normal range (2.6 mg/day) compared to urinary fluoride levels of 2.7–4.3 mg/day with normal creatinine clearance (90–120 mL/minute). Although these data provide suggestive evidence that individuals with chronic renal failure may be unusually susceptible to the toxicity of fluoride, these data are not conclusive and it is not known if diet influenced fluoride retention and studies examining the potential toxicity of fluoride in chronic renal failure patients were not identified.

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. Calcium deficiency was found to increase bone fluoride levels in a 2-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.

Although the possible relationship between fluoride in drinking water and the risk of fractures has been extensively investigated, the data are inconclusive with studies finding beneficial (Madans et al. 1983; Phipps et al. 2000; Simonen and Laittenen 1985) and deleterious (Cooper et al. 1990, 1991; Danielson et al. 1992; Jacobsen et al. 1990; Kurttio et al. 1999; Sowers et al. 1986) effects or no effects (Arnala et al. 1984; Cauley et al. 1995; Kröger et al. 1994). Clinical trials of postmenopausal women with osteoporosis have found an increased risk of nonvertebral fractures following exposure to high doses of fluoride (34 mg/day) (Haguenauer et al. 2000; Riggs et al. 1990, 1994); no effect on vertebral fracture risk was found.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to fluorine, hydrogen fluoride, and fluorides. 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, and fluorides. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to fluorine, hydrogen fluoride, and fluorides:

Bronstein AC, Currance PL. 1988. Emergency care for hazardous materials exposure. St. Louis, MO: The C.V. Mosby Company, 113-114, 165-166.

Ellenhorn MJ, Barceloux DG. 1988. Medical toxicology: Diagnosis and treatment of human poisoning. New York, NY: Elsevier Science Publishing Company, Inc. 76, 83, 531-536, 873-874, 924-929.

Goldfrank LR, Flomenvaum NE, Lewin NA, et al., eds. 1990. Goldfrank's toxicologic emergencies. Norwalk, CT: Appleton & Lange, 220-221, 745, 769-779.

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.

3.11.1 Reducing Peak Absorption Following Exposure

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).

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 precipitation (Borak et al. 1991; Browne 1974; Goldfrank et al. 1990).

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).

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.

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).

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.

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.

3.11.2 Reducing Body Burden

Hydrogen Fluoride/Hydrofluoric Acid. Hydrogen fluoride burns are characterized by intense pain and progressive tissue destruction. The damage associated with this burn occurs in two stages. The first stage is immediate tissue damage caused by a high concentration of hydrogen ions and the second is liquefaction necrosis that is caused by free fluoride ions (Seyb et al. 1995). There are a number of recommended forms of therapy; these therapies have the common goal of binding the fluoride ion and/or altering its reactivity with tissues (Dunn et al. 1992). Recommended forms of therapy include topical treatments with calcium gluconate paste, magnesium oxide paste, and iced solutions of quaternary ammonium compounds, alcohol, or magnesium sulfate and intradermal injections of either magnesium sulfate or calcium gluconate, or intraarterial injection of calcium gluconate (Dunn et al. 1992; Seyb et al. 1995). 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).

Several studies have compared different therapies in an attempt to identify the most effective treatment. 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. Seyb et al. (1995) found that subcutaneous injections of 10% calcium gluconate and magnesium sulfate solution and topically applied calcium gluconate mixed with dimethyl sulfoxide significantly reduced the damage caused by hydrogen fluoride exposure in rats exposed to 70% hydrogen fluoride for 60 seconds followed by continuously rinsing with tap water for 5 minutes. Treatment with topically applied dimethyl sulfoxide only or calcium gluconate only did not affect the degree of tissue damage. In contrast, Dunn et al. (1992) found that injection of 10% calcium gluconate was the least effective therapy in pigs following topical application of 38% hydrogen fluoride. The most effective treatments were soaking in calcium acetate or iced Zephiran (benzalkonium chloride), or injection of 5% calcium gluconate.

Fluoride. A study by Khandare et al. (2000) provides suggestive evidence that co-administration of fluoride and tamarind results in increased urinary excretion of fluoride and decreased bone fluoride levels in dogs.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Hydrogen Fluoride/Hydrofluoric Acid. The primary focus of research on reducing the toxic effects following dermal exposure to hydrogen fluoride or hydrofluoric acid is on methods for reducing absorption and decreasing the amount of fluoride ions. The tissue damage associated with hydrogen fluoride exposure is believed to be caused by the binding of fluoride ions with tissue calcium and magnesium cations to form insoluble salts, which are believed to interfere with cellular metabolism, inducing cellular death and necrosis. Thus, the most effective method for interfering with the mechanism of action is removal of the fluoride ions; these methods are discussed in Section 3.11.2.

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

Chinoy and associates have examined the effectiveness of calcium, ascorbic acid, vitamin E, and vitamin D in reversing the reproductive effects associated with oral exposure to sodium fluoride. Administration of ascorbic acid and/or calcium and cessation of sodium fluoride exposure enhanced the recovery of sperm function and morphology and testicular damage, as compared to no treatment, in rats (Chinoy et al. 1993), mice (Chinoy and

Sharma 2000), and rabbits (Chinoy et al. 1991). The combined administration of ascorbic acid and calcium was the most effective treatment. Postexposure administration of vitamins E and/or D was also effective in the recovery of sodium-fluoride induced testicular effects in mice (Chinoy and Sharma 1996). Likewise, posttreatment administration of ascorbic acid and/or calcium and vitamins E and/or D also aided in the recovery of ovarian effects in mice (Chinoy and Patel 1998; Chinoy et al. 1994). It is believed that the antioxidant properties of ascorbic acid and vitamin E aid in the recovery of fluoride damage. Vitamin D promotes the intestinal absorption of calcium and phosphorus, thus maintaining the optimal blood concentration of these elements (Chinoy and Patel 1998). The calcium may act by forming insoluble complexes with fluoride (Chinoy and Patel 1998; Chinoy et al. 1994).

3.12 ADEQUACY OF THE DATABASE

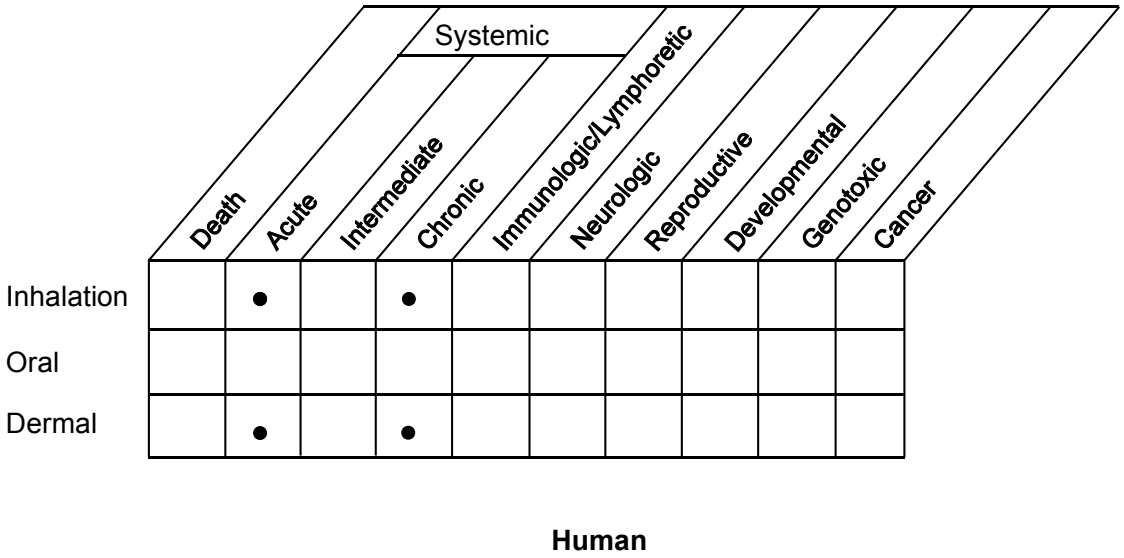
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of fluorine, hydrogen fluoride, or fluoride is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (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 fluorine, hydrogen fluoride, or fluoride.

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 the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

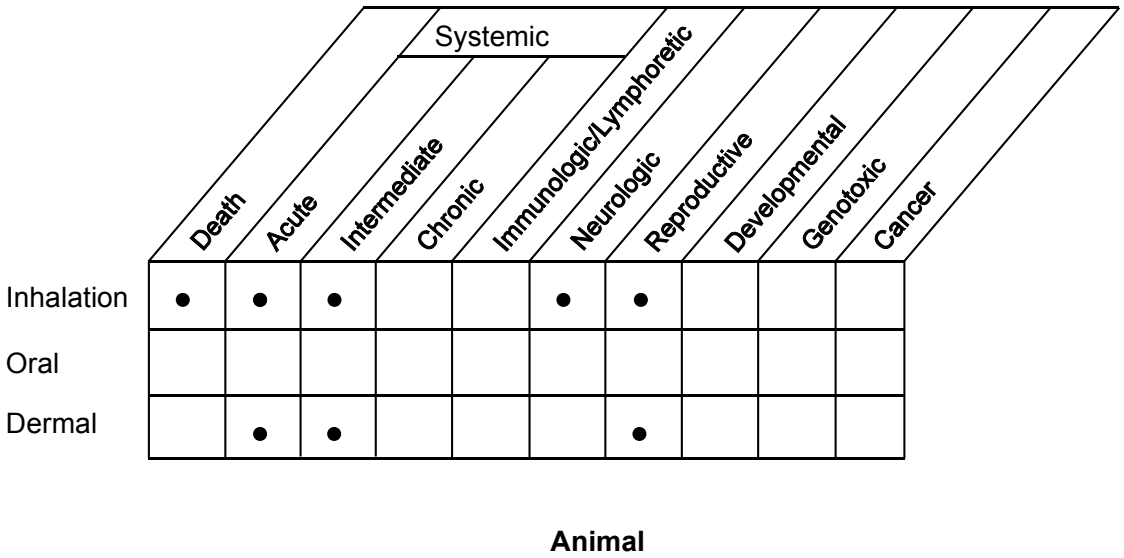
3.12.1 Existing Information on Health Effects of Fluorine, Hydrogen Fluoride, and Fluorides

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to fluorine, hydrogen fluoride, or fluoride are summarized in Figures 3-5, 3-6, and 3-7, respectively. The purpose of these figures are to illustrate the existing information concerning the health effects of fluorine, hydrogen fluoride, or fluoride. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to

Figure 3-5. Existing Information on Health Effects of Fluorine



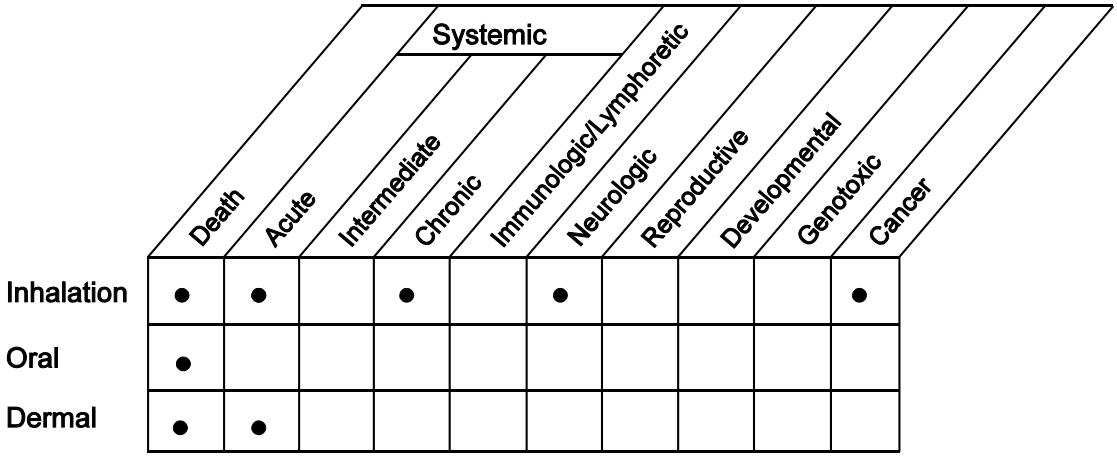
Human



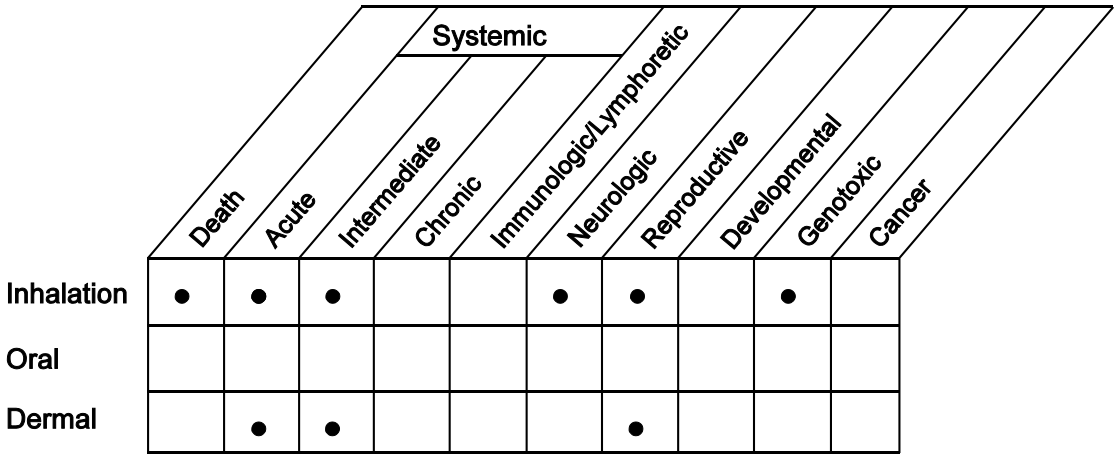
Animal

- Existing Studies

Figure 3-6. Existing Information on Health Effects of Hydrogen Fluoride/ Hydrofluoric Acid



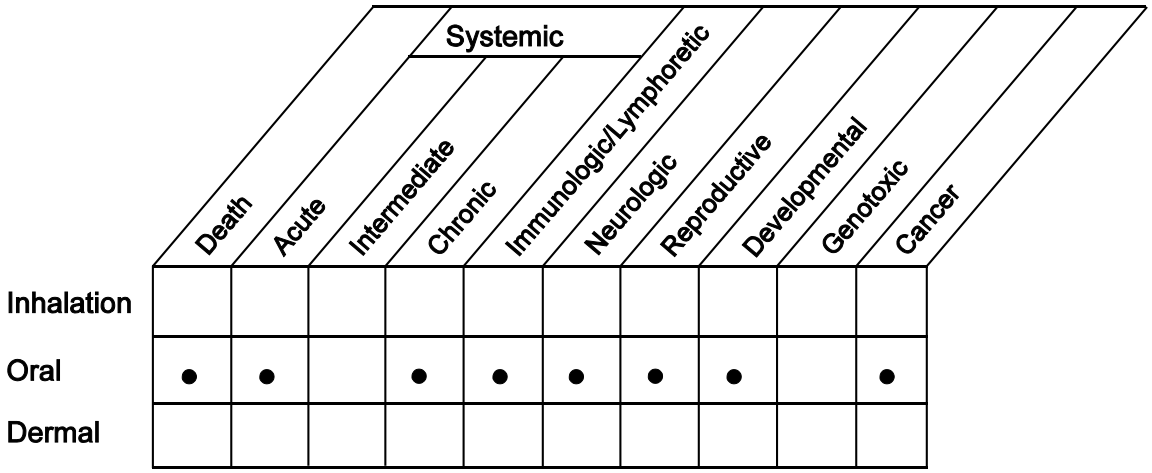
Human



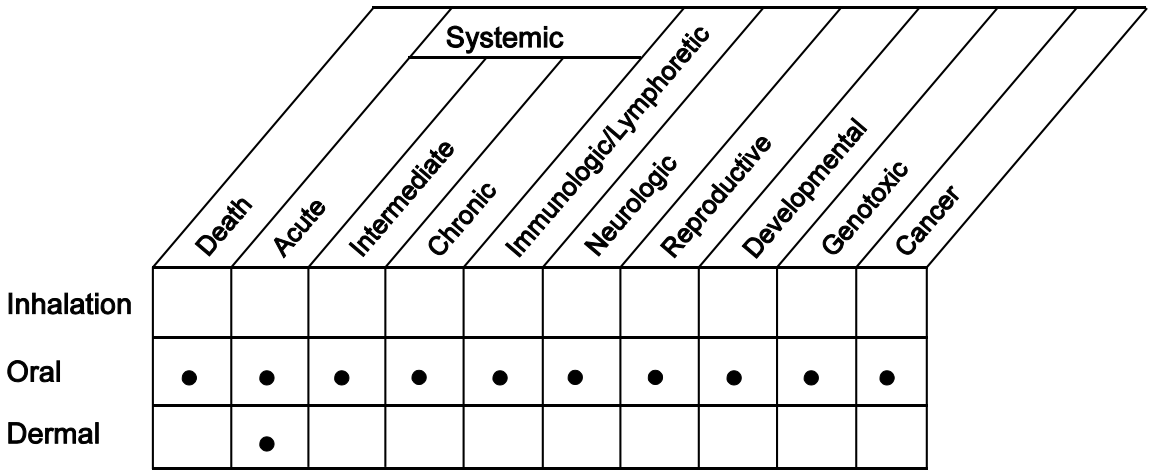
Animal

● Existing Studies

Figure 3-7. Existing Information on Health Effects of Fluoride



Human



Animal

● Existing Studies

conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

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 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.

3.12.2 Identification of Data Needs

The following section will discuss data needs by category and by chemical (fluorine, hydrogen fluoride, and fluorides). 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. 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 available data were sufficient to derive acute-duration inhalation MRLs for fluorine and hydrogen fluoride. The data were inadequate for derivation of an acute-duration oral MRL for fluoride. 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. There are limited data on the toxicity of fluorine following intermediate-duration exposure; pulmonary effects were observed in rats, dogs, and rabbits (Stokinger 1949). The data were not considered sufficient for derivation of an intermediate-duration inhalation MRL for fluorine. The limited database for hydrogen fluoride also suggests that the respiratory tract is a sensitive target. Nasal irritation has been observed in humans (Largent 1960) and pulmonary effects have been observed in animals (Stokinger 1949). The database for hydrogen fluoride was considered adequate for derivation of an intermediate-duration inhalation MRL. 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 are no data from such high exposures in humans. The toxicity and pharmacokinetic data at the present time are not sufficient to derive an intermediate-duration oral MRL for fluoride. Studies examining the long-term toxicity of fluorine and ingested fluoride are needed for derivation of intermediate-duration MRLs.

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). The mechanisms of action include incorporation of fluoride into enamel preeruptively, inhibition of demineralization, enhancement of remineralization, and inhibition of bacterial activity in dental plaque (DHHS 2000). 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 dental 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. 1942; Pandit et al. 1940). Epidemiological studies addressing the effect of nutrition on the prevalence and severity of dental and skeletal fluorosis may be useful. Numerous epidemiology studies have examined the possible association between consumption of fluoride in drinking water and the risk of fractures (Arnala et al. 1986; Cauley et al. 1995; Cooper et al. 1990, 1991; Danielson et al. 1992; Jacobsen et al. 1990; Kröger et al. 1994; Kurttio et al. 1999; Madans et al. 1983; Phipps and Burt 1990; Phipps et al. 2000; Simonen and Laittinen 1985; Sowers et al. 1986); these studies provide conflicting results and limitations of the study design preclude establishing a causal relationship. Clinical studies of women with osteoporosis treated with fluoride provide evidence that ingesting high doses of fluoride can result in an increase in nonvertebral fracture risk (Haguenauer et al. 2000; Riggs et al. 1990, 1994). The Riggs et al. (1990, 1994) study was used as the basis of a chronic-duration oral MRL for fluoride. 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.

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 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. Evidence of genotoxicity was seen in *in vitro* studies at very high concentrations of fluoride. It is questionable whether these findings are relevant to humans (Caspary et al. 1987, 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. The results have been inconsistent in many instances, but a consensus is developing that at toxic levels (>10 µg/mL, and usually seen at >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. The reproductive toxicity of fluoride has been assessed in animals following inhalation exposure to fluorine and hydrogen fluoride and in humans and animals following oral exposure to fluoride compounds. No dermal reproductive toxicity data were identified. Reproductive toxicity data following inhalation exposure are limited to a report of testicular degeneration in rats exposed to a high concentration of fluorine gas (Stokinger 1949); and in dogs exposed to hydrogen fluoride (Stokinger 1949). Some reproductive effects have been observed in humans consuming drinking water with high levels of fluoride. A decrease in fertility was found in women living in communities with high fluoride levels in municipal water, as compared to women living in areas with low fluoride levels (Freni et al.

1994). Another study found decreased serum testosterone levels in men with skeletal fluorosis and in men consuming water with high levels of fluoride (Susheela and Jethanandani 1996). Although some studies have reported an increased incidence of Down's syndrome among populations exposed to high levels of fluoride, these studies have been refuted (Berry 1958; Erickson et al. 1976; Needleman et al. 1974). The available human studies have limited value in assessing the reproductive potential of fluoride. A number of animal studies provide evidence that the reproductive system is a target of fluoride toxicity at high exposure levels. The observed reproductive effects include decreases in serum testosterone levels in rats (Araibi et al. 1989; Narayana and Chinoy 1994), testicular damage in rats (Araibi et al. 1989; Krasowska and Wlostowski 1992; Susheela and Kumar 1991), and alterations in spermatogenesis or sperm morphology in rats (Araibi et al. 1989; Chinoy et al. 1992, 1995), mice (Chinoy and Sequeira 1992), rabbits (Kumar and Susheela 1994, 1995; Susheela and Kumar 1991), and guinea pigs (Chinoy et al. 1997). Mating the exposed males with unexposed females resulted in decreased fertility (Chinoy and Sequeira 1992; Chinoy et al. 1992). However, other studies have not found alterations in testosterone levels (Sprando et al. 1997), testicular histopathology (Sprando et al. 1998), or in sperm (Dunipace et al. 1989; Li et al. 1987a) in rats or mice exposed to similar concentrations of sodium fluoride. Reproductive effects have also been observed in females. Reduced fertility was observed in female mice (Messer et al. 1973); a similarly designed study did not support these results (Tao and Suttie 1976). 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). The available human and animal data provide suggestive evidence that the reproductive system is a target of fluoride toxicity at high exposure levels; however, additional studies are needed to resolve the apparent conflicting results. An oral multigeneration study would be useful to establish dose-response relationships; inhalation and dermal exposure studies would be useful for determining whether the reproductive system is also a target of toxicity following these routes of exposure.

Developmental Toxicity. There are no studies in humans or animals regarding the developmental effects of inhaled hydrogen fluoride or following dermal exposure to fluoride compounds. Several human and animal studies have examined the developmental toxicity of fluoride following oral exposure. No effect on the incidence of birth defects were found in the children of women drinking fluoridated water (Erickson et al. 1976). Other epidemiology studies have suggested that exposure to high levels of fluoride in water can result in developmental effects in humans. An increase in the occurrence of spina bifida was found in children living in area of India with high fluoride levels in water (4.5–8.5 ppm) (Gupta et al. 1995). A decrease in intelligence, as measured by IQ scores, was found in children exposed to high levels of fluoride in the water (Li et al. 1995a; Lu et al. 2000). However, as noted previously, the Gupta et al. (1995), Li et al. (1995a), and Lu et al. (2000) studies appear to have considerable study design inadequacies. In general, studies in conventional laboratory species have not found developmental effects in rats exposed to 12.26–21 mg fluoride/kg/day (Collins et al. 1995; Heindel et al. 1996; Ream et

al. 1983) or rabbits exposed to 13.21 mg fluoride/kg/day (Heindel et al. 1996). A two-generation study in rats did not find developmental effects in the first generation offspring of dams exposed 23 mg/kg/day, but an increased number (statistical analysis was not performed) of abnormal pups and affected litters was seen the second generation (Marks et al. 1984). 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). Additional developmental toxicity studies are needed to assess whether the developing organism is a sensitive target of fluoride toxicity. These studies should assess multiple routes of exposure, involve multigenerational exposure, and evaluate the potentially sensitive developing nervous system.

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 (Chan-Yeung et al. 1983a, 1983b; Czerwinski et al. 1988; 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.

Exposure. 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.

Effect. 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.

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 vs. 10 hours) (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. Fluoride can accumulate in the kidney (Whitford and Taves 1973) and aorta (Smith et al. 1960). Further information 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. These *in vitro* studies were carried out using concentrations that exceed body fluid concentrations by a factor greater than 100. 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 of <10 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 generally present 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). Whitford et al. (1991) compared the major features of fluoride pharmacokinetics (the plasma, renal, and skeletal clearances) in adult dogs, cats, rabbits, rats, and hamsters. While the clearances among the species were qualitatively similar, the dog most closely resembled pharmacokinetics in humans.

Methods for Reducing Toxic 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 that has been contaminated with fluoride.

Children's Susceptibility. The available human studies that examined the toxicity of fluoride in children primarily focused on the skeletal system. The studies showed that exposure to moderate levels of fluoride can result in dental fluorosis. However, the effect is widely considered a cosmetic rather than function effect. Because more fluoride is deposited in children's bones than adults, there is a need for additional studies to assess whether children are more susceptible to skeletal effects. Human studies have suggested that high doses of fluoride may result in spina bifida (Gupta et al. 1995) or decreased intelligence (Li et al. 1995a; Lu et al. 2000) but, as noted previously, the Gupta et al. (1995), Li et al. (1995a), and Lu et al. (2000) studies appear to have major study design deficiencies. In general, animal studies have not found developmental effects following oral exposure; however, these studies did not examine neurodevelopmental end points that may be a sensitive target. Additional animal studies are needed to assess neurodevelopmental potential of fluoride.

In general, the available toxicokinetic data did not examine potential differences between adults and children; toxicokinetic studies examining how aging can influence absorption rates would be useful in assessing children's susceptibility to fluoride toxicity.

Child health data needs relating to exposure are discussed in Section 6.8.1 Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

Ongoing studies pertaining to fluorine, hydrogen fluoride, or fluoride have been identified and are shown in Table 3-9.

Table 3-9. Ongoing Studies on the Health Effects of Fluoride

Investigator	Affiliation	Research description
Ziegler, EE	University of Iowa	Toxicokinetic properties in infants
Levy, SM	University of Iowa	Bone development in children
Boskey, AL	Hospital for Special Therapies	Osteoporosis therapy

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

The common synonyms and other information for fluorine, hydrogen fluoride, and sodium fluoride are listed in Table 4-1. The terms "fluorine" and "fluoride" are often used interchangeably in the literature as generic terms. In this document, we will use the terms "fluoride" as a general term to refer to all combined forms of fluorine unless the particular compound or form is known and there is a reason for referring to it. We will sometimes use the term "fluorine gas" to emphasize the fact that we are referring to the elemental form of fluorine rather than a combined form. In general, the differentiation between different ionic and molecular or gaseous and particulate forms of fluorine-containing substances is uncertain and may also be unnecessary.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Fluorine is the lightest member of Group 17 (VIIA) of the periodic table. This group, the halogens, also includes chloride, bromine, and iodine. As with the other halogens, fluorine occurs as a diatomic molecule, F_2, in its elemental form. It has only one stable isotope and its valence in all compounds is -1. Fluorine is the most reactive of all the elements, which may be attributed to its large electronegativity (estimated standard potential +2.85 V). It reacts at room temperature or elevated temperatures with all elements other than nitrogen, oxygen, and the lighter noble gases. Fluorine is also notable for its small size; large numbers of fluorine atoms fit around atoms of another element. This, along with its electronegativity, allows the formation of many simple and complex fluorides in which the other element is in its highest oxidation date. Important physical and chemical properties of fluorine, hydrogen fluoride, and sodium fluoride are presented in Table 4-2.

Table 4-1. Chemical Identity of Fluorine, Hydrogen Fluoride, and Sodium Fluoride[a]

Characteristic	Fluorine	Hydrogen fluoride	Sodium fluoride
Synonym(s)	Fluorine-19	Hydrofluoric acid; hydrofluoride	Monosodium fluroride[b]
Registered trade name(s)	No data	No data	Alcoa sodium fluoride[b]
Chemical formula	F_2	FH	FNa
Chemical structure	F-F	H-F	Na-F
Identification numbers:			
CAS registry	7782-41-4	7664-39-3	7681-49-4
NIOSH RTECS	NIOSH/LM64750000	NIOSH/MW7890000	NIOSH/WB0350000
EPA hazardous waste	P056	U134	No data
OHM/TADS	No data	7216750	7216897
DOT/UN/NA/IMO shipping	UN1045; fluorine	UN1790; hydrofluoric acid solution UN1052; anhydrous hydrogen fluoride	UN1690; sodium fluoride
HSDB	541	546	1766
EINECS	231-954-8	231-634-8	231-667-8
NCI	No data	No data	C55221

[a]All information obtained from HSDB 2001 and ChemID 2001 except where noted.
[b]Sodium fluoride is an ingredient in many dental care products and rodenticides. Since it is not the only component in these products, they cannot properly be considered trade names or synonyms. Some of these products are: Floridine, Antibulit, Cavi-trol, Chemifluor, Credo, Duraphat, F1-tabs, Florocid, Flozenges, Fluoral, Fluorident, Fluorigard, Fluorineed, Fluorinse, Fluoritab, Fluorocid, Fluor-o-kote, Fluorol, Fluoros, Flura, Flura drops, Flura-gel, Flura-Loz, Flurcare, Flursol, Fungol B, Gel II, Gelution, Gleem, Iradicav, Karidium, Karigel, Kari-rinse, Lea-Cov, Lemoflur, Luride, Luride Lozi-tabs, Luride-SF, Nafeen, Nafpak, Na Frinse, Nufluor, Ossalin, Ossin, Osteofluor, Pediaflor, Pedident, Pennwhite, Pergantene, Phos-flur, Point Two, Predent, Rafluor, Rescue Squad, Roach salt, So-flo, Stay-flo, Studafluor, Super-dent, T-fluoride, Thera-flur, Thera-Flur-N, Villiaumite, Zymafluor. Another compound of sodium and fluorine is sodium bifluoride (also called sodium hydrofluoride and sodium hydrofluoride), $NaF·HF$ or $NaHF_2$, which is not discussed here.

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Oganization Code; EINECS = European INventory of Existing Chemical Substances; 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 4-2. Physical and Chemical Properties of Fluorine, Hydrogen Fluoride, and Sodium Fluoride[a]

Property	Fluorine	Hydrogen fluoride	Sodium fluoride
Molecular weight	37.997	20.006	42.00
Color	Pale yellow	Colorless	Colorless
Physical state	Gas	Gas	Cubic or tetragonal crystals
Molecular formula	F_2	FH	FNa
Melting point, EC	-219.61	-83.36	993
Boiling point, EC	-188.13	19.51[b]	1,704
Density, g/cm^3	1.5127 at -188.13 EC	0.991 at 19.54 EC	2.78
Odor	Pungent, irritating odor	Strong, irritating odor	Odorless
Odor threshold:			
Water	Not relevant	No data	No data
Air	0.035 ppm	0.5–3 ppm	No data
Solubility:			
Water	1.69 mg/L	Miscible	43 g/L at 25 EC
Organic solvents, weight. % at 5 EC	No data	Benzene (2.54); toluene (1.80); ethanol (very soluble); *m*-xylene (1.28); tetraline (0.27)[b]	Very slightly soluble in ethanol
Partition coefficients:			
Log K_{ow}	Not relevant	No data	No data
Log K_{oc}	Not relevant	Not relevant	No data
Vapor pressure	0.4 kPa (3 mmHg) at 55 K[c] 12.3 kPa (92.3 mmHg) at 70 K	400 mmHg at 2.5 EC	1 mmHg at 1,077 EC
Henry's law constant at 20 EC	No data	0.104 atm-L/mole[e]	No data

Table 4-2. Physical and Chemical Properties of Fluorine, Hydrogen Fluoride, and Sodium Fluoride[a] *(continued)*

Property	Fluorine	Hydrogen fluoride	Sodium fluoride
Autoignition temperature	No data	No data	No data
Flashpoint	Not flammable	Not flammable	Not flammable
Flammability limits	No data	No data	No data
Conversion factors	1 mg/m^3 = 1.554 ppm[d] 1 ppm = 0.64 mg/m^3	1 mg/m^3 = 1.223 ppm[d] 1 ppm = 0.82 mg/m^3	Not applicable
Explosive limits	No data	No data	No data

[a]All information obtained from HSDB 2001 except where noted
[b]Budavari 1996
[c]Lide 1992
[d]NAS 1971a
[e]Betterton 1992; apparent Henry's law constant (ratio of the gas phase concentration to that of the total dissolved solute)

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

The most important natural starting material for the production of fluorine chemicals, including fluorine, hydrogen fluoride, and sodium fluoride, is the mineral fluorite (calcium fluoride [CaF_2]), commonly called fluorspar. Other important fluorine minerals are fluorapatite ($Ca_5(PO_4)_3F$) and cryolite (Na_3AlF_6). There has been no fluorspar mine production in the United States since 1996; supplies were imported or purchased from the National Defense Stockpile. In addition, some byproduct calcium fluoride was recovered from industrial waste streams. An estimated 8,000–10,000 metric tons of fluorspar are recovered each year from uranium enrichment, stainless steel pickling, and petroleum alkylation. To supplement fluorspar supplies, fluorosilicic acid is recovered from phosphoric acid plants processing phosphate rock. In 1999, 69,100 tons of byproduct fluorosilicic acid (equivalent to 122,000 tons of fluorspar) was produced by 10 plants owned by 5 companies. In 1999, the main fluorspar-producing countries, in order of importance, were China, Mexico, Russia, Spain, and France. The apparent consumption of fluorspar (excluding fluorspar equivalents of fluorosilicic acid, hydrofluoric acid, and cryolite) in the United States was 615,000 metric tons in 1999 and was estimated to be 612,000 metric tons in 2000 (USGS 2001). Approximately 60–65% of the fluorspar consumed goes into the production of hydrogen fluoride. Large amounts are also used as a flux in steel production.

Fluorine is produced commercially by electrolyzing anhydrous hydrogen fluoride containing dissolved potassium fluoride to achieve adequate conductivity (Jaccaud and Faron 1988; Shia 1994). Potassium fluoride and hydrogen fluoride form potassium bifluoride (KHF_2 or KF•HF). Fluoride is oxidized at the anode, producing fluorine, and the hydrogen ion is reduced at the cathode, producing hydrogen gas. Information concerning the amount of fluorine produced is not available. The commercial fluorine production capacity of the United States and Canada is over 5,000 tons/year (Shia 1994).

Anhydrous hydrogen fluoride is manufactured by the action of sulfuric on calcium fluoride. Powdered acid-grade fluorspar (≥97% CaF_2) is distilled with concentrated sulfuric acid; the gaseous hydrogen fluoride that leaves the reactor is condensed and purified by distillation (Smith 1994). The U.S. capacity for hydrogen fluoride production was 198,000 metric tons in 2000 (SRI 2000). The demand for hydrogen fluoride, which was 340,000 metric tons in 1998, is expected to increase to 390,000 metric tons in 2002 (CMR 1999).

Sodium fluoride is manufactured by the reaction of hydrofluoric acid with sodium carbonate or sodium hydroxide. The salt is centrifuged and dried (Mueller 1994). Information concerning the amount of sodium fluoride produced is not available.

Current U.S. manufacturers of fluorine, hydrogen fluoride, and sodium fluoride are given in Table 5-1. Tables 5-2 and 5-3 list the number of facilities in each state that manufacture, process, or use hydrogen fluoride and fluorine, respectively, their intended uses, and the range of maximum amounts of these substances that are stored on-site. In 1999, there were, respectively, 1,022 and 14 reporting facilities that produced, processed, or used hydrogen fluoride or fluorine in the United States. The data listed in Tables 5-2 and 5-3 are derived from the Toxics Release Inventory (TRI99 2001). Only certain types of facilities were required to report. Therefore, this is not an exhaustive list. Sodium fluoride or other fluoride salts are not listed on TRI.

5.2 IMPORT/EXPORT

In 1999, the United States imported 419,000 metric tons of acid grade (>97%) fluorspar and 59,000 metric tons of metallurgical-grade (<97%) fluorspar (USGS 2001). This importation was supplemented by the fluorspar equivalent of 192,000 metric tons from hydrofluoric acid plus cryolite. The estimated imports of fluorspar for 2000 were 510,000 metric tons of acid-grade, 41,000 of metallurgical-grade, and 215,000 tons from hydrofluoric acid plus cryolite. Between 1996 and 1999, 67% of fluorspar imports came from China, 22% from South Africa, and 11% from Mexico. Exports of fluorspar for 1999 were 55,000 metric tons (USGS 2001) and are estimated to fall to 48,000 in 2000. Exports consist of imported material that was reexported or material obtained from the National Defense Stockpile. In 2000, 43,000 metric tons of metallurgical-grade fluorspar from the stockpile were disposed of. In 1999, most of the exports were to Italy and Canada (USGS 1999).

U.S. imports for consumption are available for three other fluorides: hydrofluoric acid, cryolite, and aluminum fluoride. For 1999, these were 120,000, 9,560, and 19,300 metric tons, respectively. For hydrofluoric acid, 76% of imports came from Mexico and 22% from Canada.

5.3 USE

Fluorine gas is used captively for the production of various inorganic fluorides. The preparation of fluorides of an element in its highest oxidation state makes use of fluorine's oxidizing and fluorinating ability. The most important product is uranium hexafluoride (UF_6), which is used in the gaseous diffusion process for producing enriched uranium-235 for the nuclear industry. This use consumes 70–80% of fluorine production. The second most important product is sulfur hexafluoride (SF_6), which is used as a gaseous dielectric for electrical and electronic equipment and a tracer gas for determining ventilation rates and air movements in buildings. Other uses of fluorine include: the treatment of polyolefin containers to reduce their permeability to organic liquids; the treatment of a polymer surface for the application of an

Table 5-1. U.S. Manufacturers of Hydrogen Fluoride, Fluorine and Sodium Fluoride[a]

Company	Location	Annual capacity[b] (10^3 metric tons)
Hydrogen Fluoride[c]		
Dupont	La Porte, Texas	80
General Electric[d]	Geismar, Louisiana	118
Fluorine		
General Electric[d]	Metropolis, Illinois	
Sodium fluoride		
Chemtech Products Inc.	Alorton, Illinois	
Elf Atochem North America, Inc.	Tulsa, Oklahoma	
Mallinckrodt Baker Inc.	Phillipsburg, New Jersey	

[a]Derived from SRI 2000
[b]Plant capacity available only for hydrogen fluoride
[c]Merchant producers. Alcoa produces hydrogen fluoride as a nonisolatable product.
[d]Formerly Honeywell, and before that, Allied Signal.

Table 5-2. Facilities that Produce, Process, or Use Hydrogen Fluoride

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	1	100	999	1, 5
AL	8	0	9,999,999	1, 5, 7, 12, 13
AR	5	0	999,999	1, 5, 6, 7, 8, 12
AZ	13	0	999,999	1, 5, 6, 7, 8, 10, 11, 12, 13
CA	21	0	49,999,999	1, 2, 3, 4, 7, 8, 10, 11, 12, 13
CO	5	0	999,999	1, 5, 8, 10, 12, 13
CT	3	1,000	99,999	1, 5, 11, 12, 13
DE	2	0	999,999	1, 5, 7
FL	15	0	999,999	1, 3, 5, 6, 7, 8, 10, 11, 12, 13
GA	10	0	999,999	1, 5, 6, 8, 12, 13
HI	1	1,000	9,999	12
IA	6	0	999,999	1, 5, 6, 13
ID	5	100	999,999	1, 5, 6, 11, 12, 13
IL	20	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
IN	11	0	99,999	1, 3, 5, 8, 11, 12, 13
KS	5	0	9,999,999	1, 5, 6, 7, 8, 11
KY	12	0	9,999,999	1, 2, 3, 5, 7, 10, 11, 12, 13
LA	13	0	9,999,999	1, 2, 3, 4, 5, 7, 11, 12, 13
MA	7	0	99,999	1, 5, 11, 12, 13
MD	2	0	999	1, 5
ME	2	1,000	9,999	11, 12
MI	14	0	999,999	1, 2, 5, 7, 8, 11, 12, 13
MN	4	0	99,999	1, 5, 7, 11, 12, 13
MO	7	0	99,999	1, 5, 6, 12, 13
MS	6	0	9,999,999	1, 5, 6, 8, 12
MT	5	0	999,999	1, 5, 11
NC	11	0	999,999	1, 5, 6, 7, 12, 13
ND	4	0	999,999	1, 5, 6, 11
NE	3	0	99,999	1, 5, 6
NH	3	0	99,999	1, 5, 12, 13
NJ	10	0	9,999,999	1, 2, 3, 5, 7, 8, 11, 12, 13
NM	6	0	999,999	1, 5, 6, 11, 12

Table 5-2. Facilities that Produce, Process, or Use Hydrogen Fluoride *(continued)*

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
NV	3	0	999,999	1, 2, 3, 5, 9
NY	14	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 10, 11, 12, 13
OH	19	0	999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13
OK	10	0	99,999,999	1, 2, 3, 5, 6, 7, 8, 10, 11, 13
OR	14	0	999,999	1, 2, 3, 4, 5, 10, 11, 12, 13
PA	23	0	49,999,999	1, 2, 3, 5, 6, 7, 8, 10, 11, 12, 13
PR	3	100	999,999	7, 12
RI	3	100	99,999	7, 12, 13
SC	11	0	999,999	1, 3, 5, 7, 11, 12, 13
SD	2	0	9,999	1, 5, 12
TN	7	0	999,999	1, 2, 5, 6, 11, 12, 13
TX	30	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13
UT	9	0	999,999	1, 5, 6, 7, 11, 12, 13
VA	6	0	999,999	1, 5, 11, 12, 13
VT	2	1,000	99,999	12
WA	8	0	999,999	1, 3, 5, 11, 12, 13
WI	11	0	999,999	1, 5, 6, 8, 11, 12, 13
WV	5	0	999,999	1, 2, 3, 5, 11, 12
WY	5	0	999,999	1, 2, 3, 5, 11, 12

Source: TRI99 2001

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses

Table 5-3. Facilities that Produce, Process, or Use Fluorine

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	1	0	99	1, 6
GA	1	0	99	1, 5
IL	1	10,000	99,999	1, 3, 7
KS	1	0	99	1, 5, 13
LA	1	1,000	9,999	1, 3, 7, 13
MD	1	10,000	99,999	9
NC	3	10,000	999,999	9
NJ	1	100	999	2, 3, 7
OK	1	100,000	999,999	9
PA	1	1,000	9,999	1, 3, 4, 7, 10
PR	1	1,000	9,999	12
TX	1	1,000	9,999	13

Source: TRI99 2001

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses

adhesive or coating; and the production of some fluorinated organic compounds (Guo et al. 2001; Shia 1994).

Hydrogen fluoride is the most important compound of fluorine. Anhydrous hydrogen fluoride is used in the production of most fluorine-containing chemicals. It is used in the production of refrigerants, herbicides, pharmaceuticals, high-octane gasoline, aluminum, plastics, electrical components, and fluorescent light bulbs. Aqueous hydrofluoric acid is used in stainless steel pickling, glass etching, metal coatings, exotic metal extraction, and quartz purification (Hance et al. 1997). The most important use of hydrogen fluoride is in the production of fluorocarbon chemicals, including hydrofluorocarbons, hydrofluorochlorocarbons, and fluoropolymers; 60% of production is used for this purpose. Demand for hydrogen fluoride for fluorocarbons, broadly used as refrigerants, is increasing as a nonchlorinated alternative to ozone-depleting chlorofluorocarbons. (Production of fluorocarbons uses more hydrogen fluoride than production of chlorofluorocarbons.) The next most important uses of hydrogen fluoride are: chemical derivatives, 18%; aluminum manufacturing, 6%; stainless steel pickling, 5%; petroleum alkylation catalysts, 4%; and uranium chemicals production, 3%. Miscellaneous other uses include glass etching, herbicides, and rare metals (CMR 1999). Generally, the aluminum industry consumes 10–40 kg of fluoride per metric ton of aluminum produced. The AlF_3 used in aluminum reduction cells may be produced directly from acid-grade fluorspar or byproduct fluorosilicic acid, rather than from hydrogen fluoride. Anhydrous hydrogen fluoride is used as a catalyst in the petroleum alkylation, a process that increases the octane rating of petroleum. In uranium chemicals production, hydrogen fluoride is used to convert uranium oxide (yellow cake, U_3O_8) to UF_4 before further fluorination to UF_6.

One of the principal uses of sodium fluoride is the fluoridation of public water supplies for the prevention of dental caries. Generally, 1.5–2.2 mg of sodium fluoride is added per liter of water (0.7–1.0 mg/L as fluoride). Sodium fluoride may also be applied topically to teeth as a 2% solution to prevent tooth decay. It is also used as a flux for deoxidizing rimmed steel, as a component of laundry sours (removal of iron stains), and in the re-smelting of aluminum, manufacture of vitreous enamels, pickling of stainless steel, wood preservative compounds, casein glues, manufacture of coated papers, and heat-treating salts (Mueller 1994).

5.4 DISPOSAL

Fluorine gas can be disposed of by conversion to perfluorocarbons or fluoride salts. Because of the long atmospheric lifetimes of perfluorocarbons, conversion to fluoride salts is preferable. Industrially, the waste stream is scrubbed with a caustic solution, KOH or NaOH, and for dilute streams, allowed to react with limestone (Shia 1994). Adequate contact and residence time is essential in the scrubber to ensure complete neutralization of the intermediate oxygen difluoride to prevent it from leaving the scrub tower.

According to the TRI, in 1999, 58,400 pounds of fluorine were treated on-site and 20,400 pounds were treated off-site (TRI99 2001).

According to the TRI, in 1999, an estimated 582,000 pounds of hydrogen fluoride were transferred off-site, including to publicly owned-treatment works (POTWs), by 1,022 reporting facilities presumably for disposal (TRI99 2001). No fluorine was transferred off-site in 1999 by 14 reporting facilities. According to the TRI, in 1999, 99.3% of hydrogen fluoride that was recycled or treated was performed on-site (TRI99 2001). Of the hydrogen fluoride recycled, 142 million was performed on-site and 146,000 pounds was performed off-site. Of the hydrogen fluoride that was treated, 130 million pounds were treated on-site and 2.4 million pounds were treated off-site. No information was found concerning how hydrogen fluoride is generally treated for disposal.

No information was found regarding the disposal of sodium fluoride. It would appear from its use that most of it is disposed of in municipal landfills or POTWs.

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Fluorides have been identified in at least 177 of the 1,585 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2001). However, the number of sites evaluated for fluorides is not known. The frequency of these sites can be seen in Figure 6-1. All of these sites are located within the United States; none are located in the Commonwealth of Puerto Rico or Guam.

Fluorides are naturally-occurring components of rocks and soil and are also found in air, water, plants, and animals. They enter the atmosphere through volcanic emissions and the resuspension of soil by wind. Volcanos also emit hydrogen fluoride and some fluorine gas. Fluorine is a highly reactive element and readily hydrolyzes to form hydrogen fluoride and oxygen. Hydrogen fluoride reacts with many materials both in the vapor phase and in aerosols. The resultant fluorides are typically nonvolatile, stable compounds. Marine aerosols also release small amounts of gaseous hydrogen fluoride and fluoride salts into the air (Friend 1989). Anthropogenic fluoride emissions include the combustion of fluorine-containing materials, which releases hydrogen fluoride, as well as particulate fluorides, into the air. Coal contains small amounts of fluorine, and coal-fired power plants constitute the largest source of anthropogenic hydrogen fluoride emissions. Major sources of industrial fluoride emissions are aluminum production plants and phosphate fertilizer plants; both emit hydrogen fluoride and particulate fluorides (EPA 1998b). Other industries releasing hydrogen fluoride are: chemical production; steel; magnesium; and brick and structural clay products. Hydrogen fluoride would also be released by municipal incinerators as a consequence of the presence of fluoride-containing material in the waste stream. In addition to industrial effluent and natural releases (e.g., weathering of rocks and runoff from soil), fluorides are released into surface water in municipal waste water as a result of water fluoridation.

In the atmosphere, gaseous hydrogen fluoride will be absorbed by atmospheric water (rain, clouds, fog, snow) forming an aerosol or fog of aqueous hydrofluoric acid. It will be removed from the atmosphere primarily by wet deposition. Particulate fluorides are similarly removed from the atmosphere and deposited on land or surface water by wet and dry deposition. Atmospheric precipitation weathers crustal rocks and soil, but dissolves out very little fluoride; most of the fluoride mobilized during weathering is bound to solids such as clays. Upon reaching bodies of water fluorides gravitate to the sediment (Carpenter 1969). Fluorides have been shown to accumulate in some marine aquatic organisms (Hemens and Warwick 1972). When deposited on land, fluoride is strongly retained by soil, forming complexes with soil components. Fluorides in soils are transported to surface waters through leaching or runoff of

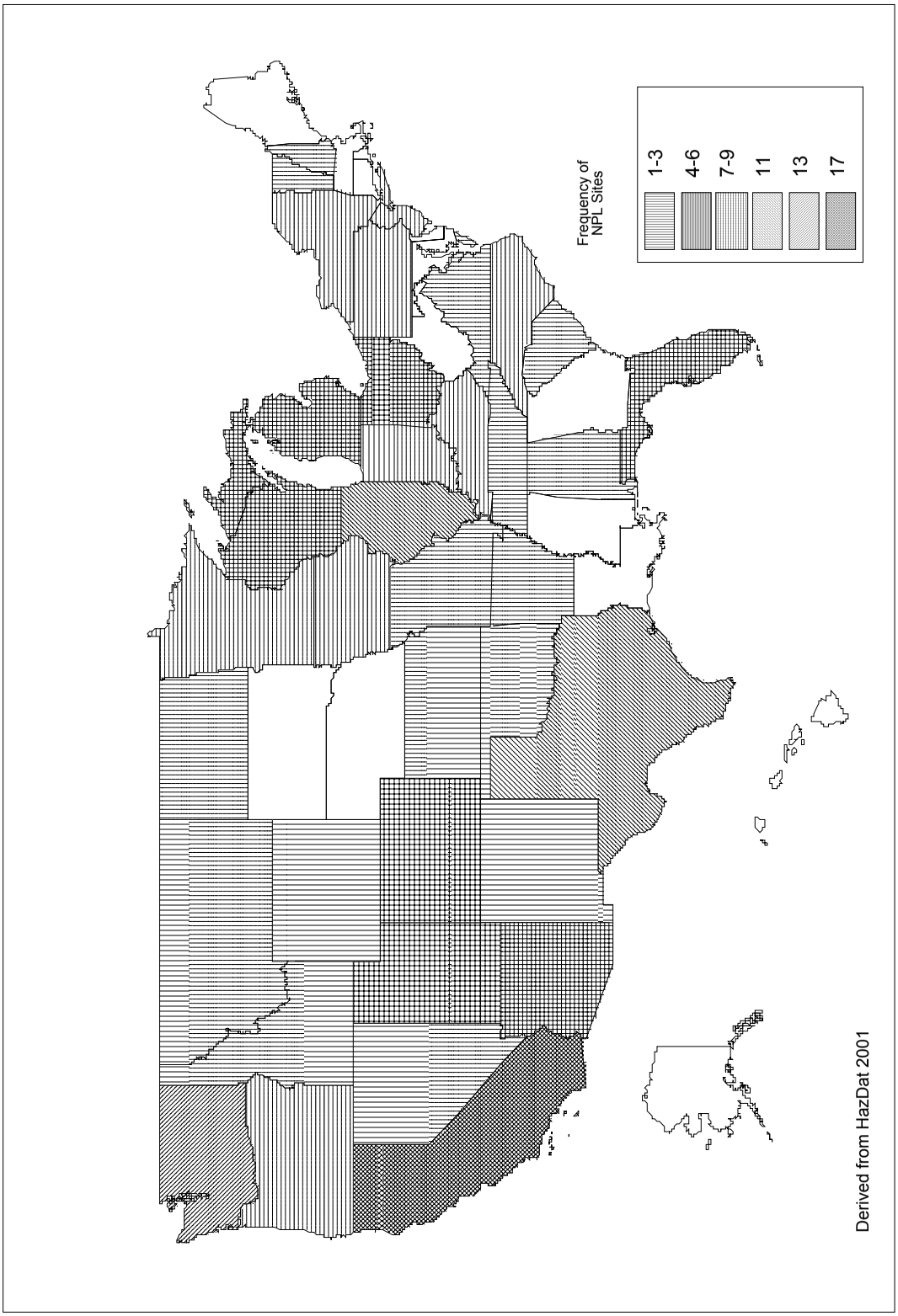


Figure 6-1. Frequency of NPL Sites with Fluorine Contamination

particulate-bound fluorides. Leaching removes only a small amount of fluorides from soils. Fluorides may be taken up from soil and accumulate in plants. The amount of fluorides accumulated depends on the type of plant and soil and the concentration and form of fluoride in the soil. Fluorides may also be deposited on above-ground surfaces of the plant. Tea plants are particularly known to accumulate fluoride, 97% of which is accumulated in the leaves (Fung et al. 1999). Fluoride accumulates primarily in the skeletal tissues of terrestrial animals that consume fluoride-containing foliage. However, milk and edible tissue from animals fed high levels of fluorides do not appear to contain elevated fluoride concentrations (NAS 1971a).

In natural water, fluoride forms strong complexes with aluminum in water and fluorine chemistry in water is largely regulated by aluminum concentration and pH (Skjelkvale 1994). Below pH 5, fluoride is almost entirely complexed with aluminum and consequently, the concentration of free F^- is low. As the pH increases, Al-OH complexes dominate over Al-F complexes and the free F^- levels increase. Fluoride forms stable complexes with calcium and magnesium, which are present in sea water. Calcium carbonate precipitation dominates the removal of dissolved fluoride from sea water (Carpenter 1969). Fluorine is incorporated into the calcium salt structure and removed from solution when the latter precipitates. Fluoride occurs in soil in a variety of minerals and complexes with aluminum, iron, and calcium. Fluorides occur predominantly as aluminum fluorosilicate complexes in acidic soils and calcium fluoride in alkaline soils. The availability of these soluble complexes increases with decreasing pH (Fung et al. 1999; Shacklette et al. 1974). This explains why acidic soils have both higher water-soluble fluoride and higher extractable aluminum levels. The retention of fluoride in alkaline soils depends largely upon the aluminum content of the soil.

The general population is exposed to fluoride through consumption of drinking water, foods, and dentifrices. Fluorides used in dentifrices are sodium fluoride, sodium monofluorophosphate, and stannous fluoride (Pader 1993). Populations living in areas with naturally high fluoride levels in water and soil my be exposed to high levels of fluoride in water. This is especially true if drinking water is derived from wells. Some plants, most notably tea, accumulate fluorides, and people who drink large quantities of tea may be exposed to high levels of fluoride in their diets. Populations living near industrial sources of fluoride may be exposed to higher levels of fluorides in the air they breathe. Vegetables and fruits grown near such sources may contain higher levels of fluorides particularly from fluoride-containing dust settling on the plant. Populations exposed to relatively high concentrations of fluoride include workers in fluoride-processing industries and individuals residing near such industries. Similarly, populations living near hazardous waste sites may also be exposed to high levels of fluoride by analogous routes.

6.2 RELEASES TO THE ENVIRONMENT

According to the Toxic Chemical Release Inventory, in 1999, total releases of hydrogen fluoride to the environment (including air, water, soil, and underground injection) from 1,022 reporting facilities that produced, processed, or used hydrogen fluoride were 77.0 million pounds (TRI99 2001). Table 6-1 lists amounts released from these facilities grouped by state. In addition, 582,000 pounds of hydrogen fluoride were transferred off-site by these facilities (TRI99 2001). Starting in 1998, metal mining, coal mining, electric utilities and Resource Conservation and Recovery Act (RCRA)/solvent recovery industries were required to report to the TRI, industries with potentially large releases of hydrogen fluoride. The industrial sector producing, processing, or using hydrogen fluoride that contributed the greatest environmental releases was electrical utilities that contributed 76% of the total environmental releases.

According to the TRI, in 1999, total releases of fluorine to the environment (including air, water, soil, and underground injection) from 16 reporting facilities that produced, processed, or used fluorine were 246,000 pounds (TRI99 2001). Table 6-2 lists amounts of fluorine released from these facilities grouped by state. The two largest contributing industrial sectors were electrical utilities and stone/clay/glass, which respectively contributed 43 and 33% of the total environmental releases. No fluorine was transferred off-site. Neither sodium fluoride nor any other fluorides are listed on TRI. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

Fluorides have been identified in a variety of environmental media (air, surface water, leachate, groundwater, soil, and sediment) collected at 178 of 1,585 current or former NPL hazardous waste sites (HazDat 2001).

6.2.1 Air

The major natural source of hydrogen fluoride emissions to the atmosphere is volcanoes. These emissions are estimated to range from 0.6 to 6 million metric tons per year. On average, <10% of these emissions are a result of large eruptions that are efficiently injected into the stratosphere (Symonds et al. 1988). Passive degassing of volcanoes is a major source of tropospheric hydrogen fluoride. In addition to hydrogen fluoride, volcanic gases also contain other fluorine compounds, namely SiF_4, H_2SiF_6, and F_2. Soil naturally contains fluoride, and resuspension of soil by wind also contributes to the atmospheric burden of fluorides in the form of soil minerals (NAS 1971a). Another source 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 (Friend 1989). However, these releases would be confined to the air over the oceans.

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Hydrogen Fluoride

		Reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Underground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on and off-site release
AK	1	46,285	No data	No data	No data	46,285	No data	46,285
AL	25	3,983,259	0	No data	0	3,983,259	17,527	4,000,786
AR	12	920,097	No data	No data	No data	920,097	135	920,232
AZ	24	700,278	No data	No data	0	700,278	1,318	701,596
CA	47	9,823	5	No data	0	9,828	414	10,242
CO	17	747,419	No data	No data	No data	747,419	No data	747,419
CT	3	1,019	0	No data	0	1,019	No data	1,019
DE	3	156,129	No data	No data	No data	156,129	No data	156,129
FL	29	2,988,867	5	0	615	2,989,487	340	2,989,827
GA	35	4,359,289	0	No data	No data	4,359,289	No data	4,359,289
HI	1	32	0	0	No data	32	No data	32
IA	16	1,250,170	0	No data	No data	1,250,170	No data	1,250,170
ID	5	130,955	0	No data	0	130,955	705	131,660
IL	46	2,504,137	42	No data	0	2,504,179	6,736	2,510,915
IN	37	4,186,760	5	No data	32	4,186,797	3,588	4,190,385
KS	15	741,885	0	No data	0	741,885	2,200	744,085
KY	31	2,149,358	0	No data	250	2,149,608	5	2,149,613
LA	21	559,476	326	No data	65	559,867	No data	559,867
MA	11	158,232	No data	No data	No data	158,232	No data	158,232
MD	12	1,570,837	No data	No data	No data	1,570,837	No data	1,570,837
ME	2	2,381	No data	No data	No data	2,381	No data	2,381

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Hydrogen Fluoride *(continued)*

		Reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Underground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on and off-site release
MI	29	2,412,653	0	0	0	2,412,653	2,075	2,414,728
MN	12	139,747	0	No data	No data	139,747	120	139,867
MO	25	2,370,885	0	No data	0	2,370,885	2	2,370,887
MS	9	614,385	32	No data	3,662	618,079	No data	618,079
MT	8	387,815	0	No data	No data	387,815	No data	387,815
NC	38	5,053,418	5	No data	No data	5,053,423	No data	5,053,423
ND	8	644,032	5	No data	No data	644,037	0	644,037
NE	8	1,178,771	No data	No data	No data	1,178,771	No data	1,178,771
NH	5	192,460	No data	No data	No data	192,460	No data	192,460
NJ	15	257,023	0	No data	0	257,023	0	257,023
NM	8	230,793	No data	No data	0	230,793	555	231,348
NV	3	413,300	No data	No data	No data	413,300	No data	413,300
NY	30	1,638,044	0	No data	0	1,638,044	4	1,638,048
OH	67	6,648,502	2	4,100,000	0	10,748,504	501,653	11,250,157
OK	19	1,142,949	72	No data	0	1,143,021	No data	1,143,021
OR	22	170,038	0	No data	0	170,038	35	170,073
PA	73	4,638,649	25	No data	7	4,638,681	2,400	4,641,081
PR	4	539	No data	No data	No data	539	No data	539
RI	3	2,476	No data	No data	No data	2,476	1,400	3,876
SC	32	2,100,535	1	No data	No data	2,100,536	0	2,100,536

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Hydrogen Fluoride *(continued)*

		Reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Underground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on and off-site release
SD	2	85,010	No data	No data	No data	85,010	No data	85,010
TN	19	1,893,633	0	No data	0	1,893,633	10,501	1,904,134
TX	77	3,677,457	2	0	17	3,677,476	24,630	3,702,106
UT	14	485,174	No data	No data	44,000	529,174	No data	529,174
VA	23	1,670,413	0	No data	0	1,670,413	No data	1,670,413
VT	2	2,775	0	No data	1,200	3,975	No data	3,975
WA	20	1,819,099	5	No data	5	1,819,109	1,237	1,820,346
WI	24	1,228,618	0	No data	29	1,228,647	No data	1,228,647
WV	19	4,288,093	16,458	0	0	4,304,551	0	4,304,551
WY	11	146,208	5	No data	85,591	231,804	4,673	236,477
Total	1,022	72,700,182	16,995	4,100,000	135,473	76,952,650	582,253	77,534,903

Source: TRI99 2001

[a]Data in TRI are maximum amounts released by each facility.
[b]Post office state abbreviations are used.
[c]The sum of fugitive and stack releases are included in releases to air by a given facility.
[d]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[e]Total amount of chemical transferred off-site, including to publicly owned treatment works (POTW).

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Fluorine

		Reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Underground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on and off-site release
AL	1	No data	27,573	No data	No data	27,573	No data	27,573
GA	1	206	No data	No data	No data	206	No data	206
IL	1	4,015	0	No data	No data	4,015	No data	4,015
KS	1	427	No data	No data	105,417	105,844	No data	105,844
LA	1	1,600	No data	No data	No data	1,600	No data	1,600
MD	1	3,805	No data	No data	No data	3,805	No data	3,805
NC	4	76,330	No data	No data	No data	76,330	No data	76,330
NJ	1	No data	No data	No data	No data	No data	No data	No data
OH	1	No data	No data	No data	No data	No data	No data	No data
OK	1	346	No data	No data	No data	346	No data	346
PA	1	No data	No data	No data	No data	No data	No data	No data
PR	1	No data	26,580	No data	No data	26,580	No data	26,580
TX	1	No data	No data	No data	No data	No data	No data	No data
Total	16	86,729	54,153	No data	105,417	246,299	No data	246,299

Source: TRI99 2001

[a]Data in TRI are maximum amounts released by each facility.
[b]Post office state abbreviations are used.
[c]The sum of fugitive and stack releases are included in releases to air by a given facility.
[d]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[e]Total amount of chemical transferred off-site, including to publicly owned treatment works (POTW).

The largest anthropogenic source of hydrogen fluoride emissions to air in the United States is electrical utilities. Coal naturally contains fluorides as impurities and this will be released primarily in the form of hydrogen fluoride during combustion. Some of the fluoride in the coal may be absorbed onto fly ash or bottom ash. A typical 650 megawatt coal-burning power plant running at 67% capacity (the average for U.S. coal plants) would release 180,000 pounds of hydrogen fluoride per year (Rubin 1999). EPA (1998a) reports an emission factor of 0.15 pounds/ton (0.075 kg/Mg) for coal combustion under a variety of firing conditions. Canadian Environmental Protection Act (CEPA) (1996) reports hydrogen fluoride emission factors for bituminous and lignite coals of 0.12 and 0.01 kg/Mg coal, respectively. Hydrogen fluoride is water soluble and emission are readily controlled by acid gas scrubbers. Other gaseous fluorides that may occur in the flue gas are SiF_4 and H_2SiF_6. Emissions of fluorides from aluminum reduction processes are primarily gaseous hydrogen fluoride and particulate fluorides, principally aluminum fluoride and calcium fluoride. Emission factors for aluminum production are 0.03 pounds of total fluorides and 0.02 pounds of hydrogen fluoride per ton of aluminum produced (EPA 1998b). Fluorine-containing compounds are contained in the raw materials used to produce brick and structural clay products and, therefore, hydrogen fluoride and other fluoride compounds are emitted from kilns used to manufacture these products. In addition, coal may be used to fire the kilns and contribute to the fluoride emissions. In the production of phosphate fertilizers, gaseous fluorides (hydrogen fluoride and silicon tetrafluoride), as well as particulate fluorides, may be released. EPA's Office of Air Quality Planning and Standards has developed emission factors for hydrogen fluoride for these and other hydrogen fluoride emitting industries. Hydrogen fluoride would be released by municipal incinerators as a consequence of the presence of fluoride-containing material in the waste stream. The amount of hydrogen fluoride released in flue gas would depend on the fluorine content of the waste stream and the efficiency of pollution control devises used in the stack.

Anthropogenic hydrogen fluoride emissions to the atmosphere in Canada were estimated to be 5,400 metric tons per year, of which 75% was contributed by primary aluminum producers. Other industries releasing hydrogen fluoride in Canada and their relative contributions were: coal-burning utilities, 10%; chemical production, 6%; steel production, 4%; phosphate fertilizer production, 2%; and magnesium production, 1% (CEPA 1996).

On a global scale, emissions of fluorides from coal combustion and other anthropogenic sources are minor and of local concern compared with natural emissions, estimated as 2.5×10^{10} kg/year (Carpenter 1969). Anthropogenic releases of total fluorides into the atmosphere were 155,300 tons/year from the major fluoride-processing industries measured between 1964 and 1970 (EPA 1980a). The major contributors were steel, brick, tile, and aluminum manufacturing, combustion of coal, and production of phosphorus and phosphate fertilizer (EPA 1980a; NAS 1971a). In 1977 and 1978, monthly atmospheric emission factors for fluorides from the Kitimat aluminum plant in British Columbia, Canada ranged from

4.0 to 6.8 kg fluoride per ton of aluminum produced; production capacity was 300,000 tons of aluminum per year (Sauriol and Gauthier 1984). Subsequently, regulations were established that set emissions standards for aluminum manufacturing (EPA 1980b) and phosphate fertilizer plants (EPA 1975). Fluorides can also enter the atmosphere in dusts and aerosols from the manufacture and use of pesticides such as sodium fluoride, sodium fluorosilicate, barium fluorosilicate, and cryolite (NAS 1971a). In the United States, fluoride emissions from coal-burning electric utilities are estimated to be around $37x10^6$ kg/year (Bauer and Andren 1985).

There is evidence that emissions of fluorides have been declining. Fluoride in precipitation has declined since 1967 (Ares 1990). A recent study from a forested area near Cologne, Germany registered a sharp decline in the fluoride content of Roe deer antlers from peak levels in the 1950s and 1960s (Kierdorf and Keirdorf 2000). In the 1990s, levels were almost an order of magnitude lower than the peak levels, which is attributed to reduced emissions from stationary sources. Fluoride is a skeletally-deposited contaminant, and it can be assumed that fluoride is mobilized during the annual antler growth period and transported to the mineralizing antlers. Therefore, the fluorine content of antlers is a good indicator of fluoride release.

According to the TRI, in 1999, releases of 72.7 million pounds of hydrogen fluoride to air from 1,022 reporting facilities accounted for 95% of the total environmental releases of this substances (TRI99 2001). Four percent of these emissions to air were fugitive emissions. Table 6-1 lists amounts of hydrogen fluoride released to air from these facilities grouped by state. The industrial sector contributing the largest release of hydrogen fluoride to air was electrical utilities, which contributed 80% of releases to air. According to the TRI, in 1999, releases of 87,000 pounds of fluorine to air from 16 reporting facilities accounted for 35% of the total environmental releases of this substances (TRI99 2001). Table 6-2 lists amounts of fluorine released to air from these facilities grouped by state. The TRI data should be used with caution, however, since only certain types of facilities are required to report. This is not an exhaustive list.

Fluorides have been identified in air samples at 6 of the 177 current or former NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2001).

6.2.2 Water

Natural sources of fluoride released to waters is primarily a result of runoff from the weathering of fluoride-containing rocks and soils and the leaching of fluorides from the soil into groundwater. 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 may result in water with high-fluoride levels (EPA 1980a; NAS 1971a).

Anthropogenic sources contributing to fluoride levels in water include atmospheric deposition of emissions from coal-fired power plants and other industrial sources that are deposited directly into water or that are first deposited on land and enter waterways in runoff. Most of this deposition is in the form of precipitation. Waste water may enter surface water directly or as effluent of water treatment plants. Since much of the nation's water supplies are fluoridated to a level of 0.7–1.2 ppm to decrease the incidence of tooth decay (DHHS 1991), this will contribute to fluoride in effluents from treatment plants.

According to the TRI, in 1999, releases of 17,000 pounds of hydrogen fluoride to water from 1,022 reporting facilities accounted for 0.022% of the total environmental releases of this substances (TRI99 2001). Table 6-1 lists amounts of hydrogen fluoride released to water from these facilities grouped by state. According to the TRI, in 1999, releases of 54,200 pounds of fluorine to water from 16 reporting facilities accounted for 22% of the total environmental releases of this substances (TRI99 2001). Table 6-2 lists amounts of fluorine released to water from these facilities grouped by state. As of 1998, TRI no longer separately collects data on substances released indirectly to POTWs, part of which may ultimately be released to surface waters. The TRI data should be used with caution, however, since only certain types of facilities are required to report. This is not an exhaustive list.

Fluorides have been identified in groundwater and surface water samples at respectively 134 and 52 of the 177 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2001).

6.2.3 Soil

Fluoride comprises about 0.09% of the earth's crust, ranking 13th in order of abundance (Lindahl and Mahmood 1994). Fluoride-containing minerals include biotite, muscovite, hornblende, apatite, and fluorspar (NAS 1971a). Fluorides are released to soils from the weathering of crustal rock and minerals, deposition of fluorides released to air from natural and anthropogenic sources, and plant and animal residues. Man-made sources applied directly to soil include phosphate fertilizers, mine tailings, and landfilled industrial and municipal waste (EPA 1980a; NAS 1971a). In a study by Oelschläger (1971), fertilization with superphosphates added 8–20 kg fluoride/hectare to the soil. 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 fluoride/g (Polomski et al. 1982).

According to the TRI, in 1999, releases of 135,000 pounds and 4.1 million pounds of hydrogen fluoride respectively to land and underground injection from 1,022 reporting facilities accounted for respectively 0.18 and 5.3% of total environmental releases of this substances (TRI99 2001). Table 6-1 lists amounts of hydrogen fluoride released to land and underground injection from these facilities grouped by state. According to the TRI, in 1999, 105,000 pounds of fluorine were released to land from 16 reporting facilities accounted for 43% of the total environmental releases of this substances (TRI99 2001). However, it is not clear how a gaseous substance can be released to land and this figure is likely in error. Table 6-2 lists amounts of fluorine released to air from these facilities grouped by state. The TRI data should be used with caution, however, since only certain types of facilities are required to report. This is not an exhaustive list.

Fluorides have been identified in soil and sediment samples collected at respectively 32 and 20 of the 177 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2001).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

In the atmosphere, gaseous hydrogen fluoride will be absorbed by atmospheric water (rain, clouds, fog, snow) forming an aerosol or fog of aqueous hydrofluoric acid. It will be removed from the atmosphere primarily by wet deposition (including rainout or in-cloud scavenging and washout or below-cloud scavenging). Particulate fluorides are similarly removed from the atmosphere and deposited on land or surface water by wet and dry deposition. Atmospheric precipitation weathers crustal rocks and soil, but dissolves out very little fluoride; most of the fluoride mobilized during weathering is bound to solids such as clays. Upon reaching bodies of water fluorides gravitate to the sediment (Carpenter 1969).

Most of the fluoride in the oceans are received from rivers; a lesser amount comes from atmospheric deposition. Losses occur in aerosols to the atmosphere and incorporation into the tissue of aquatic organisms. Fluorides have been shown to accumulate in some marine 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.

Fluoride is strongly retained by soil, forming complexes with soil components. Fluorides in soils are transported to surface waters through leaching or runoff of particulate-bound fluorides. Leaching removes only a small amount of fluorides from soils. Oelschläger (1971) reported that about 0.5–6.0% of the yearly increment of fluoride added to forest and agricultural areas through the application of phosphate fertilizer was lost in the leaching process. In this study, superphosphates added 8–20 kg

fluoride/hectare to the soil, while seepage water contained between 52 and 208 µg fluoride/L, depending upon soil levels of clay, lime, and fluoride.

Fluorides may be taken up from soil and accumulate in plants. They may also be deposited on above-ground surfaces of the plant. Tea plants are known to accumulate fluoride, 97% of which is accumulated in the leaves and 3% in the other parts of the plant. Fung et al. (1999) observed that the fluoride content of tea leaves were 1,000 times the soluble fluoride content of the soil and 2–7 times the total fluoride content. The amount of fluoride taken up by plants is more a function of the soil type, its pH, and calcium and phosphorous content that the total fluoride content of the soil (Brewer 1966). The addition of soluble fluoride to unlimed soil will result in increased fluoride uptake. In studies of plants grown on heavily polluted soil near aluminum smelters, uptake was via the roots and the stomata. Fluoride concentrations were much lower in the leaves than in the roots of plants, and most of the fluoride adsorbed by the roots was desorbed in water. Others have found that fluoride uptake is increased by the presence of aluminum, probably due to the uptake of aluminum–fluoride complexes. The fluoride uptake in ryegrass and clover from contaminated soil was strongly correlated with water and calcium chloride-extractable fluoride in the soil (Arnesen 1997). In this study, the fluoride content of pasture ryegrass exceeded the recommended fluoride limit only in grass grown in the most polluted soil, while that in clover exceeded this limit even in moderately polluted soil.

Fluoride accumulates primarily in the skeletal tissues of terrestrial animals that consume fluoride-containing foliage. However, milk and edible tissue from animals fed high levels of fluorides do not appear to contain elevated fluoride concentrations (NAS 1971a). Fluoride is taken up by hens and concentrate in the shell of their eggs. Hens living in the vicinity of two major coal-fired power plants had fluoride levels in egg shells of 1.75 mg/kg compared with reference means of 0.07 mg/kg, indicating significant uptake of anthropogenic fluoride (de Moraes Flores and Martins 1997).

6.3.2 Transformation and Degradation

6.3.2.1 Air

Hydrogen fluoride is the most abundant gaseous fluoride released into the atmosphere. It reacts with many materials both in vapor and in aerosols. For example, hydrogen fluoride reacts with silica, forming silicon tetrafluoride. However, no information was found on the reactions of hydrogen fluoride with common atmospheric species or estimates of its overall atmospheric half-life. The predominant mode of degradation of inorganic fluorides in the air is hydrolysis. Silicon tetrafluoride, a major industrial pollutant, reacts with water vapor in air to form hydrated silica and fluorosilicic acid. Sulfur hexa-fluoride, a gaseous dielectric for electrical and electronic equipment, reacts with water at elevated

temperatures (>850 EC) to form sulfuric acid and hydrogen fluoride (Guo et al. 2001). 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 (NAS 1971a). Fluorides emitted by industries in particulate matter are stable compounds that do not readily hydrolyze.

6.3.2.2 Water

Contrary to traditional thought, hydrogen fluoride, a very weak acid in dilute solution, is dissociated in solution, but forms tight ion pairs $F^-...H^+–OH_2$, unique to F^- which reduce the thermodynamic activity coefficient of H_3O^+ (Cotton et al. 1999). In natural water, fluoride ions form strong complexes with aluminum, and fluorine chemistry in water is largely regulated by aluminum concentration and pH. Below pH 5, fluorine is almost entirely complexed with aluminum and consequently, the concentration of free F^- is low. As the pH increases, Al-OH complexes dominate over Al-F complexes and the free F^- level increases. The dominant Al-F complex at pH<5 is AlF^{2+} (Skjelkvale 1994). In the absence of aluminum, dissolved fluorides are usually present as free F^- at neutral pH (Bell et al. 1970). As the 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. Fluorine can form stable complexes with calcium and magnesium, which are present in sea water. Using the stability constants valid for sea water, 51.0% of fluorine will be present as free F^-, 47.0% as MgF^+, and 2.0% as CaF^+ (Stumm and Morgan 1981). Calcium carbonate precipitation dominates the removal of dissolved fluoride from sea water. Fluoride is incorporated into the calcium salt structure and is removed from solution when the latter precipitates. The next most important removal mechanism is incorporation into calcium phosphates (Carpenter 1969). The residence time of dissolved fluoride in the oceans, as calculated from its sedimentation rate, is 2–3 million years (Carpenter 1969).

6.3.2.3 Sediment and Soil

Fluoride occurs in soil as a variety of minerals and complexes with aluminum, iron, and calcium. At low pH, aluminum complexes, AlF_3, AlF_2^+, AlF^{2+}, are the dominant dissolved species, and the availability of these soluble complexes increases with decreasing pH (Fung et al. 1999; Shacklette et al. 1974). This explains why more acidic soils have both higher water-soluble fluoride and higher extractable aluminum levels. While aluminum may complex with organic ligands, this does not appear to alter aluminum-fluoride complexation significantly (Ares 1990). In certain soils in which calcium is present mostly as calcium fluoride and in which there is sufficient alumina, fluoride is fixed by the formation of relatively insoluble aluminum fluorosilicate, $Al_2(SiF_6)_3$ (Brewer 1966).

6.3.2.4 Other Media

Several species of plants have the capacity to convert fluoride obtained from soil or water into carbon-fluorine compounds such as monofluoroacetic acid, ω-fluoro-oleic acid, ω-fluoropalmitic acid, and ω-fluoromyristic acid (Marais 1944; NRC Canada 1971; Ward et al. 1964). These compounds have a higher mammalian toxicity than inorganic fluoride salts.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

6.4.1 Air

The concentration of fluoride in ambient air depends on the presence of industrial sources of fluoride in the area, the distance from the sources, meteorologic conditions, and topography (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, 87% of all measurements at urban stations and 97% of all measurements at nonurban stations showed fluoride concentrations below 0.05 $\mu g/m^3$, the threshold of detectability. Only 18 measurements (0.2%) exceeded 1.00 $\mu g/m^3$; the maximum concentration was 1.89 $\mu g/m^3$ at urban locations and 0.16 $\mu g/m^3$ at nonurban locations (Yunghans and McMullen 1970). The ambient air concentration of gaseous fluoride varies from 0.01 to 1.65 $\mu g/m^3$ in Canada and the United States, approximately 75% of which exists as hydrogen fluoride (CEPA 1996).

Atmospheric hydrogen fluoride concentrations were measured at nine sites in Southern California during the last 8 months of 1986. Samples were collected every 6th day for a 24-hour sampling period. Average hydrogen fluoride concentrations ranged between 0.13 $\mu g/m^3$ (0.15 ppb) and 0.22 $\mu g/m^3$ (0.25 ppb) (Hance et al. 1997). The lowest concentration was at a remote off-shore location (San Nicolas Island). The maximum hydrogen fluoride levels at the eight on-shore sites varied from 0.34 $\mu g/m^3$ (0.38 ppb) to 1.91 $\mu g/m^3$ (2.14 ppb). Ambient hydrogen fluoride levels were fairly constant throughout the year. However there were occasional isolated peaks in the hydrogen fluoride levels. These are thought to be the result of accidental releases and although there are major refineries and chemical plants in the area that use hydrogen fluoride, it was not possible to correlate the spike in hydrogen fluoride levels with any reported accidental releases.

Atmospheric fluoride levels are often elevated near fluorine-related industrial operations. A 1976 study reported fluoride levels 1.5 km from an aluminum plant that emitted 34 kg fluoride/hour (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). An indicator of atmospheric fluoride levels is the amount of fluoride dust deposited on foliage. After an aluminum plant

began operating in 1958 in Oregon, the average fluoride content of foliage in cherry and peach trees jumped from 13 to 65 and 76 ppm, respectively. The highest average values occurred 2 years later, measuring 196 and 186 ppm, respectively (NAS 1971a). Since then, the fluoride levels in foliage dropped appreciably.

6.4.2 Water

Surface Water. Fluoride levels in water vary according to local geology and proximity to emission sources. In rivers, fluoride concentrations range from <1 to 6,500 µg/L; the average fluoride concentration is around 200 µg/L (Fleischer et al. 1974). Fluoride levels may be higher in lakes especially in saline lakes and lakes in closed basins in areas of high evaporation. The Great Salt Lake in Utah has a fluoride content of 14,000 µg/L (Fleischer et al. 1974). Lakes in East Africa where fluoride leaches from the alkalic rocks in the region contain 1,000–1,600 mg/L of fluoride. Fluoride levels in the Norwegian '1,000 lake survey' ranged from <5 to 560 µg/L with one outlier at 4,120 µg/L and a median of 37 µg/L (Skjelkvale 1994). The highest levels were found in lakes in Southern Norway that receive the greatest amounts of acid rain. Fluoride concentrations at these lakes are correlated with sulfate concentrations, an indicator of acid rain. In studies of natural water in the Rift Valley of Kenya and Tanzania, high fluoride levels in water and a high incidence of fluorosis were correlated with low levels of calcium and magnesium in the water (Gaciri and Davies 1993). Calcium carbonate entraps fluorides and removes it from solution. These results are consistent with researchers who maintain that waters low in hardness and high in alkalinity present the highest risk of fluorosis. Other reasons for high fluoride levels in some Kenyan waters are evaporative concentration resulting in much higher fluoride levels in surface water than groundwater, fluoride-rich volcanic rocks in the region, and contamination by waste water from fluorspar mining. Seawater contains more fluoride than fresh water, approximately 1,200–1,500 µg/L (Bowen 1966; Carpenter 1969; Fleischer et al. 1974; Goldschmidt 1954).

Groundwater. The fluoride content of groundwater generally ranges from 20 to 1,500 µg/L (EPA 1980a; Fleischer 1962). Fleischer et al. (1974) contains a map of the fluoride content in groundwater in the conterminous United States by county. Highest fluoride levels in groundwater are generally found in the southwest, and maximum groundwater levels in Nevada, southern California, Utah, New Mexico, and western Texas exceed 1,500 µg/L. In a survey of fluoride levels in Texas groundwater in which water from nearly 7,000 wells in 237 counties were analyzed, Hudak (1999) identified four regions with high fluoride levels. In one region in northwest Texas, at least 50% of the wells sampled in each of five counties had fluoride levels exceeding the primary drinking water standard of 4,000 µg/L. County-median fluoride concentrations ranged from 90 to 5,110 µg/L. Twenty-five counties had median fluoride levels above the secondary standard of 2,000 µg/L and 84 counties had median concentrations higher than 1,000 µg/L, the target fluoride concentration for many water fluoridation programs. Factors responsible

for the elevated fluoride levels were the mineral constitution of the aquifers, seepage from nearby saline formations, and low recharge and dilution rates in the aquifers. Groundwater constitutes approximately 60% of the water consumed in Texas.

Fluoride levels in groundwater are higher than in surface water because they are more influenced by the rocks in which they occur (EPA 1980a; Fleischer et al. 1974; NAS 1971a; WHO 1984). Groundwater from granitic rock, basaltic rock, limestones and dolomites, and shales and clays average 1,200, 100, 300, and 400 µg fluoride/L, respectively, while groundwater from alkalic rocks average 8,700 µg fluoride/L (Fleischer et al. 1974). An example of the influence of geology on the concentration of fluorides in groundwater is illustrated by a region in the Pampa in Argentina where groundwater is alkaline and moderately saline (Nicolli et al. 1989). Forty-two percent of groundwater samples from this area had fluoride levels exceeding 1,400 µg/L and the maximum level was 6,300 µg/L. The highest levels of fluoride were found in waters with the highest sodium and potassium contents.

Drinking Water. The concentration of fluoride in 384 Norwegian waterworks sampled during the winter of 1983 ranged from 13 to 1,210 µg/L with a mean and median of 87 and 58 µg/L, respectively (Flaten 1991). Fluoride is a naturally-occurring constituent of groundwater and the fluoride in the water was mostly a consequence of local soil or rock formations. In addition, there was evidence that the fluoride levels were influenced by local sources and long-range transport. In a random survey of farmstead wells by the Kansas Department of Health and Environment, 2 of the 103 wells sampled contained fluoride levels above EPA's maximum contaminant level (MCL), of 1,800 µg/L for public water supplies (Steichen et al. 1988). The highest fluoride level found was 2,300 µg/L.

Rainwater. Rain water sampling was conducted in eight arctic catchments in Northern Europe from May to September in 1994 (Reimann et al. 1997). Some of the world's largest industrial sources are in this region. The median concentrations of fluoride in all of the 30-day composite rain water samples from the eight catchments were <0.05 mg/L. In five of the catchments, all samples contained <0.05 mg/L of fluoride. The maximum concentration of fluoride was 1.53 mg/L. Concentrations of fluoride in precipitation in Norway ranged from 0 to 253 µg/L with volume-weighted averages from 13 to 25 µg/L (Skjelkvale 1994). Correlations of fluoride content with other ions, indicated that the fluoride is not of marine origin and is mostly correlated with industrial sources of sulfur oxides. Higher fluoride levels in some rain samples were due to nearby aluminum smelters.

6.4.3 Sediment and Soil

Fluorides are widely distributed in the earth's crust. The concentration of fluoride in soils and other surficial materials in the conterminous United States ranges from <10 to 3,700 ppm with a mean of 430 ppm (Shacklette and Boerngen 1984). Other values for the mean fluoride content of mineral soils ranges from 200 to 300 ppm (Bowen 1966; NAS 1971a; Worl et al. 1973). The fluoride content of organic soils is usually lower. 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). In most soils, fluorine is associated with micas and other clay minerals. Robinson and Edgington (1946) reported the fluorine content of 137 soil samples in 30 soil profiles as ranging from trace to 7.07% fluorine, with an average of 0.029%. While the highest fluoride concentration was found in a Tennessee soil high in rock phosphate (apatite), the main source of fluoride in the soil were micaceous clays. In general, silt and clay loam soils had a higher fluoride content than sandy soils. Average fluoride soil 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).

The fluoride content of soil may be increased by the addition of fluoride-containing phosphate fertilizers (WHO 1984). 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). Humus near an elementary phosphorus plant in Newfoundland, Canada, where 80–95% of balsam fir trees were dead because of the pollution, contained average fluoride levels of 58 ppm dry weight in 1973 and 24.2 ppm in 1974 (Sauriol and Gautier 1984). In 1975, when the plant was not in operation during the growing season, the humus fluoride content was 8.1 ppm. Humus fluoride levels in an uncontaminated zone was 2.0 ppm.

The fluoride concentrations in recent oceanic sediments appear to vary between 450 and 1,100 ppm (Carpenter 1969). Similar levels have been reported for fresh water lakes.

6.4.4 Other Environmental Media

Several factors influence the level of fluorides in food. These include the locality in which the food is grown and whether there were sources of fluoride emissions in the area, 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 fish and 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 fluoride/cup (Cook 1969; Kumpulainen and Koivistoinen 1977).

During a comprehensive total diet study, foods were collected in Winnipeg, Canada in 1987 and were processed into 148 composite food samples (Dabeka and McKenzie 1995). The mean, median, and range of fluoride in all samples were 325, 99, and <11–4,970 ng/g, respectively. Food categories with the highest mean fluoride levels were fish (2,118 ng/g), beverages (1,148 ng/g), and soups (606 ng/g). Individual samples with the highest fluoride levels were tea (4,970 ng/g), canned fish (4,570 ng/g), shellfish (3,360 ng/g), cooked veal (1,230 ng/g), and cooked wheat cereal (1,020 ng/g). The drinking water used to prepare the food came from a single source containing the optimal fluoride concentration of 1 mg/L. This fluoride would contribute substantially to the fluoride levels in the food. The fluoride level in 68 samples of cows' milk purchase in retail stores throughout Canada ranged from 7 to 86 ng/g, with a mean and median concentration of 41 and 40 ng/g, respectively (Dabeka and McKenzie 1987). Provincial mean levels varied from 25 to 74 ng/g. Other studies of fluoride levels in cows from uncontaminated areas reported similar fluoride levels in milk (Dabeka and McKenzie 1987).

Beverages may contain fluoride from the fluoride content of the water used in their production, as well as the base ingredients (e.g., fruit, flavoring) in the product. In a North Carolina study, beverages purchased from six regions of the state showed considerable differences in the fluoride content of the product. This was especially true for carbonated beverages. The range (mean) of fluoride concentrations in various beverage types were: sodas, 0.07–1.37 ppm (0.28 ppm); juices, 0.01–1.70 ppm (0.36 ppm); punches, 0.00–1.44 ppm (0.33 ppm); tea, 0.61–6.68 ppm (2.56 ppm); and gaterade, 0.02–1.04 ppm (0.85 ppm) (Pang et al. 1992).

The fluoride content of most plant foliage growing in areas removed from sources of fluoride pollution ranges from 2 to 20 ppm dry weight (Brewer 1966). A notable exception if tea plants. The highest fluoride concentrations reported in vegetation was over 8,000 ppm in tea leaves. Tea plants take up fluoride from soil and accumulate it in the leaves. A large percentage of the total fluoride, 25–84%, is released during infusion, and tea is considered to be a major source of fluoride. The older tea leaves contain more fluoride and brick tea, which is prepared from older leaves, may be very high in fluoride

content, 4.73–7.34 mg/L compared with quality green and black tea, which is prepared from younger leaves and may contain 1.2–1.7 and 0.9–1.9 mg/L, respectively (Fung et al. 1999).

Fruits and vegetables grown in industrial areas where fluoride emissions are high contain elevated fluoride levels compared with those grown in control areas. The highest levels are found in the leafy parts of the plants rather than the roots. In a Polish study, vegetables grown 1.5 and 5 km from a steel plant contained average fluoride levels of 0.54–8.82 and 0.39–4.95 mg/kg, respectively, compared with 0.02–0.41 mg/kg for controls (Krelowska-Kulas 1994). Fruits grown 1.5 and 5 km from the steel plant contained average fluoride levels of 1.42–5.44 and 1.24–2.75 mg/kg, respectively, compared with 0.40–1.05 mg/kg for controls. Vegetables from the Saint-Régis Mohawk Indian reservation contained an average of 1.54–45.17 ppm fluoride dry weight compared with 0.63–11.3 ppm fluoride for vegetables from an uncontaminated site (Sauriol and Gauthier 1984). The reservation is located along the St. Lawrence River, straddling territory in New York State, Québec, and Ontario, where there are three potential sources of industrial fluoride emissions, namely two aluminum plants and a phosphate fertilizer plant.

The fluoride concentration in most dental products available in the United States ranges from 230 ppm (0.05% NaF mouth rinse) to 12,000 ppm (1.23% acidulated phosphate fluoride gel) (NRC 1993). The most commonly used dental products, toothpastes, contain 900–1,100 ppm fluoride (ca. 0.10%), most often as sodium fluoride, but also as disodium monophosphate.

The fluoride concentration of a bituminous coal used in power generation is around 65.0 ppm dry weight and may contain up to 200 mg fluoride/kg (Rubin 1999; Skjelkvale 1994). The fluoride in the coal occurs predominantly as fluorapatite and fluorspar. Hydrogen fluoride and other fluorides are released from the coal during combustion. Bauer and Andren (1985) studied fluoride emissions from an electricity-generating plant in Portage, Wisconsin that consisted of two nearly-identical 527-MW pulverized-coal units, differing only in the type of coal burned and the operating conditions. In one unit, emissions contained a median of 1.9 mg fluoride/scm (86% of available fluoride in coal) and the other contained a median of 0.22 mg fluoride/scm (4.2% of available fluoride in coal). The first unit burned a bituminous coal from Colstrip, Montana containing 9% ash and 46 ppm fluoride and the second unit burned a bituminous coal from Gillette, Wyoming containing 5% ash and 45 ppm fluoride. It was thought that the greater mineral matter in the coal feeding the first unit may have played a role in the greater release of fluoride in the vapor phase from this unit. The concentration of hydrogen fluoride reported in emissions from a modern municipal waste incinerator in Germany was 0.2–0.3 mg/m^3 (Greim 1990).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The major sources of fluoride intake by the general population are water, beverages, food, and fluorine-containing dental products. 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. Hodge and Smith (1977) estimated air intake of fluoride of about 0.01 mg/day. In occupational settings where airborne concentrations are frequently at the exposure limit of 2.5 mg/m^3, fluoride intake via inhalation can be 25 mg/day (OSHA 1985). The daily intake of fluoride from drinking water fluoridated at the optimal levels (0.7–1.2 mg/L) would be 1.4–2.4 mg.

Based on a comprehensive total diet study conducted in Winnipeg, Canada in 1987, the estimated daily dietary intake of fluoride by the average Canadian was 1,763 µg and varied from 353 µg for the 1–4 year-old-age group to 3,032 µg for 40–64-year-old males (Dabeka and McKenzie 1995). The results for all age groups are shown in Table 6-3. The drinking water used to prepare the food came from a single source containing the optimal fluoride concentration of 1 µg/mL (1 mg/L). This fluoride would contribute substantially to the fluoride intake in the food. In an earlier study in which the dietary intake of 24 adult Canadians was assessed, Dabeka et al. (1987) compared the intake of half of the participants who lived in communities with 1 µg/g (1 mg/L) fluoride in their drinking water with those that lived in communities with <0.2 µg/g (<0.2 mg/L)of fluoride in water. The respective median intakes of fluoride were 2,090 or 30.3 µg/kg/day and 414 or 7.0 µg/kg/day. For the cities with fluoridated water, the majority of fluoride was contributed by beverages (68%) and water (13%); for the nonfluoridated cites, beverages contributed 58% of the fluoride intake. These results can be compared with earlier estimates of fluoride intake by U.S. adults. San Filippo and Battistone (1971) estimated the average daily adult fluoride intake from food ranged from 0.8 to 0.9 mg, while the daily intake from food and water was 2.1–2.4 mg. Spencer et al. (1970) estimated the fluoride intake as 1.2–2.7 mg/day from food and 2.82–5.9 mg/day from food and water. Kumpulainen and Koivistoinen (1977) reported the average total dietary intake in 12 fluoridated U.S. cities as 2.7 mg/day. 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). However, there are exceptions, such as an area in China where the fluoride content of the water is low, but the intake from food and tea is high enough that the rate of dental fluorosis exceeds 80% (Han et al. 1995). 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 areas near sources of fluoride emissions, oral intake may also be increased from dust contamination of food (WHO 1984). Fluoridated dentifrices and mouth rinses are additional sources of fluoride (Barnhart et al. 1974; Ericsson and Forsman 1969). Fluorides approved by the FDA for use in dentifrices are sodium fluoride (0.22%), sodium monofluorophosphate (0.76%), and stannous fluoride (0.41%) (Pader 1993). The concentration of fluoride in each of these formulations is 0.1% (equivalent to 1,000 mg/kg or 1,000 ppm). Fluoride

Table 6-3. Mean Daily Dietary Intake of Fluoride for Selected Canadian Population Groups[a]

Population	Mean daily intake (µg/day)
1–4 years, males and females	353
5–11 years, males and females	530
12–19 years, males and females	1,025
12–19 years, females	905
20–39 years, males	2,544
20–39 years, females	2,172
40–65 years, males	3,032
40–65 years, females	2,615
65+ years, males	2,588
65+ years, females	2,405
All ages male and female	1,763

[a]Dabeka and McKenzie 1995

tablets or drops are ingested in some areas where water fluoride levels are low, providing 0.25, 0.50, or 1.00 mg/day depending on the age of the child and the drinking water fluoride concentration. In his analysis of systemic fluoride intake, Burt (1992) found that there is no evidence from dietary surveys to show that fluoride intake in adults has increased since the 1970s.

In considering dietary intake, it is important to take bioavailability into account, and not simply the fluoride content of the consumed substance. 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). The bioavailability of fluoride as sodium fluoride is high. In contrast, absorption of calcium fluoride is rather inefficient, but is enhanced when administered with food. Thus, the actual absorbed dose could be smaller than the intake levels reported above. NRC (1993) reports that approximately 75–90% of ingested fluoride is absorbed from the alimentary tract.

The fluoride content of urine and plasma are useful as short-term indicators of fluoride exposure; hair, fingernails, and tooth enamel are indicators of longer-term response. The mean and median serum fluoride levels of 168 representative Danish adults were 470±270 and 400 nmol/L, respectively (Poulsen et al. 1994). Levels were significantly higher in urban inhabitants than rural inhabitants and increased significantly with age. Shida et al. (1986) measured fluoride concentrations in five different layers of enamel of incisors that had been extracted due to periodontal disease. Half of the teeth were treated with 0.9% acidified fluoriphosphate for 4 minutes. In the fluoride-treated group, the outer layer of enamel contained 1,660–5,910 ppm fluoride compared with 147–698 ppm in the untreated group. 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 among individuals.

The NIOSH National Occupational Exposure Survey (NOES) conducted in 1981–1983 estimated that about 182,589 workers were potentially exposed to hydrogen fluoride (NIOSH 1989). The NOES was based on field surveys of 4,490 facilities that included virtually all workplace environments, except mining and agriculture, where eight or more persons are employed. The principal exposure pathway would be inhalation.

Workers in the electronics industry in Japan who used hydrogen fluoride for glass etching (e.g., TV picture tubes) and as a silicon cleaner (e.g., semiconductors) are exposed daily to mean air hydrogen fluoride concentrations of up to 5 ppm (Kono et al. 1987). The mean urinary fluoride levels were linearly related to the hydrogen fluoride concentration in the air and there were also significant differences in pre- and postshift urinary fluoride level of the workers. The workers in this study were only exposed to gaseous hydrogen fluoride. The wide variation of fluoride levels in serum and urine in the workers and

controls has been ascribed to dietary differences, particularly the consumption of tea and seafood (water fluoridation is not practiced in Japan). In a followup, study Kono et al. (1993) found a linear correlation between urine fluoride levels and hair fluoride levels.

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7 Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Children are exposed to fluorides primarily through their diets. Normal dietary sources of fluorides are augmented by fluoridation of water supplies. Based on data obtained from a 1987 total diet study in Winnipeg, Canada, the average 1–4 and 5–11 year olds consume 353 and 530 µg fluoride/day, respectively, compared with 1,763 µg/day for all age groups combined (Dabeka and McKenzie 1995). The mean daily dietary intakes of fluoride by 6-month-old infants and 2-year-old children in four regions of the United States were 0.21–0.54 and 0.32–0.61 mg/day (NRC 1993; Ophaug et al. 1985). The mean intake of 2-year-old children, but not 6-month-old infants, was directly related to the fluoride concentration in the drinking water. Dietary intake may increase in areas where there are industrial emissions containing fluorides. Increased incidences of mottled teeth were observed in children living within 3 km of a superphosphate fertilizer plant in Port Maitland, Ontario (Sauriol and Gauthier 1984). The most plausible reason for the increased fluoride intake is higher fluoride levels in vegetables and fruits from dust deposited on the plants.

It has been assumed that children in communities without fluoridated water consume a negligible amount of fluoride other than from food. Because of the marked increase in dental fluorosis in nonfluoridated populations and the increased consumption of beverages that may have been prepared with fluoridated water, a study was conducted to estimate the average daily amount of fluoride ingested by a sample of North Carolinian children aged 2–10 from these beverages (Pang et al. 1992). The study found that children of ages 2–3, 4–6, and 7–10 consumed daily means of 0.36, 0.54, and 0.6 mg fluoride,

respectively, from beverages. This is a significant source of fluoride intake. Beverages contributed about 60% of the children's total liquid consumption. While fluoride consumption increased with age, little difference was found between males and females. Children in a high fluoride area of Kenya consume high levels of fluoride from the water (9 µg/g) and from the practice of giving tea to young children. In this area, children aged 0–1 and 1–4 years old had mean daily fluoride intakes of 0.62 and 1.23 mg/kg body weight, respectively (Opinya et al. 1991a). Tea accounted for nearly half of the fluoride intake of 1–2-year-old children. The daily fluoride consumption from breast milk supplements and substitutes averaged 7.6 mg, >250 times the amount of fluoride provided by 800 mL of breast milk.

Fluoride intake in infants depends on whether the child is nursed or not. Human breast milk contains very little fluoride (about 0.5 µmol/L) and provides <0.01 mg fluoride/day (NRC 1993). The results of a survey of fluoride levels in 68 samples of cows' milk and 115 samples of infant formulas and oral electrolytes is shown in Table 6-4. Mean fluoride levels in cows' milk, evaporated milk, and ready-to-use formula were 0.041, 0.23, and 0.79 µg/g, respectively. Mean levels in concentrated liquid and powder formula were 0.60 and 1.13 µg/g, respectively (Dabeka and McKenzie 1987). A major source of fluoride in the infant formulas appears to be the processing water used in its manufacture. In the United States where manufacturers remove fluoride from the processing water, mean levels of fluoride were much lower than in the Canadian products. All U.S. products were well within the upper guideline of 0.40 µg/g for ready-to-use formula proposed by the Committee on Nutrition of the American Academy of Pediatrics. Fluorinated organic chemicals are widely used and may accumulate in breast milk due to their high fat solubility and slow rate of metabolism and excretion. The breast milk fluoride concentration from a German study was 25 ppb (Broomhall and Kovar 1986).

Levy et al. (2001) found that for most children, water fluoride intake was the predominant source of fluoride, especially through age 12 months. This was due in large part to children receiving fluoridated water mixed with infant formula concentrate (Levy et al. 1995b, 2001).

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 were 0.30, 0.13, and 0.07 g (Barnhart et al. 1974). Average fluoride intake from these sources in children younger than 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). Other studies indicated that an average of 25% (range, 10–100%) of the toothpaste introduced into the mouth was swallowed. The average amount of fluoride in toothpaste used in one brushing is about 1.0 mg. From these studies, it has been estimated that the amount of fluoride ingested in toothpaste by children who live in communities with fluoridated water, who have good control of swallowing, and brush their teeth twice a day is

Table 6-4. Comparison of Fluoride Levels (µg/g) in Cow Milk and Infant Formulas[a]

	Number	Mean	Median	Range[a]
Cow milk	64	0.041	0.040	0.007–0.086
Evaporated milk	9	0.23	0.12	0.06–0.55
Ready-to-use formula, all				
Canadian	34	0.90	0.86	0.35–2.31
U.S.	7	0.23	0.26	0.15–0.28
Ready-to-use formula, glass[b]				
Canadian	20	0.82	0.83	0.46–1.13
U.S.	3	0.28	0.28	0.28–0.28
Ready-to-use formula, canned				
Canadian	14	1.02	0.95	0.35–2.31
U.S.	4	0.19	0.17	0.15–0.26
Concentrated liquid formula, canned	33	0.60	0.60	0.15–1.47
Formula, powdered concentrate	18	1.13	0.80	0.14–5.53
Electrolytes (water), glass[b]	12	0.066	0.04	0.01–0.15

[a]Dabeka and McKenzie 1995
[b]Product not available on retail market, obtained from hospitals.

is approximately equal to dietary fluoride intakes. For younger children who have poor control of swallowing, intakes from dental products could exceed dietary intakes.

Although Burt (1992) concludes that data on fluoride intake by children from food and beverages, infant foods included, are not strong enough to conclude that an increase in fluoride ingestion has occurred since the 1970s, he warns that the suggested upper limit of fluoride intake is substantially being reached by many children by ingestion of fluoride from food and drink (0.2–0.3 mg/day) and from fluoride toothpaste (0.2–0.3 mg/day). Levy (1994) also found substantial variation in ingestion among individuals; 10–20% of individuals received up to several times as much exposure as the mean. Some children appeared to ingest enough fluoride from one source to exceed the total recommended fluoride intake, and are therefore at increased risk of fluorosis. Levy et al. (1995a) made the following recommendations concerning use of fluoride by children:

> "(1) the fluoride content of foods and beverages, particularly infant formulas and water used in their reconstitution, should continue to be monitored closely in an effort to limit excessive fluoride intake; (2) ingestion of fluoride from dentifrice by young children should be controlled, and the use of only small quantities of dentifrice by young children should be emphasized; and (3) dietary fluoride supplements should be considered a targeted preventive regimen only for those children at higher risk for dental caries and with low levels of ingested fluoride from other sources (Levy et al. 1995a)."

Schamschula et al. (1985) analyzed various body fluids and tissue from a group of Hungarian children exposed to low, intermediate, and high levels of fluoride in their drinking water. These tissue levels, included in Table 6-5, are indicators of exposure over the short and long term. Fluoride dentifrices were not in general use in the villages from which the sample populations were drawn.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Populations living in areas with high fluoride levels in groundwater may be exposed to higher levels of fluorides in their drinking water or in beverages prepared with the water. Among these populations, outdoor laborers, people living in hot climates, and people with polydipsia will generally have the greatest daily intake of fluorides because they consume greater amounts of water. Groundwater fluoride levels are especially high in the southwest; maximum groundwater levels in Nevada, southern California, Utah, New Mexico, and western Texas exceed 1,500 µg/L. In one region of northwest Texas, the median level in well water exceeded 4,000 µg/L. People who drink large amounts of tea or consume large quantities of seafood, may also have high intakes of fluoride.

Table 6-5. Levels of Fluoride in Human Tissue and Urine—Selected Studies

Site	Population	Sample	Concentration	Type	Units	Reference
Poland (1980)	Employee of electrolysis shop of aluminum plant	urine, random	1.87		mg/dm^3	Miszke et al. 1984
HF workers in the electronics industry, Japan						Kono et al. 1987
	Unexposed controls (n=82)	urine, random	0.58 (0.23)	Geometric mean (GSD)	ppm	
	All workers (n=142)		2.34 (1.40)			
	Hydrogen fluoride exposure level					
	0.3 ppm (n=16)		0.91 (0.26)			
	0.5 ppm (n=20)		1.04 (0.34)			
	0.6 ppm (n=12)		1.07 (0.41)			
	1.2 ppm (n=14)		2.02 (0.57)			
	1.6 ppm (n=17)		2.40 (0.68)			
	2.8 ppm (n=21)		3.94 (1.07)			
	4.2 ppm (n=32)		5.05 (1.30)			
	5.0 ppm (n=10)		6.50 (1.98)			
HF workers in the electronics industry, Japan						Kono et al. 1993
	All hydrogen fluoride workers (n=142)	hair	61.1 (101.6)	Geometric mean (GSD)	µg/g	
	Controls (n=237)		13.4 (6.4)			

Table 6-5. Levels of Fluoride in Human Tissue and Urine—Selected Studies *(continued)*

Site	Population	Sample	Concentration	Type	Units	Reference
HF workers, Japan						Kono et al. 1984
	Hydrogen fluoride workers (n=120)	serum	40.10 (23.72)	Mean (SD)	µg/L	
	Controls (n=320)		24.50 (12.10)			
	Hydrogen fluoride workers (n=120)	urine, 24 hour	0.98 (0.75)	Mean (SD)	mg/L	
	Controls (n=320)		0.54 (0.30)			
Danish adults	Representative population (n=168)	serum	470 (270)	Mean (SD)	nmol/L	Poulsen et al. 1994
Hungarian children exposed to three levels of fluoride in drinking water						Schamschula et al. 1985
	Low exposure[a] (n=45)	urine	0.15 (0.07)	Mean (SD)	ppm	
	Medium exposure[b] (n=53)		0.62 (0.26)			
	High exposure[c] (n=41)		1.24 (0.52)			
	Low exposure[a] (n=45)	nails	0.79 (0.26)	Mean (SD)	ppm	
	Medium exposure[b] (n=53)		1.31 (0.49)			
	High exposure[c] (n=41)		2.31 (1.14)			
	Low exposure[a] (n=45)	hair	0.18 (0.07)	Mean (SD)	ppm	
	Medium exposure[b] (n=53)		0.23 (0.11)			
	High exposure[c] (n=41)		0.40 (0.25)			
	Low exposure[a] (n=45)	saliva	6.25 (2.44)	Mean (SD)	ppb	
	Medium exposure[b] (n=53)		11.23 (4.29)			
	High exposure[c] (n=41)		15.87 (6.01)			

Table 6-5. Levels of Fluoride in Human Tissue and Urine—Selected Studies *(continued)*

Site	Population	Sample	Concentration	Type	Units	Reference
	Low exposure[a] (n=45)	enamel (0.44–0.48 µm depth)	1,549 (728)	Mean (SD)	ppm	
	Medium exposure[b] (n=53)		2,511 (1,044)			
	High exposure[c] (n=41)		3,792 (1,362)			
	Low exposure[a] (n=45)	enamel (2.44–2.55 µm depth)	641 (336)	Mean (SD)	ppm	
	Medium exposure[b] (n=53)		1,435 (502)			
	High exposure[c] (n=41)		2,107 (741)			

[a]Low exposure: concentration of fluoride in water 0.06–0.11 ppm, 0.09 ppm, mean.

[b]Medium exposure: concentration of fluoride in water 0.5–1.1 ppm, 0.82 ppm, mean.

[c]High exposure: concentration of fluoride in water 1.6–3.1 ppm, 1.91 ppm, mean.
GSD = geometric standard deviation; SD = standard deviation

Populations living downwind of facilities emitting high levels of fluorides (e.g., phosphate fertilizer plants, aluminum plants, or coal-fired power plants) may be exposed to higher fluoride levels in the air (Ernst et al. 1986). Emissions from these plants may contaminate vegetables and fruit with fluorides from industrial emissions, exposing people eating local produce to potentially high levels of fluorides in their diets. Workers in industries where fluoride-containing substances are used, most notably the aluminum and phosphate fertilizer plants, may be occupationally exposed to high levels of both gaseous and particulate fluorides. Workers using sulfur hexafluoride as a tracer gas for determining ventillation rates and air flow in buildings may be exposed to hydrogen fluoride when unvented combustion sources are present in the building because SF_6 reacts with water vapor at high temperatures, forming hydrogen fluoride (Guo et al. 2001).

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 may 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.

6.8 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 National Toxicology Program (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 the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical/chemical properties of fluorine, hydrogen fluoride, and sodium fluoride are sufficiently well characterized to enable assessment of the environmental fate of these compounds.

Production, Import/Export, Use, Release, and Disposal. Information on the production and importation of fluorspar and hydrogen fluoride are available (CMR 1999; USGS 2001). Information on exports is only available for fluorspar. No data are available on the production, import, or export of fluorine, sodium fluoride, and other fluorides. Information is readily available on the uses of fluorine, hydrogen fluoride, and other fluorides (Mueller 1994). Because of its high reactivity, fluorine is disposed of by conversion to fluoride salts in a scrubber (Shia 1994). The TRI contains information on the amounts of hydrogen fluoride transferred off-site, presumably for disposal, and the amount recycled. No information was found regarding the disposal of sodium fluoride. Additional quantitative information on production, import, and export of fluorides, as well as 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 TRI, which contains this information for 1999, became available in April of 2001. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. Upon release to the atmosphere, fluorine gas will readily react to form hydrogen fluoride. Both hydrogen fluoride and particulate fluorides will be transported in the atmosphere and deposited on land or water by wet and dry deposition. Fluorides undergo transformations in soil and water, forming complexes and binding strongly to soil and sediment (NAS 1971a; WHO 1984). 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.

Bioavailability from Environmental Media. Fluorides are absorbed by humans following inhalation of workplace and 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 (Browne 1974; Buckingham 1988). 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). However, accumulation is primarily in skeletal tissue and therefore, it is unlikely that fluoride will biomagnify up the food chain.

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; Hudak 1999; Waldbott 1963b). However, the existing monitoring data are not current. Air concentrations are expected to be different today in view of changes in industries and the wider use of pollution control devises. Groundwater contains higher fluoride levels than surface water. Although Fleischer (1962) mapped the levels of fluoride in groundwater in the United States and these levels would not be expected to change, it would be useful to survey the concentration of fluoride in groundwater used for drinking. This is particularly important in areas where groundwater has a high fluoride content as in northwest Texas where 50% of the well water in some counties exceed 4 µg/L (Hudak 1999). The fluoride level in food depends on the locality in which the food is grown, including the geology, potential sources of fluorine emissions in the area, 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 include tea, seafood, and bone products such as bone meal and gelatin (Cook 1969; Kumpulainen and Koivistoinen 1977). Old 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). Recent data are available on the concentration of fluoride in different foods in Canada and the daily dietary intakes for different Canadian age groups (Dabeka and McKenzie 1995). However, recent analogous information is not available for the United States. Up-to-date data on concentrations of fluoride in food items and the dietary intake of fluorides in the United States is important in view of the changes in fluoride emissions and the effect that the use of fluoridated water or water with a high natural fluoride content may have on the fluoride levels in processed food and beverages (Pang et al. 1992).

Fluorides have also been detected in a limited number of surface water, groundwater, and soil samples taken at hazardous waste sites (HazDat 2001; Van Hook 1974). Additional information is needed on concentrations in ambient air, surface water, groundwater, and soils at these 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.

Exposures of Children. Children are exposed to fluorides primarily through their diets and the use of dental products, particularly toothpaste. Normal dietary sources of fluorides are augmented by fluoridation of water supplies. Human breast milk contains very little fluoride (NRC 1993). Information is available on the levels of fluoride in infant formula in Canada and results show that major source of fluoride appears to be the processing water used in its manufacture (Dabeka and McKenzie 1987). In the United States, manufacturers remove fluoride from the processing water and thus, fluoride levels in infant formulas are much lower. The mean dietary intake of fluoride by infants and children is available for Winnipeg, Canada and four regions of the United States (Dabeka and McKenzie 1995; NRC 1993). The mean daily dietary intakes fluoride by 6-month-old infants and 2-year-old children in four regions of the United States were 0.21–0.54 and 0.32–0.61 mg/day. The mean intakes of 2 year olds, but not 6 month olds, was directly related to the fluoride concentration in the drinking water. Pang et al. (1992) noted that children obtain a sizeable amount of fluoride from beverages. Since beverages may not be prepared with water from the local community and beverages constitute 60% of children's total liquid consumption, more information on the fluoride content of beverages would be useful in estimating children's dietary intake of fluoride. Intake of fluoride by children from fluoridated dentifrices and mouth rinses have been estimated (Barnhart et al. 1974; Ericsson and Forsman 1969). For younger children who have poor control of swallowing, intakes from dental products could exceed dietary intakes.

Fluoride exposure in communities near mining and other industrial facilities where fluoride-containing rock or minerals are processed are a public health concern, especially for infants and children. The same is true for hazardous waste sites containing fluoride waste. Since fluoride remains in the surface soil indefinitely and long past land uses may be forgotten, people may not realize that they are living in areas where high levels of fluoride may occur in soil. Contaminated soils pose a particular hazard to children because of both hand-to-mouth behavior and intentional ingestion of soil (pica) that contains fluorides and other contaminants. In these communities, fluorides may have been tracked in from outdoors and contaminate carpeting. Fluoride-containing dust may be brought home in the clothing of parents working

in industries where they are exposed to fluoride. Children may be exposed to this fluoride while crawling around or playing on contaminated carpeting. Exposure may also result from dermal contact with soil, or by inhaling dust and then swallowing it after mucociliary transport up out of the lungs. Because much of the fluoride in soil is embedded in or strongly adsorbed to soil particles or insoluble, it may not be in a form accessible for uptake by the body.

Child health data needs relating to susceptibility are discussed in Section 3.12.2 Identification of Data Needs: Children's Susceptibility.

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.

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2001) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1.

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.

J.G. Schumacher of USGS, Water Resources Division, Weldon Spring, Missouri, is doing research sponsored by USGS to determine the geochemical controls on contaminant migration from the raffinate pits, Weldon Spring chemical plant, St. Charles County, Missouri. The former U.S. army facility processed uranium ore-concentrates and scrap into uranium trioxide, uranium tetrafluoride, and uranium metal. Waste from these operations (referred to as raffinate) were pumped into four large pits that contain various quantities of uranium, thorium, nitrate, sulfate, fluoride, magnesium, and other elements. The raffinate pits have been determined to be leaking and Li, U, NO_3, and SO_4, and various trace elements have been found in groundwater and surface water both on and off site.

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

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring fluorides, its metabolites, and other biomarkers of exposure and effect to fluorides. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations 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 modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

Fluorine gas is too reactive to exist in biological or environmental samples. Indeed, fluorine is too reactive to be analyzed directly by conventional methods, but rather is quantitatively converted to chlorine gas and the latter is analyzed (Shia 1994). The methods discussed below are for the analysis of the fluoride ion, or in the case of gaseous acid fluorides, hydrogen fluoride. The particular fluorine molecule is rarely identified.

7.1 BIOLOGICAL MATERIALS

Trace levels of fluoride in biological media are determined primarily by potentiometric (ion selective electrode [ISE]) and gas chromatographic (GC) methods. Colorimetric methods are available, but are more time consuming and lack the sensitivity of the other methods (Kakabadse et al. 1971; Venkateswarlu et al. 1971). Other methods that have been used include fluorometric, enzymatic, and proton activation analysis (Rudolph et al. 1973). The latter technique is sensitive to trace amounts of sample and requires minimal sample preparation. Urine and blood and other bodily fluids can be analyzed with a minimum of sample preparation. Tissue will require ashing, digestion with acid, or even fusion with alkali to free the fluoride from its matrix. During sample preparation, the analyst must be careful to avoid sample contamination, incomplete release from matrices, and losses due to volatilization (NRC Canada 1971). Table 7-1 describes some analytical methods for determining fluorides in biological materials.

There is extensive literature on the ISE methodology because it is the most frequently used method for fluoride measurement in biological media. The fluoride ion selective membrane utilizes a membrane consisting of a slice of a single crystal of lanthanum fluoride that has been doped with europium (II) fluoride to improve its conductivity (Skoog et al. 1990). It has a theoretical response to changes in

Table 7-1. 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)	GC	4 µg/L	935	Chiba et al. 1982
	Add equal volume TISAB solution.	ISE, NIOSH 8308	0.1 mg/L	95%	NIOSH 1994
	Add TMCS toluene solution; centrifuge; inject toluene layer	GC	>5 ng/mL	No data	Ikenishi et al. 1988
Biological fluids and tissue extracts (ionic and ionizable fluoride)	Absorb with calcium phosphate; centrifuge; analyze	ISE	10 µg/L	92–102%	Venkateswarlu et al. 1971
Saliva	Resuspend in TISAB buffer; analyze	ISE	No data	99.8%	Peterson et al. 1987; Schamschula et al. 1985
Biological fluids	Add TMCS toluene solution; centrifuge; inject toluene layer and analyze by measuring TMFS peak height	GC	5 ng/L	88.1–97.2%	Ikenishi et al. 1988
Biological tissues and fluids	Extraction from acidified sample as fluorosilane; reverse extraction as fluoride ion into alkaline solution	ISE with hanging drop assembly	>0.04 ng/sample	No data	Venkateswarlu 1974
Biological tissues	Sample pulverized to fine powder; irradiate with energetic beam of protons; detect gamma rays emitted	PAA	<10 ng/sample	No data	Rudolph et al. 1973
	Decomposition of sample at 700–1,000 EC (pyrohydrolytic technique)	Colorimetry	1 µg/sample	No data	Kakabadse et al. 1971
Tooth enamel	Soak teeth; decalcify in $HClO_4$; add TISAB; analyze	ISE	No data	No data	Schamschula et al. 1982; Shida et al. 1986
Plaque	Dried; microdiffusion; analyze	ISE	No data	97%	Schamschula et al. 1985

Table 7-1. Analytical Methods for Determining Fluoride in Biological Materials *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Bone	Ash sample; dissolve in perchloric acid; add 1,2-cyclohexylenedinitro-tetraacetic acid	ISE	No data	No data	Boivin et al. 1988
Hair/fingernail	Wash in diethylether; dry; decompose in NaOH	ISE	No data	94–96%	Schamschula et al. 1985

GC = gas chromatography; $HCl0_4$ = perchloric acid; ISE = ion selective electrode; NaOH = sodium hydroxide; NIOSH = National Institute for Occupational Safety and Health; PAA = proton activation analysis; TISAB = total ionic strength activity buffer; TMCS = trimethylchlorosilane; TMFS = trimethylfluorosilane

fluoride ion activity in the range of 10^0–10^{-6} M. It is selective to fluoride over other common anions by several orders of magnitude; only hydroxide ion causes serious interference. ISE is the methodology recommended by National Institute of Occupational Safety and Health (NIOSH) in Method 8308 for the determination of fluoride in urine (NIOSH 1994). Fluoride analyses using the ion selective electrode are simple, sensitive, and rapid. Recoveries are usually >90%, but this is dependent on the type of sample and sample preparation required. Sample for ISE analysis must be prepared to solubilize the fluorine in the sample. For some samples, ashing or NaOH fusion is required. A total-ionic strength buffer (TISAB) is used to adjust samples and standards to the same ionic strength; this allows the concentration, rather than the activity, to be measured directly and often read directly off a meter. The pH of the buffer is about 5, a level at which F^- is the predominant fluorine-containing species. The buffer contains cyclo-hexylenedinitrilotetraacetic acid, which forms stable complexes with Fe(III) and Al(III), thus removing interferences by freeing fluoride ions from complexes with these ions (NIOSH 1994; Schamschula et al. 1985; Tusl 1970). Bone fluoride levels can be measured using the ISE technique after ashing of the sample (Boivin et al. 1988).

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). In this method, derivatization and extraction is achieved using trimethylchlorosilane (TMCS) in toluene to produce trimethylfluorosilane (TMFS). The organic layer is injected into the GC system and the TMFS peak height is compared with those of standard solutions. The GC method has the advantage of high sensitivity—nanogram quantities of fluoride are detectable in a milliliter of urine or plasma. This method is also useful for assessing the fluoride released from fluorine-containing drugs in biological fluids. The detection of bound fluorine provides an advantage over the ISE technique, which is not suitable for bound or organic fluoride measurements. It should also be noted that the aluminum ion may cause interference under the operating conditions of the GC, as it does with the ISE method.

7.2 ENVIRONMENTAL SAMPLES

The ISE method is the most widely used method for determining fluoride levels in the environmental media. Table 7-2 describes this and other methods for determining fluoride in environmental samples. Table 7-3 describes methods for determining hydrogen fluoride in air. ISE methods are simple to perform and have good precision and sensitivity. Fluoride-specific electrodes are commercially available. The method detects only free fluoride ions in solution. 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 EC in borosilicate vials. This closed-system approach decreases contamination, eliminates dry

Table 7-2. 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	ISE	0.1 µg/L	No data	Danchik et al. 1980
	Sample at 1–2 L/minute using cellulose ester membrane filter and alkaline-impregnated backup pad to collect particulate and gaseous fluorides. Extract hydrogen fluoride and soluble fluorides with water; insoluble fluorides require NaOH fusion.	IC/conductivity detector NIOSH 7906	3 µg/sample (gas); 120 µg/sample (particulate)	No data	NIOSH 1994
	Sample at 1–2 L/min using cellulose ester membrane filter and alkaline-impregnated backup pad to collect particulate and gaseous fluorides; extract hydrogen fluoride and soluble fluorides with 50 mL 1:1 TISAB: water; insoluble fluorides require NaOH fusion	ISE, NIOSH 7902	3 µg/sample	No data	NIOSH 1994
	Syringe-sampling; dilute with 50% (v/v) 1,2-dioxane containing Amadec-F	Colorimetry	0.3 ppm	No data	Bethea 1974
Water	Dilute sample; add barium chloride; complex with zirconium-xylenol orange for color development	Colorimetry	2,000 µg/L	No data	Macejunas 1969
	Sample added to sulfuric acid and distilled to remove interferences; distilled sample treated with SPADNS reagent; color loss resulting from reaction of reagent with fluoride is determined at 570 nm and concentration read off standard curve	Colorimetry EMSLC Method 340.1	0.10 mg/L	No data	EPA 1997
	Mix sample and standard 1:1 with TISAB (for soluble fluorides)	ISE, OSW Method 9214	0.500 mg/L	No data	EPA 1996
	No sample treatment required	ISE, EMSLC Method 340.2	0.100 mg/L	No data	EPA 1997
	Bellack distillation[a], after which fluoride ion reacts with the red cerous chelate of alizarin complexone in an autoanalyzer.	Colorimetry, EMSLC Method 340.3	0.050 mg/L	No data	EPA 1997
	Extract with TMCS; analyze organic phase (microwave induced plasma emission detector)	GC	4 µg/L	93–100%	Chiba et al. 1982

Table 7-2. Analytical Methods for Determining Fluoride in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Waste water	Centrifuge sample to settle solids; filter and dilute	Anion exclusion chromatography	200 µg/L	No data	Hannah 1986
Water, rain	Dilute sample with TISAB buffer; analyze in flow injection system	ISE	2 µg/L	No data	Fucsko et al. 1987
Food, beverage	Homogenize sample; acid hydrolysis in a closed system	ISE	-0.1 µg/g	97%	Lopez and Navia 1988
	Sample pulverized to powder	PAA	1 µg/g dry weight	No data	Shroy et al. 1982
Tea, cocoa, tobacco	Decomposition at 700–1,000 EC in moist current of oxygen or air; collect hydrogen fluoride; react to form Ce(III)alizarin-complexan	Colorimetry	>1 µg	No data	Kakabadse et al. 1971
Milk, peas, pears	Sample is dried and ground to powder; microdiffusion in Petri dish; analyze	ISE	0.2–5 µg/g	54–109%	Dabeka and McKenzie 1981
Vegetation	Fluorine-19 sample activation	INAA	14 µg/sample	No data	Knight et al. 1988
	Extraction of sample	ISE	>0.05 µg/g	>95%	Jacobson and Heller 1971
	Fusion with NaOH; dissolve in tiron buffer	ISE	10 µg/g	No data	Sager 1987
Feed	Sample is dried and acidified	ISE	15 µg/g	90–108%	Melton et al. 1974
Household products	Dilute sample, add buffer; addition procedure	ISE	No data	98–104%	Schick 1973
Plants	Sample dried and fused in nickel crucibles; filter	ISE	>0.3 µg/g	87–102%	Eyde 1982

[a]Bellack distillation uses $HClO_4/AgClO_4$ to remove chloride.
Ce III = cesium ion (+3 oxidation state); EMSLC = EPA Environmental Monitoring Systems Laboratory in Cincinnati; GC = gas chromatography; HPLC = high pressure liquid chromatography; IC = ion chromatography; INAA = instrumental neutron activation analysis; ISE = ion selective electrode; NaOH = sodium hydroxide; NIOSH = National Institute for Occupational Safety and Health; OSW = Office of Soild Waste; PAA = proton activation analysis; SPADNS = sodium 2-(parasulfophenylazo)-1,8-dihydroxy-3,6-naphthalene disulfonate; TISAB = total ionic strength activity buffer; TMCS = trimethylchlorosilane; (v/v) = volume/volume

Table 7-3. Analytical Methods for Determining Hydrogen Fluoride in Environmental Samples[a]

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Personal air sampled at 1–2 L/minute for total sample of 12–800 L onto treated pad; soak pad in 25 mL water and 25 mL TISAB; collect using teflon tubing and analyze with continuous flow analyzer.	ISE, NIOSH 7902	0.7 µg fluoride/sample	No data	NIOSH 1994
	Personal air sampled at 0.2–0.3 L/min for total sample size of 3–100 L using silica gel sample tube; boil sorbent from sample tube in bicarbonate/ carbonate buffer for 10 minutes.	IC/conductivity detector, NIOSH 7903	0.7 µg/sample	No data	NIOSH 1994
	Personal air sampled at 1–2 L/minute using cellulose ester membrane filter and alkaline-impregnated backup pad to collect particulate and gaseous fluorides; extract hydrogen fluoride and soluble fluorides with water; insoluble fluorides requires NaOH fusion.	IC/conductivity detector, NIOSH 7906	3 µg/sample (gas); 120 µg/sample (particulate)	No data	NIOSH 1994
	Hydrogen fluoride vapor collected with dosimeter containing polypropylene element.	ISE	100 µg/L	No data	Young and Monat 1982
	Dual cellulose filter to separate particulate and gaseous fluoride; heat filters at 75EC; extract; dilute with TISAB buffer.	ISE	1.2 µg/filter	No data	Einfeld and Horstman 1979

[a]Some methods measure both gaseous (HF) and particulate fluorides.
IC = ion chromatography; ISE = ion selective electrode; NIOSH = National Institute for Occupational Safety and Health; TISAB = total ionic strength activity buffer, v/v = volume/volume

ashing, and yields high recoveries. Dabeka and McKenzie (1981) employed microdiffusion to food samples in Petri dishes at 60 EC 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 EC. The ash was diluted and filtered for analysis. This method is more tedious than the others, and fluoride loss is expected from the high fusion 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 colorimetric or ISE analysis. Decomposition of the sample at 700–1,000 EC 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.

Fluoride ions form stable, colorless complexes with certain multivalent ions, such as $(AlF_6)^{3-}$, $(FeF_6)^{3-}$, and $(ZrF_6)^{3-}$. Most colorimetric methods for the determination of fluoride are based on the bleaching of colored complexes of these metals with organic dyes when fluoride is added (WHO 1984). The degree of bleaching is determined with a spectrophotometer and the concentration of fluoride ions is assessed by comparison with standard solutions. In EPA Method 340.1, the sodium 2-(parasulfophenylazo)-1,8-dihydroxy-3,6-naphthalenedisulfonate (SPADNS) reagent is used and the color loss is measured at 570 nm (EPA 1997). In EPA Method 340.3, the red cerium complex with alizarin complex one turns blue on the addition of fluoride (EPA 1997).

Ion chromatography (IC) utilizes anion exchange resins as a stationary phase to separate fluoride ions from other species. In most cases, conductivity detectors are used to detect the ions in the eluent. Both the stationary phase and the eluent must be chosen to separate fluoride from overlapping ions. Hannah (1986) used a variant of ion exchange chromatography, namely anion exclusion chromatography, to analyze fluoride in waste water. This method is generally applied to the separation of weak organic acids and its use for fluoride determinations is based on the fact that fluoride is an anion of a weak acid, hydrogen fluoride, with a pK_a similar to that of weak organic acids. The acids elute in order of increasing pK_a. At low pH, anions of strong acids remain disassociated and are excluded from the resin and rapidly eluted. Hydrogen fluoride exists primarily in the molecular form, and interacts with the resin, delaying its elution. In this way, fluoride is sufficiently separated from ionic interferences to be reliably quantified. Interfering anions, such as chloride, emerge as one peak before the fluoride elutes. Resolution can be controlled by adjusting the pH.

Fluorides in air may be present in the gas phase (generally hydrogen fluoride) or in the particulate phase. Sampling may involve trapping the particulate phase on a membrane filter and the hydrogen fluoride on a alkaline impregnated backup pad as in NIOSH Method 7906 (NIOSH 1994). 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).

For the analysis of pollutants in the environment, EPA has approved the ISE (Method 340.2) and colorimetric methods (Methods 340.1 and 340.3) for determining inorganic fluoride in water (EPA 1998). NIOSH recommends the use of ISE (Method 7902) and IC methods (Methods 7903 and 7906) for the determination of fluoride and hydrogen fluoride in air (NIOSH 1994).

Fluoride gas or vapors in ambient air are measured primarily with the ISE method. NIOSH Method 7902 uses this technique for the determination of hydrogen fluoride and particulate fluorides in air (NIOSH 1994). The hydrogen fluoride gas and particulate fluorides are collected on separate filters before determination. Several modifications have been suggested for the air sample collection. Einfeld and Horstman (1979) found that gaseous fluoride may get trapped in the filter for particulate fluoride to some extent. They utilized postsampling heat treatment to desorb hydrogen fluoride from particulates. The use of Teflon® tubing and materials in the analyzer is indicated for controlling fluoride loss (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 TISAB 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. Wind, temperature, and atmospheric pressure can affect results. The 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 neutron or proton activation of fluorine-19 (Knight et al. 1988; Shroy et al. 1982). Instruments measure the emitted gamma rays or x-rays using lithium-drifted germanium detectors. This approach has wide application, since it does not depend on a specific sample matrix or chemical form. However, the need a special facility with a source of neutrons or protons limits its use.

7.3 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 National Toxicology Program (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 the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. 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 common technique is the ISE method because it is reliable, simple, sensitive, and has good recoveries (NIOSH 1994; 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.

Urinary fluoride 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), hair (Schamschula et al. 1982), nails (Schamschula et al. 1982), 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.

Effect. 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. Methods are available for determining fluoride levels in environmental samples. Methods determine the fluoride concentration and not the particular fluorine-containing compound. Therefore, analytical methods do not distinguish between parent compound and degradation product. The ISE method is the most common method for measuring fluoride in environmental samples. It is a convenient, sensitive, and reliable method, but fluoride ions must first be released from any matrix and rendered free in solution. Methods are available for preparing various types of environmental samples for analysis (Dabeka and McKenzie 1981; EPA 1997; Eyde 1982; Kakabadse et al. 1971; Lopez and Navia 1988; NIOSH 1994; NRC Canada 1971; WHO 1984).

7.3.2 Ongoing Studies

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

8. 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 8-1.

An acute-duration inhalation MRL of 0.01 ppm has been derived for fluorine. This MRL is based on a NOAEL of 10 ppm for respiratory effects in humans exposed to fluorine for 15 minutes (Keplinger and Suissa 1968). The MRL was derived by adjusting the NOAEL for <24-hour exposure and dividing by an uncertainty factor of 10 (to account for human variability).

An acute-duration inhalation MRL of 0.03 ppm fluoride has been derived for hydrogen fluoride. This MRL is based on a NOAEL of 98 ppm for nasal irritation in rats exposed to hydrogen fluoride for 60 minutes (Rosenholtz et al. 1963). The MRL was derived by adjusting the NOAEL for less than 24-hour exposure and multiplying by the RDGR to calculated a $NOAEL_{HEC}$. This value was then divided by an uncertainty factor of 30 (3 for interspecies extrapolation using dosimetric adjustments and 10 to account for human variability).

An intermediate-duration inhalation MRL of 0.02 ppm fluoride has been derived for hydrogen fluoride. This MRL is based on a LOAEL of 2.98 ppm for slight nasal irritation in subjects exposed to hydrogen fluoride 6 hours/day for 15–50 days (Largent 1960). The MRL was derived by adjusting the LOAEL for intermittent exposure and dividing by an uncertainty factor of 30 (3 for use of a LOAEL for a minimal effect and 10 to account for human variability).

A chronic-duration oral MRL of 0.06 mg fluoride/kg/day has been derived for fluoride. This MRL is based on a LOAEL of 0.56 mg fluoride/kg/day for skeletal effects (increased fracture rate) in postmenopausal women with osteoporosis (Riggs et al. 1990, 1994). The MRL was derived by dividing the LOAEL by an uncertainty factor of 10 (for use of a LOAEL in a sensitive population).

EPA (IRIS 2001) derived an oral reference dose (RfD) of 0.06 mg/kg/day for fluorine (soluble fluoride). The RfD was based on a NOAEL of 0.06 mg/kg/day and a LOAEL of 0.12 mg/kg/day for the cosmetic effect of dental fluorosis in children (Hodge 1950). The NOAEL was divided by an uncertainty factor of 1 to derive the RfD.

Table 8-1. Regulations and Guidelines Applicable to Fluoride, Fluorine, Hydrogen Fluoride, and Sodium Fluoride

Agency	Description	Information	Reference
INTERNATIONAL Guidelines:			
IARC	Carcinogenicity classification		IARC 2001
	Fluoride and sodium fluoride	Group 3[a]	
WHO	Drinking water guideline		WHO 2001
	Fluoride	1.5 mg/L	
NATIONAL Regulations and Guidelines:			
a. Air:			
ACGIH	TLV-TWA		ACGIH 2000
	Fluoride	2.5 mg/m^3	
	Fluorine	1.0 ppm	
	STEL (ceiling)		
	Fluorine	2.0 ppm	
	Hydrogen fluoride	3.0 ppm	
EPA	Accidental release prevention		EPA 2001b
	Threshold quantity		40CFR68.130
	Fluorine	1,000 pounds	Table 1
	Hydrogen fluoride	1,000 pounds	
	Accidental release prevention		EPA 2001a
	Toxic end point		40CFR68
	Fluorine	0.0039 mg/L	Appendix A
	Hydrogen fluoride	0.0160 mg/L	
OSHA	PEL (8-hour TWA)		OSHA 2001c
	General industry		29CFR1910.1000
	Fluoride	2.5 mg/m^3	Table Z-1
	Fluorine	0.2 mg/m^3	
	Hydrogen fluoride	2.0 mg/m^3	
	PEL (8-hour TWA)		OSHA 2001f
	Construction industry		29CFR1926.55
	Fluoride	2.5 mg/m^3	Appendix A
	Fluorine	0.2 mg/m^3	
	Hydrogen fluoride	2.0 mg/m^3	
	PEL (8-hour TWA)		OSHA 2001a
	Shipyards		29CFR1915.1000
	Fluoride	2.5 mg/m^3	Table Z
	Fluorine	0.2 mg/m^3	
	Hydrogen fluoride	2.0 mg/m^3	

Table 8-1. Regulations and Guidelines Applicable to Fluoride, Fluorine, Hydrogen Fluoride, and Sodium Fluoride *(continued)*

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
OSHA	Highly hazardous chemicals—Threshold quantity		
	Fluorine	1,000 pounds	OSHA 2001d 29CFR1910.119 Appendix A
	Hydrogen fluoride	1,000 pounds	OSHA 2001e 29CFR1926.64 Appendix A
	Brazing and gas welding fluxes shall have a cautionary wording to indicate that they contain fluorine compounds		OSHA 2001b 29CFR1910.252(c)(1)
NIOSH	REL (TWA)		
	Fluorine	0.2 mg/m^3	NIOSH 2001a
	Hydrogen fluoride	2.5 mg/m^3	NIOSH 2001b
	Sodium fluoride	2.5 mg/m^3	NIOSH 2001c
	IDLH		
	Fluorine	25 ppm	NIOSH 2001a
	Hydrogen fluoride	30 ppm	NIOSH 2001b
	Sodium fluoride	250 ppm	NIOSH 2001c
USC	HAP		USC 2001 42USC7412
b. Water			
EPA	BPT effluent limitation—fluoride		EPA 2001c 40CFR415.82
	Maximum for 1 day	6.1 kg/kkg	
	Average of daily values for 30 consecutive days	2.9 kg/kkg	
	Effluent limitation—fluoride		EPA 2001e 40CFR422.42
	Maximum for 1 day	75 mg/L	
	Average of daily values for 30 consecutive days	25 mg/L	
	Groundwater protection standards at inactive uranium processing sites—listed constituents include fluorine and hydrogen fluoride		EPA 2001f 40CFR192 Appendix I

Table 8-1. Regulations and Guidelines Applicable to Fluoride, Fluorine, Hydrogen Fluoride, and Sodium Fluoride *(continued)*

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	MCLG—fluoride	4.0 mg/L	EPA 2001j 40CFR141.51(b)
	MCL—fluoride	4.0 mg/L	EPA 2001k 40CFR141.62(b)
	Secondary MCL—fluoride	2.0 mg/L	EPA 2001l 40CFR143.3
	Water pollution—hazardous substance designation Hydrogen fluoride Sodium fluoride		EPA 2001r 40CFR116.4
c. Food			
EPA	Pesticides—fluorine compounds; residue tolerances apricots, beets, blackberries, blueberries, boysenberries, broccoli, brussels sprouts, cabbage, cauliflower, citrus fruits, collards, cranberries, cucumbers, dewberries, eggplant, grapes, kale, kohlrabi, lettuce, loganberries, melons, nectarines, peaches, peppers, plums, pumpkins, radish, raspberries, rutabaga, squash, strawberries, tomatoes, turnip, youngberries	7 ppm	EPA 2001n 40CFR180.145
	potatoes	2 ppm	
	potatoes, processing waste	22 ppm	
	kiwifruit	15 ppm	
FDA	Adhesive component, indirect food additive—for use only as bonding agent for aluminum foil, stabilizer, or preservative Hydrogen fluoride Sodium fluoride	Total fluoride from all sources not to exceed 1% by weight of the finished adhesive	FDA 2000e 21CFR175.105(c)(5)

Table 8-1. Regulations and Guidelines Applicable to Fluoride, Fluorine, Hydrogen Fluoride, and Sodium Fluoride *(continued)*

Agency	Description	Information		Reference
NATIONAL *(cont.)*				
FDA	Bottled water—no fluoride added	Temperature[b]	mg/L	FDA 2000g 21CFR165.110
		53.7–below	2.4	
		53.8–58.3	2.2	
		58.4–63.8	2.0	
		63.9–70.6	1.8	
		70.7–79.2	1.6	
		79.3–90.5	1.4	
	Bottled water—fluoride added	Temperature[b]	mg/L	
		53.7–below	1.7	
		53.8–58.3	1.5	
		58.4–63.8	1.3	
		63.9–70.6	1.2	
		70.7–79.2	1.0	
		79.3–90.5	0.8	
	Over-the-counter drug products Labeling—fluoride, fluorine, and sodium fluoride			FDA 2000b 21CFR355.50 FDA 2000c 21CFR355.60
	Over-the-counter drug products Testing—fluoride			FDA 2000d 21CFR355.70
	Over-the-counter drug products Active ingredient—fluorine, hydrogen fluoride, and sodium fluoride			FDA 2000a 21CFR355.10 FDA 2000f 21CFR310.545(a)(2)
	Surface component, food contact—sodium fluoride for use as preservative only			FDA 2000h 21CFR177.2800(d)(5)
d. Other				
ACGIH	Carcinogenicity classification Fluoride	A4[c]		ACGIH 2000
	BEI Fluorides in urine Prior to shift End of shift	 3 mg/g creatinine 10 mg/g creatinine		
CPSC	Requirements for child-resistant packaging for household products containing elemental fluoride	More than 50 mg and more than 0.5%		CPSC 2001 16CFR1700

Table 8-1. Regulations and Guidelines Applicable to Fluoride, Fluorine, Hydrogen Fluoride, and Sodium Fluoride *(continued)*

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
DOT	Hazardous materials		DOT 2001
	Reportable quantity		40CFR172.101
	Fluorine	10 pounds	Appendix A
	Hydrogen fluoride	100 pounds	
	Sodium fluoride	1,000 pounds	
EPA	RfD—fluorine	$6x10^{-2}$ mg/kg/day	IRIS 2001
	Toxic chemical release reporting; Community Right-to-Know—effective date		EPA 2001q 40CFR372.65
	Fluorine	01/01/95	
	Hydrogen fluoride	01/01/87	
	Contaminated soil—fluoride	Concentrations greater than 10 times UTS	EPA 2001d 40CFR268.49(f)
	Hazardous waste—health based limits for exclusion of waste-derived-residue		EPA 2001g 40CFR266 Appendix VII
	Fluorine residue concentration limit	4.0 mg/kg	
	Hazardous waste—identification and listing		EPA 2001h 40CFR261.33(e)
	Fluorine	P056	EPA 2001i
	Hydrogen fluoride	U134	40CFR261.33(f)
	Pesticides—residue tolerances		EPA 2001m
	Sodium fluoride	Not more than 25% of pesticide formulation	40CFR180.1001(d)
	Superfund—reportable quantity		EPA 2001o
	Fluorine	1 pound	40CFR302.4
	Hydrogen fluoride	5,000 pounds	Appendix A
	Sodium fluoride	5,000 pounds	
	Superfund—extremely hazardous		EPA 2001p 40CFR355
	Reportable quantity		Appendix A
	Fluorine	10 pounds	
	Hydrogen fluoride	100 pounds	
	Threshold planning quantity		
	Fluorine	500 pounds	
	Hydrogen fluoride	100 pounds	

Table 8-1. Regulations and Guidelines Applicable to Fluoride, Fluorine, Hydrogen Fluoride, and Sodium Fluoride *(continued)*

Agency	Description	Information	Reference
STATE			
a. Air			
Connecticut	HAP—fluoride, fluorine, and hydrogen fluoride		BNA 2001
Hawaii	Air contaminant—hydrogen fluoride		BNA 2001
Idaho	Toxic air pollutants		BNA 2001
	Fluoride		
	OEL	2.5 mg/m^3	
	EL	0.167 pounds/hour	
	AAC	0.125 mg/m^3	
	Fluorine		
	OEL	2.0 mg/m^3	
	EL	0.133 pounds/hour	
	AAC	0.1 mg/m^3	
Michigan	PEL (TWA)		BNA 2001
	Fluoride	2.5 mg/m^3	
	Fluorine	0.2 mg/m^3	
	Hydrogen fluoride	3.0 ppm	
Montana	Air contaminant (TWA)		BNA 2001
	Fluoride	2.5 mg/m^3	
	Fluorine	0.2 mg/m^3	
	Hydrogen fluoride	2.0 mg/m^3	
New Mexico	Toxic air pollutant		BNA 2001
	Fluorides		
	OEL	2.5 mg/m^3	
	Emissions	0.167 pounds/hour	
	Fluorine		
	OEL	2.0 mg/m^3	
	Emissions	0.133 pounds/hour	
New York	Air contaminant (TLV)		BNA 2001
	Fluoride	2.5 mg/m^3	
	Fluorine	0.2 mg/m^3	
	Hydrogen fluoride	2.0 mg/m^3	
Washington	Toxic air pollutant—ASIL		BNA 2001
	Fluoride	8.3 $\mu g/m^3$	
	Fluorine	5.3 $\mu g/m^3$	
	Hydrogen fluoride	8.7 $\mu g/m^3$	

Table 8-1. Regulations and Guidelines Applicable to Fluoride, Fluorine, Hydrogen Fluoride, and Sodium Fluoride *(continued)*

Agency	Description	Information		Reference
STATE *(cont.)*				
Washington	PEL			BNA 2001
	Fluoride	2.5 mg/m^3		
	Fluorine	0.2 mg/m^3		
	Hydrogen fluoride (STEL)	3.0 ppm		
Wisconsin	Emission rate (pounds/hour)	<25 feet	>25 feet	BNA 2001
	Fluoride	0.2088	0.8640	
	Fluorine	0.1656	0.6720	
	Hydrogen fluoride	0.1272	0.4800	
b. Water				
Alaska	MCL—fluoride	4.0 mg/L		BNA 2001
	Secondary MCL—fluoride	2.0 mg/L		
Arizona	Drinking water guideline—fluoride	4.0 mg/L		HSDB 2001
	Reporting limit—fluoride	2.0 mg/L		BNA 2001
California	Drinking water standards—fluoride	2.0 mg/L		HSDB 2001
Connecticut	MCL—fluoride	4.0 mg/L		BNA 2001
Delaware	Drinking water standards—fluoride	1.8 mg/L		HSDB 2001
Georgia	MCL—fluoride	4.0 mg/L		BNA 2001
Hawaii	Drinking water standards—fluoride	1.4–2.4 mg/L		HSDB 2001
Idaho	Groundwater quality standards—fluoride	4.0 mg/L		BNA 2001
Kansas	Agriculture—fluoride			BNA 2001
	Livestock	2.0 mg/L		
	Irrigation	1.0 mg/L		
	Public health food—fluoride			
	Domestic water supply	2.0 mg/L		
Maine	Drinking water guideline—fluoride	2.4 mg/L		HSDB 2001
	Maximum exposure guideline	2.4 mg/L		BNA 2001
	Action level	1.2 mg/L		

Table 8-1. Regulations and Guidelines Applicable to Fluoride, Fluorine, Hydrogen Fluoride, and Sodium Fluoride *(continued)*

Agency	Description	Information	Reference
STATE *(cont.)*			
Mississippi	Groundwater standards—fluoride	4.0 ppm	BNA 2001
Nebraska	MCL—fluoride	4.0 mg/L	BNA 2001
New Jersey	Groundwater quality criteria—fluoride	2.0 mg/L	BNA 2001
	PQL—fluoride	0.5 mg/L	
New York	Groundwater effluent limitations—fluoride	3.0 mg/L	BNA 2001
	MCL—fluoride	2.2 mg/L	BNA 2001
North Carolina	Drinking water standards—fluoride	4.0 mg/L	HSDB 2001
North Dakota	MCL—fluoride	4.0 mg/L	BNA 2001
Oklahoma	MCL—fluoride	4.0 mg/L	BNA 2001
Pennsylvania	Drinking water standards—fluoride	2.0 mg/L	HSDB 2001
Rhode Island	MCLG—fluoride	4.0 ppm	BNA 2001
	MCL—fluoride	4.0 ppm	
South Dakota	Groundwater quality standards—fluoride	2.4 mg/L	BNA 2001
Tennessee	MCL—fluoride	4.0 ppm	BNA 2001
Texas	MCL—fluoride	4.0 mg/L	BNA 2001
Utah	Groundwater standards	4.0 mg/L	BNA 2001
	MCL—fluoride	4.0 mg/L	BNA 2001
Vermont	Groundwater quality standards—fluoride		BNA 2001
	Enforcement standard	4.0 mg/L	
	Preventive action level	2.0 mg/L	
	MCL—fluoride	4.0 mg/L	BNA 2001
Washington	MCL—fluoride	4.0 mg/L	BNA 2001
West Virginia	Groundwater standards	Not to exceed 4.0 mg/L	BNA 2001

Table 8-1. Regulations and Guidelines Applicable to Fluoride, Fluorine, Hydrogen Fluoride, and Sodium Fluoride *(continued)*

Agency	Description	Information	Reference
STATE *(cont.)*			
Wisconsin	MCLG—fluoride MCL—fluoride	4.0 mg/L 4.0 mg/L	BNA 2001
	Groundwater standards—fluoride Enforcement standard Preventive action limit	 4.0 mg/L 0.8 mg/L	BNA 2001
c. Food		No data	
d. Other			
Connecticut	Use of pesticides; control of registrations and uses—sodium fluoride	For use as a wood preservative	BNA 2001
Minnesota	Hazardous substance—fluoride (as F, as dust), fluorides (inorganic), fluorine, and hydrogen fluorine		BNA 2001
New Jersey	Hazardous substance—fluorine and hydrogen fluoride		BNA 2001

[a]Group 3: not classifiable as to its carcinogenicity to humans
[b]Temperature: annual average of maximum daily air temperatures (EF)
[c]A4: not classifiable as a human carcinogen

AAC = acceptable ambient concentrations; ACGIH = American Conference of Governmental Industrial Hygienists; ASIL = acceptable source impact levels; BEI = biological exposure indices; BNA = Bureau of National Affairs; BPT = best practicable control technology; CFR = Code of Federal Regulations; CPSC = Consumer Product Safety Commission; DOT = Department of Transportation; EL = emissions levels; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HAP = hazardous air pollutant; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life and health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; OEL = occupational exposure limit; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; PQL = practical quantitation level; REL = recommended exposure limit; RfD = reference dose; STEL = short term exposure limit; TLV = threshold limit values; TWA = time-weighted average; USC = United States Code; UTS = universal treatment standards; WHO = World Health Organization

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

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

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

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.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

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.

Biomarkers—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.

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.

Case-Control Study—A type of epidemiological study which examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research but are not actual research studies.

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.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups which examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

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.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

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 occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (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.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

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

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

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.

Immunological Effects—Functional changes in the immune response.

***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 caused death in 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 has been reported 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 exposure level 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.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

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

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a minimal risk level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

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

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a 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*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) which represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

Organophosphate or Organophosphorus Compound—A phosphorus containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The science of quantitatively predicting the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments which, in general, do not represent real, identifiable anatomic regions of the body whereby the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically-based dose-response model which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

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 µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation

reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

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 no-observed-adverse-effect level (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 the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 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.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed.

Standard cubic meter (scm)—Cubic meter of gas at standard conditions of temperature and pressure, generally 293 K 101.3 kilopascals.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) 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 Threshold Limit Value - Time Weighted Average (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)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

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

Toxic Dose$_{(50)}$ (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.

Toxicokinetic—The study of the absorption, distribution and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) 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 lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A

ATSDR MINIMAL RISK LEVEL AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR

uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Fluorine
CAS Number: 7782-41-4
Date: July 20, 2001
Profile Status: Third Draft
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to Figure: 9
Species: Humans

Minimal Risk Level: 0.01 [ ] mg/kg/day [X] ppm

Reference: Keplinger ML, Suissa LW. 1968. Toxicity of fluorine short-term inhalation. Am Ind Hyg Assoc J 29(1):10-18.

Experimental design (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Five volunteers (aged 19–50 years; gender not specified) were exposed to various concentrations of fluorine: 10 ppm for 3, 5, or 15 minutes; 23 ppm for 3–5-minute periods every 15 minutes for 2–3 hours, 50 ppm for 3 minutes, 67 ppm for 1 minute, 78 ppm for 1 minute, and 100 ppm for 0.5 or 1 minute. No information was provided on the amount of time between exposures or whether all subjects were exposed to all concentrations.

Effects noted in study and corresponding concentrations: No nasal, eye, or skin irritation were reported at 10 ppm. Eye, nasal, and skin irritation were reported at doses of $50, 67, or 78 ppm, respectively; the severity of the irritation was concentration-related. Exposure to 100 ppm was considered very irritating and the subjects did not inhale during the exposure period. No incidence data were reported.

Concentration and end point used for MRL derivation: The MRL is based on a NOAEL of 10 ppm fluorine for no irritation.

[X] NOAEL [] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: NA

Was a conversion used from intermittent to continuous exposure? Yes. The NOAEL of 10 ppm fluorine for 15 minutes was adjusted for intermittent exposure using the following equation:

10 ppm x 0.25 hours/24 hours = 0.1 ppm

Other additional studies or pertinent information that lend support to this MRL: Respiratory effects have also been observed in rats, mice, guinea pigs, rabbits, and dogs exposed to fluorine for 1–60 minutes (Keplinger and Suissa 1968). The observed effects include diffuse lung congestion, dyspnea, irritation, and alveolar necrosis and hemorrhage. The severity of the lung congestion was concentration-related and no species differences were found.

Agency Contact (Chemical Manager): Carolyn Tylenda, D.M.D., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Hydrogen Fluoride
CAS Number: 7664-39-3
Date: August 22, 2001
Profile Status: Fourth Draft
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to Figure: 9
Species: Rats

Minimal Risk Level: 0.03 [ ] mg/kg/day [X] ppm

Reference: Rosenholtz MJ, Carson TR, Weeks MH, et al. 1963. A toxicopathologic study in animals after brief single exposures to hydrogen fluoride. Am Ind Hyg Assoc J 24:253-261.

Experimental design (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Groups of 15–20 male Wistar rats were exposed to 0, 98, 120, 276, or 465 ppm fluoride as hydrogen fluoride for 60 minutes.

Effects noted in study and corresponding concentrations: At the lowest concentration (98 ppm), occasional pawing at the nose and blinking of the eyes were reported; this concentration was considered a NOAEL. At 120 ppm, general discomfort, pawing at the nose, and tearing from the eyes were observed. Exposure to 465 ppm fluoride, produced respiratory distress lasting a few hours after exposure termination, as well as lacrimation, nasal discharge, and reddened conjuctivae. Animals appeared depressed and weak for 24 hours and sluggish for an additional day.

Concentration and end point used for MRL derivation: The MRL is based on a NOAEL of 98 ppm fluoride as hydrogen fluoride for nasal irritation.

[X] NOAEL [] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans with dosimetric adjustments
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration:

Extrathoracic surface area in rats and humans: 15 and 200 cm^2, respectively
Inhalation rate in Wistar rats and humans: 0.42 and 20 m^3/day, respectively

The $NOAEL_{HEC}$ was calculated using the following equation:

$$98 \text{ ppm} \times [(0.43 \text{ m}^3/\text{day} / 15 \text{ cm}^2) / (20 \text{ m}^3/\text{day} / 200 \text{ cm}^2)] = 27 \text{ ppm}$$

Was a conversion used from intermittent to continuous exposure? Yes. The $NOAEL_{HEC}$ of 27 ppm for 60 minutes was adjusted for intermittent exposure using the following equation:

$$27 \text{ ppm} \times 1 \text{ hour}/24 \text{ hours} = 1 \text{ ppm}$$

Other additional studies or pertinent information that lend support to this MRL:

Nasal irritation was also observed in rats exposed to higher concentrations of hydrogen fluoride for shorter durations (Rosenholtz et al. 1963). Respiratory distress was observed in rats exposed to 50% of the LC_{50} value for 5, 15, 30, or 60 minutes (2,310, 1,339, 1,308, and 465 ppm fluoride, respectively) (Rosenholtz et al. 1963). Dalbey et al. (1998a, 1998b) reported midtracheal necrosis in rats exposed to 902 or 1,509 ppm fluoride as hydrogen fluoride for 2 or 10 minutes using a mouth breathing model with a tracheal cannula. These effects were not observed when the tracheal cannula was not used.

Agency Contact (Chemical Manager): Carolyn Tylenda, D.M.D., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Hydrogen fluoride
CAS Number: 7664-39-3
Date: July 20, 2001
Profile Status: Third Draft
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to Figure: 14
Species: Humans

Minimal Risk Level: 0.02 [ ] mg/kg/day [X] ppm

Reference: Largent EJ. 1960. The metabolism of fluorides in man. AMA Archives of Industrial Health 21:318-323.

Experimental design (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Five volunteers (aged 19–50 years; gender not specified) were exposed to various concentrations of hydrogen fluoride. The ranges (and mean concentrations) for each subject were 0.85–1.9 ppm fluoride (1.3 ppm fluoride) for 15 days, 1.8–4.6 ppm fluoride (3.2 ppm fluoride) for 30 days, 2.9–7.5 ppm fluoride (2.6 ppm fluoride) for 25 days, 2.6–7.7 ppm fluoride (4.0 ppm fluoride) for 50 days, and 1.7–4.9 ppm fluoride (2.4 ppm fluoride) for 25 days. The mean of the average concentrations was 2.98 ppm fluoride.

Effects noted in study and corresponding concentrations: The study authors noted that each of the subjects reported "discomfort in the form of slight stinging sensation in the skin, eyes, and some slight irritation of the nasal passages". The irritation was more severe at higher concentrations. No other information was provided.

Concentration and end point used for MRL derivation: The MRL is based on a LOAEL of 2.98 ppm for slight nasal irritation.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 3 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: NA

Was a conversion used from intermittent to continuous exposure? Yes. The LOAEL of 2.98 ppm was adjusted for intermittent exposure using the following equation:

2.98 ppm fluoride x 6 hours/24 hours.

An assumption was made that the volunteers were exposed to hydrogen fluoride daily.

Other additional studies or pertinent information that lend support to this MRL: A number of human and animal studies support the identification of respiratory irritation as the critical effect following inhalation exposure to hydrogen fluoride. Respiratory tract irritation (throat burning and sore throat, shortness of

breath, cough) and decreased lung function were observed in residents accidentally exposed to hydrogen fluoride (Wing et al. 1991). Respiratory effects have also been reported in animal studies. In animal studies, impaired lung function and necrosis and inflammation of the ventral meatus, nasal septum, and nasoturbinates (Dalbey et al. 1998a, 1998b) were observed following acute inhalation exposure to hydrogen fluoride. Pulmonary hemorrhage and hyperplasia of the bronchial epithelium were observed in laboratory animals exposed to $18 ppm fluoride as hydrogen fluoride for 30–35 days (Machle and Kitzmiller 1935; Stokinger 1949).

Agency Contact (Chemical Manager): Carolyn Tylenda, D.M.D., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Fluoride
CAS Number: NA
Date: July 20, 2001
Profile Status: Third Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to Figure: 41
Species: Humans

Minimal Risk Level: 0.06 [X] mg/kg/day [ ] mg/m^3

Reference: Riggs BL, Hodgson SF, O'Fallon WH, et al. 1990. Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. N Engl J Med 322:802-809.

Riggs BL, O'Fallon WH, Lane A, et al. 1994. Clinical trial of fluoride therapy in postmenopausal osteoporotic women: extended observations and additional analysis. J Bone Mineral Res 9:265-275.

Experimental design (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): 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. Both groups received 1,500 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 4 years of treatment. The Riggs et al. (1994) followed 50 of the subjects in the fluoride group for an additional 2 years.

Effects noted in study and corresponding concentrations: Bone mineral density in the lumbar spine, femoral neck, and femoral trochanter increased markedly in the treatment group, but bone mineral density in the shaft of the radius decreased by 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 the 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. In the subjects followed for the additional 2 years, the incidence of vertebral fractures and nonvertebral fractures decreased. The overall occurrence of nonvertebral fractures for years 0–6 was still 3 times higher than in the control group (years 0–4).

Concentration and end point used for MRL derivation:

The MRL is based on a LOAEL of 0.56 mg fluoride/kg/day for increased fracture rate.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL in a sensitive subpopulation
[ ] 10 for extrapolation from animals to humans
[ ] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: NA

Was a conversion used from intermittent to continuous exposure? NA

Other additional studies or pertinent information that lend support to this MRL: 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. 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).

A number of studies have examined the effect on bone fracture rate in communities with high levels of fluoride in the drinking water (Cooper et al. 1990, 1991; Danielson et al. 1992; Goggin et al. 1965; Simonen and Laitinen 1985; Sowers et al. 1991. 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 on trends in hip fracture incidence and total individual fluoride consumption.

Agency Contact (Chemical Manager): Carolyn Tylenda, D.M.D., Ph.D.

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical 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 chemical.

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

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, 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 around hazardous waste sites?

The chapter covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter. 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. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint 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 chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "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 the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive 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 systemic, neurological, and developmental effects. If this 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. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both 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 uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (3-1, 3-2, and 3-3) and figures (3-1 and 3-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, 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. Use the LSE tables and figures 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. All 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), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 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 3-1

(1) Route of Exposure 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 exists, 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 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect 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 are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure 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 derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 3-1).

(5) Species The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration 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 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System 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, 1 systemic effect (respiratory) was investigated.

(8) NOAEL 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) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study 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 respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in Chapter 9 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes 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.

LEGEND

See Figure 3-1

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

(13) Exposure Period 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 exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured 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 to 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 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. 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 the EPA's Human Health Assessment 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.

SAMPLE

1 6

Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation

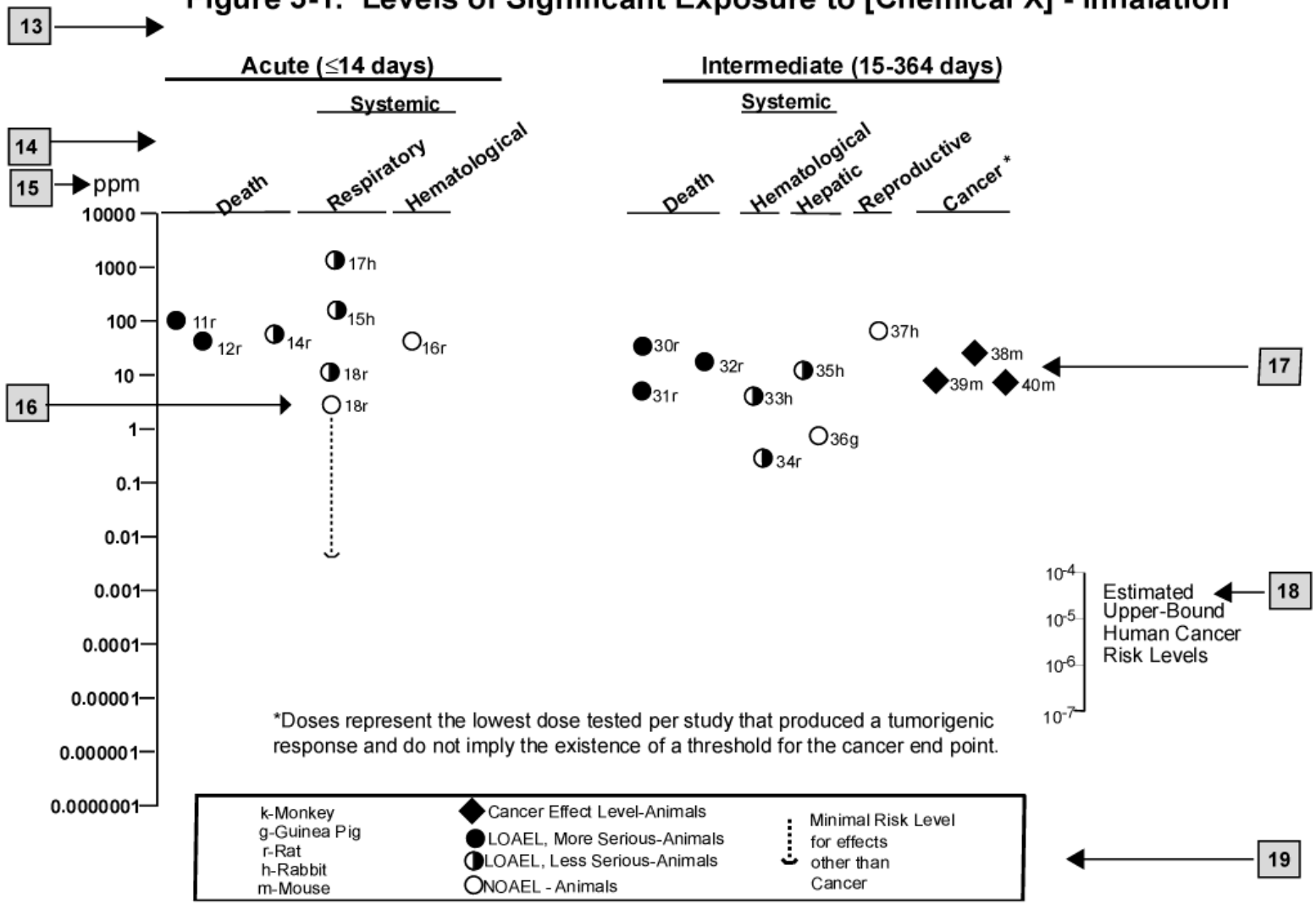
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
2 6 INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 6 Systemic	9	9	9	9	9		9
4 6 18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
Cancer					9		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 3-1.

12 6 [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 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).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	Best Available Technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	Cancer Effect Level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
Derm	dermal
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	Drinking Water Exposure Level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram

EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	Maximum Allowable Level
mCi	millicurie
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
mg	milligram
min	minute
mL	milliliter

mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
NLM	National Library of Medicine
nm	nanometer
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
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	Polycyclic Aromatic Hydrocarbon
PBPD	Physiologically Based Pharmacodynamic
PBPK	Physiologically Based Pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit

PID	photo ionization detector
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	Pretreatment Standards for New Sources
REL	recommended exposure level/limit
RfC	Reference Concentration
RfD	Reference Dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	Reportable Quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard mortality ratio
SNARL	Suggested No Adverse Response Level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	Total Organic Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
VOC	Volatile Organic Compound
yr	year
WHO	World Health Organization
wk	week

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma

δ	delta
µm	micrometer
µg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

APPENDIX D

INDEX