TOXICOLOGICAL PROFILE FOR FLUORIDES, HYDROGEN FLUORIDE, AND FLUORINE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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DISCLAIMER

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UPDATE STATEMENT

A Toxicological Profile for Hydrogen Fluoride, and Fluorine, Draft for Public Comment was released in September 2001. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

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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:

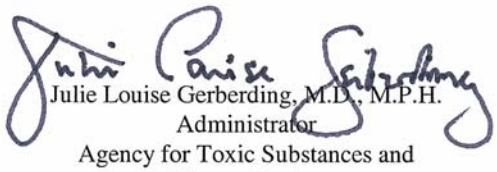
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(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.

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 was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



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*Legislative Background

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 threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on October 25, 2001 (66 FR 54014). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17,1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); and October 21, 1999 (64 FR 56792). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

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) 498-0093
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 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 fluorides, hydrogen fluoride, and fluorine. The panel consisted of the following members:

1. Jan Ekstrand, Professor & Vice Dean, Board of Research and Postgraduate Education, Nobels väg 5, Karolinska Institutet, Stockholm, Sweden;

2. Julie Glowacki, Ph.D., Department of Orthopedic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA;

3. Michael Kleerekoper, M.B., B.S., F.A.C.P., F.A.C.E., Departments of Internal Medicine, Obstetrics & Gynecology, and Pathology Wayne State University School of Medicine, Detroit, MI;

4. Gary Whitford, Ph.D., D.M.D., School of Dentistry, Medical College of Georgia, Augusta, GA.

These experts collectively have knowledge of fluorides, hydrogen fluoride, and fluorine's 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 fluorides, hydrogen fluoride, and fluorine 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. Fluorides, hydrogen fluoride, and fluorine have been found in at least 188 of the 1,636 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, hydrogen fluoride, and fluorine is 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 fluorides, hydrogen fluoride, and fluorine, 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 it/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 FLUORIDES, HYDROGEN FLUORIDE, AND FLUORINE?

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. Other fluoride compounds that are commonly used for water fluoridation are fluorosilicic acid and sodium fluorosilicate. 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 °C) 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 fluorides, hydrogen fluoride, and fluorine, and their production and use, see Chapters 4 and 5.

1.2 WHAT HAPPENS TO FLUORIDES, HYDROGEN FLUORIDE, AND FLUORINE 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 FLUORIDES, HYDROGEN FLUORIDE, AND FLUORINE?

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 part of fluoride per million parts of water (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 (one millionth of a gram) 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 162 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. Dental products used in the home such as toothpastes, rinses, and topically applied gels contain high concentrations of fluoride (range 230–12,300 ppm) and are not intended to be ingested. The most commonly used dental products, toothpastes, contain 900–1,100 ppm fluoride (ca. 0.10%), most often as sodium fluoride. If you swallow these products, you will be exposed to higher levels of fluoride. Swallowing toothpaste can account for a large percentage of the fluoride to which a child <8 years of age might be exposed 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 fluorides, hydrogen fluoride, or fluorine, see Chapter 6.

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

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 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.

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.

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.

For more information on how fluorides, hydrogen fluoride, and fluorine enter and leave your body, see Chapter 3.

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

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines and must be recertified regularly with training in updated and new guidelines.

Fluorides. 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 fluoride are added to toothpaste or drinking water to help prevent dental decay. However, exposure to higher levels of fluoride may harm your health. Skeletal fluorosis can be caused by eating, drinking, or breathing very 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 is extremely rare in the United States; it has occurred in some people consuming greater than 30 times the amount of fluoride typically found in fluoridated water. It is more common in places where people do not get proper nutrition. At fluoride levels 5 times greater than levels typically found in fluoridated water, fluoride can result in denser bones. However, these bones are often more brittle or fragile than normal bone and there is an increased risk of older men and women breaking a bone. Some studies have also found a higher risk of bone fractures in older men and women at fluoride levels typically found in fluoridated water. However, other studies have not found an effect at this fluoride dose. If you eat large amounts of sodium fluoride at one

time, it can cause stomachaches, vomiting, and diarrhea. Extremely large amounts can cause death by affecting your heart.

We do not know if eating, drinking, or breathing fluoride can cause reproductive effects in humans. Reproductive effects, such as decreased fertility and sperm and testes damage, have been seen in laboratory animals at extremely high doses (more than 100 times higher than levels found in fluoridated water). However, other studies have not found any reproductive effects in laboratory animals.

A number of studies have been done to assess whether there is an association between fluoride and 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. A study in 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 even higher doses of fluoride caused 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.

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. People breathing hydrogen fluoride have complained of eye, nose, and skin irritation. Breathing in a large amount of hydrogen fluoride with air can also harm the lungs and heart. Kidney and testes damage have been observed in animals breathing hydrogen fluoride.

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.

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 cause death due to lung damage.

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

1.6 HOW CAN FLUORIDES, HYDROGEN FLUORIDE, AND FLUORINE 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 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. The condition is called dental fluorosis. The changes increase in severity with increasing levels of fluoride. Dental fluorosis develops only while the teeth are forming in the jaw and before they erupt into the mouth (age <8 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 are fragile, and sometimes the teeth can break. The appearance of affected teeth is not identical for all children exposed to the same level of fluoride in the drinking water. Exposure to fluoride from other sources, such as fluoride tablets or rinses, may account for these differences. 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 develop a more severe form of dental fluorosis.

Fluoride can cross the placenta from the mother's blood to the developing fetus. Only a very small portion of fluoride ingested by women is transferred to a child through breast milk. Several human studies found an increase in birth defects or lower IQ scores in children living in areas with very high levels of fluoride in the drinking water. Those studies did not adequately access other factors that could have contributed to the effects. Another study did not find birth defects in children living in areas with low levels of fluoride. Birth defects have not been found in most studies of laboratory animals.

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

If your doctor finds that you have been exposed to significant amounts of fluorides, hydrogen fluoride, and fluorine, 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 naturally 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 always 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 FLUORIDES, HYDROGEN FLUORIDE, AND FLUORINE?

Urine and blood 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 or blood. 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 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. Bone sampling can be done in special cases to measure long-term exposure to fluorides. Because fluorides, hydrogen fluoride, and fluorine all enter the body as fluoride, these tests cannot distinguish among exposure to these different chemicals.

For more information on medical tests to determine exposure to fluorides, hydrogen fluoride, and fluorine, see Chapters 3 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 fluorides, hydrogen fluoride, and fluorine include the following:

Sodium fluoride, hydrogen fluoride, and fluorine 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 fluorides, hydrogen fluoride, and fluorine 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 determined 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 Public Health Service (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 FDA, ATSDR, 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 fluorides, hydrogen fluoride, and fluorine, 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: (800) 553-6847 or (703) 605-6000
Web site: http://www.ntis.gov/

2. RELEVANCE TO PUBLIC HEALTH

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

Fluorine is the most electronegative and reactive of all elements; fluoride is the ionic form of fluorine. Fluorine and anhydrous hydrogen fluoride are naturally occurring gases that have a variety of industrial uses including the production of fluorine-containing chemicals, pharmaceuticals, high octane gasoline, and fluorescent light bulbs; aqueous hydrofluoric acid is a liquid used for stainless steel pickling, glass etching, and metal coatings. The general population is typically exposed to very low levels of gaseous fluoride (primarily as hydrogen fluoride); in the United States and Canada, the levels ranged from 0.01 to 1.65 μg/m^3. Populations living near industrial sources of hydrogen fluoride, including coal burning facilities, 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. One of the more commonly used fluoride salt is sodium fluoride; its principal use is for the prevention of dental caries. Sodium fluoride and other fluoride compounds, such as fluorosilicic acid and sodium hexafluorisilicate, are used in the fluoridation of public water. Sodium monofluorophosphate and stanneous fluoride are commonly used in dentifrices such as toothpaste. The general population can be exposed to fluoride through the consumption of fluoridated drinking water, food, and dentifrices. The average dietary intake (including water) of fluoride ranges between 1.4 and 3.4 mg/day (0.02–0.048 mg/kg/day) for adults living in areas with 1.0 mg/L fluoride in the water. In areas with <0.3 mg/L fluoride in water, the adult dietary intakes ranged from 0.3 to 1.0 mg/day (0.004–0.014 mg/kg/day). In children, the dietary intakes ranged from 0.03 to 0.06 mg/kg/day in areas with fluoridated water and from 0.01 to 0.04 mg/kg/day in areas without fluoridated water. The Food and Nutrition Board of the Institute of Medicine has developed adequate intakes (AIs) for fluoride. The AI is the "estimated fluoride intake that has been shown to reduce the occurrence of dental caries maximally in a population without causing unwanted side effects including moderate dental fluorosis." The AIs for each age group are presented in Table 2-1.

Table 2-1. Adequate Intake Levels for Fluoride[a]

Age range	Adequate intake level (mg/day)	Adequate intake level (mg/kg/day)[b]
0–6 months	0.01	0.0014
6–12 months	0.5	0.056
1–3 years	0.7	0.054
4–8 years	1	0.045
9–13 years (males and females)	2	0.05
14–18 years (males)	3	0.046
14–18 years (females)	3	0.053
>18 years (males)	4	0.052
>18 years (females)	3	0.049

[a]Source: IOM 1997
[b]mg/kg/day doses were calculated by using reference body weights reported by IOM (1997)

2.2 SUMMARY OF HEALTH EFFECTS

Fluoride. The main health concern regarding fluoride is likely to be from excessive chronic oral exposure in drinking water. 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 laboratory animal species is the skeletal system (including teeth). Both beneficial and detrimental dental and skeletal effects have been observed in humans. Fluoride has been shown to decrease the prevalence of dental caries and, under certain conditions, has been used for the treatment of osteoporosis. However, excess fluoride can also result in dental fluorosis and can result in an increased prevalence of bone fractures in the elderly or skeletal fluorosis. Both the beneficial and detrimental effects of fluoride appear to be related to fluoride-induced alterations in tooth and bone mineralization.

Direct contact with fluoride can result in tissue damage. At high concentrations, fluoride can cause irritation and damage to the respiratory tract, stomach, and skin following inhalation, oral, and dermal exposure, respectively. At very high fluoride doses, fluoride can bind with serum calcium resulting in hypocalcemia and possibly hyperkalcemia; the severe cardiac effects (e.g., tetany, decreased myocardial contractility, cardiovascular collapse, ventricular fibrillation) observed at or near lethal doses are probably due to this electrolyte imbalance.

The available data on the potential of fluoride to induce reproductive and/or developmental effects is inconclusive. A study of birth records found a significant association between high levels of fluoride in municipal drinking water (3 ppm and greater) and decreases in fertility rates; another study found decreases in serum testosterone levels in men with skeletal fluorosis (fluoride concentration in water was 3.9 ppm). However, design limitations of these studies, particularly the use of poorly matched controls, limits the usefulness of these studies. Some animal studies have found alterations in reproductive hormone levels, histology of the testes, spermatogenesis, and fertility following exposure to relatively high oral doses of sodium fluoride, roughly equivalent to a human exposure level of >150 ppm in drinking water. However, other animal studies, including two-generation studies, have not found alterations in serum hormone levels in male rats, testicular histopathology, sperm morphology, or fertility. None of the available laboratory animal studies examined reproductive toxicity at low fluoride doses. The inadequate human studies and conflicting animal studies do not allow for an assessment of the potential of fluoride to induce reproductive effects in humans. Available human studies provide suggestive evidence that exposure to elevated levels of fluoride in drinking water may decrease IQ in

children; however, neither study controlled for other confounding variables. Animal studies have not found increases in the incidences of birth defects in the absence of maternal toxicity; at doses that caused maternal toxicity (decreases in body weight gain and food consumption), increases in abnormalities were found.

Numerous community-based studies have examined the possible association between fluoridated water and cancer. Most of these studies did not find significant associations between water fluoridation and cancer mortality or site-specific cancer incidence. Some studies have found associations between water fluoridation and cancer mortality/incidence or site-specific cancer incidence (osteosarcoma or bone cancer). The lack of control for potential confounding variables (i.e., age, race) limits the interpretation of the total cancer study results. The weight of the evidence indicates that fluoridation of water does not increase the risk of developing cancer. 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. IARC has determined that the carcinogenicity of fluoride to humans is not classifiable.

Hydrogen Fluoride. Hydrogen fluoride is highly corrosive, the primary effects are tissue damage resulting from direct contact. Acute inhalation exposure can result in irritation, inflammation, 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. Some evidence of early skeletal fluorosis has been observed in workers exposed to hydrogen fluoride and fluoride dusts. These studies did not adequately characterize fluoride exposure levels and, in most of the studies, there is some uncertainty regarding the diagnosis of skeletal fibrosis. 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 elevated 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. As noted previously, IARC has determined that the carcinogenicity of fluoride to humans is not classifiable.

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.

A greater detailed discussion of fluoride-induced skeletal effects and portal of entry effects following exposure to fluorides, hydrogen fluoride, hydrofluoric acid, or fluorine follows. The reader is referred to Section 3.2, Discussion of Health Effects by Route of Exposure, for additional information on other health effects.

Dental and Skeletal Effects. Human and animal data clearly indicate that fluoride accumulates in the teeth and bone resulting in beneficial and detrimental alterations in the structure. There is strong evidence that oral exposure to fluoride can reduce the risk of dental caries. However, elevated fluoride levels during enamel maturation can also result in dental fluorosis, which is characterized by hypo-mineralization of subsurface layers of enamel. In the mildest forms of dental fluorosis, the tooth is fully functional but has cosmetic alterations, almost invisible opaque white spots. In more severely fluorosed teeth, the enamel is pitted and discolored and is prone to fracture and wear. Several studies have found significant increases in the number of decayed, missing, or filled tooth surfaces in children with severe dental fluorosis. The prevalence and severity of dental fluorosis is strongly associated with fluoride exposure levels. Dose-response relationships cannot be established from most of these studies because all sources of fluoride were not considered and most studies used fluoride levels in drinking water as the dosimetric. A recent meta-analysis estimated that 48% of children living in communities with 1 ppm fluoride in the water would have evidence of dental fluorosis, most of it considered very mild. The predicted incidence of dental fluorosis of aesthetic concern was 12.5%. Although the exact mechanism of dental fluorosis is not known, it is generally believed to result in a fluoride-induced delay in the hydrolysis of the enamel matrix protein amelogenin during the early enamel maturation phase of tooth development.

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. In the more severe cases of crippling fluorosis, complete rigidity of the spine can occur. Reported cases are found almost exclusively in developing countries, particularly India and China, and are often associated with malnutrition. It is generally stated that a dose of 10–20 mg/day (equivalent to 5–10 ppm in the water, for a person who ingests 2 L/day) for at least 10 years 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.

At lower doses, fluoride can cause an increase in bone density and fragility. 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 (typically about 1 ppm), 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 exposure to 1 ppm fluoride in drinking water and the risk of bone fractures cannot be established from these studies. Studies involving exposure to higher doses of fluoride have consistently found significant increases in the risk of nonvertebral fractures, particularly hip fractures. A study involving lifetime exposure to 4.3–8 ppm fluoride in drinking water found an elevated risk of hip fractures among elderly men and women; this elevated risk of hip fracture was also observed in a community with very low fluoride (0.25–0.34 ppm) in the water. Studies of individuals using sodium fluoride for the treatment of osteoporosis also found significant increases in bone mineral density. Studies in laboratory animals have found defects in bone growth, fracture healing, and bone strength.

Respiratory, Gastrointestinal, Dermal, and Ocular Effects. Fluoride, hydrogen fluoride, hydrofluoric acid, and fluorine are extremely irritating chemicals and can cause tissue damage after direct contact. The respiratory tract is the primary target of toxicity following inhalation exposure to hydrogen fluoride or fluorine. Single exposures to relatively low concentrations of hydrogen fluoride (≥0.5 ppm) or fluorine (≥10 ppm) can result in upper respiratory tract irritation in humans. At higher concentrations pulmonary congestion, necrosis and/or edema have been observed in laboratory animals; pulmonary edema has also been observed in humans exposed to lethal concentrations of hydrogen fluoride.

Pulmonary and nasal irritations have also been reported following repeated exposures for about 30 days. Chronic exposure to hydrogen fluoride and cryolite dust has resulted in impaired lung function in workers. The observed respiratory effects are attributed to its highly corrosive properties. Human and animal data suggest that preexposure to lower levels can reduce the respiratory effects.

Acute and chronic oral exposure to high doses of sodium fluoride, typically >1 mg fluoride/kg, can result in nausea, vomiting, and gastric pain. Nausea, loss of appetite, and vomiting has also been reported by workers exposed to cryolite dust for >2 years. The effects occur shortly after ingestion and are likely due to the formation of hydrofluoric acid in the stomach. There is some evidence to suggest that these overt signs of gastric irritation may not be sensitive indicators of gastric mucosa damage. Petechiae and/or erosions were observed in most subjects exposed to sodium fluoride or a dental gel; however, nausea was only reported by 33% of the subjects. Similar findings were reported in animal studies; thickening of the glandular stomach mucosa and punctate hemorrhages were observed in rats ingesting high doses of sodium fluoride in drinking water for an intermediate duration. Gastrointestinal effects have been observed following inhalation and oral exposure to hydrogen fluoride. 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.

Fluorine and hydrogen fluoride are highly reactive chemicals; direct contact can result in severe damage to the skin or eyes. The severity of the damage is directly related to the concentration and duration of exposure. Humans exposed to hydrogen fluoride gas for an acute duration have reported symptoms of skin irritation (itching and burning sensation) and eye irritation. Most of these human data are inadequate for establishing concentration-response relationships; the data on ocular irritation do provide some information of the threshold of toxicity. Very mild eye irritation was observed in subjects exposed to 0.5–4.5 ppm hydrogen fluoride for 1 hour, mild eye irritation was reported during a 15–50-day, 6-hour/day exposure to 3 ppm. Aqueous hydrofluoric acid applied directly to the skin can cause extensive damage; it is quickly absorbed through the epidermis causing necrosis in underlying tissues (Chela et al. 1989). In rabbits, a 1-minute exposure to 2% hydrofluoric acid did not produce skin lesions; however, necrotic lesions were observed after a 1–4-hour exposure to this concentration.

There are limited data on the dermal and ocular toxicity of fluorine. A human study reported slight eye irritation following a repeated exposure to 10 ppm fluorine (no irritation was reported a during 15-minute exposure to this concentration), mild eye irritation during a 3-minute exposure to 30–50 ppm, and marked irritation during a <1-minute exposure to 100 ppm.

2.3 MINIMAL RISK LEVELS

Fluorides

Inhalation MRLs

No inhalation MRLs were derived for fluoride. Several occupational exposure studies examined fluoride toxicity in aluminum potroom workers (Carnow and Conibear 1981; Chan-Yeung et al. 1983b; Czerwinski et al. 1988; Dinman et al. 1976c; Kaltreider et al. 1972). Interpretation of these studies is limited by co-exposure to hydrogen fluoride and other chemicals including aluminum. There are limited data on the inhaled toxicity of fluoride. Significant increases in lung weight and pulmonary edema have been observed in mice exposed to 10 mg fluoride/m^3 as sodium fluoride 4 hours/day, for 10–14 days (Chen et al. 1999; Yamamoto et al. 2001). Impaired pulmonary bactericidal activity has also been observed in mice exposed to 5 mg fluoride/m^3 as sodium fluoride (Yamamoto et al. 2001). These studies cannot be used for MRL derivation because none of the studies examined the skeletal system, which has been shown to be a sensitive target following oral exposure.

Oral MRLs

A limited number of end points have been examined in humans and animals following acute oral exposure to fluorides. Most of the available data involved exposure to lethal doses of fluoride; other examined potential targets of toxicity include the gastrointestinal tract, bone, sperm morphology, and the developing organism. Symptoms of gastric irritation, such as nausea, vomiting, and gastric pain, have been observed shortly after exposure to fluoride in drinking water (Hoffman et al. 1980; Spak et al. 1989, 1990; Spoerke et al. 1980). Spak et al. (1989) reported macroscopic and microscopic signs of gastric irritation in subjects ingesting 20 mg fluoride (1,000 ppm) as sodium fluoride; other studies have not reliably identified exposure concentrations. A decrease in modulus of elasticity was observed in the bones of weanling rats exposed to 9.5 mg fluoride/kg/day as sodium fluoride in drinking water for 2 weeks (Guggenheim et al. 1976). No alterations in sperm morphology were observed in mice exposed to 32 mg fluoride/kg/day as sodium fluoride (Li et al. 1987a). In the absence of maternal toxicity, no adverse effects in rat or rabbit offsprings were observed (Heindel et al. 1996); skeletal and visceral alterations were observed in the offspring of rat dams with decreases in body weight and feed consumption (Guna Sherlin and Verma 2001). From the available data, it appears that the stomach is a

sensitive target of fluoride toxicity following consumption of a bolus dose of fluoride. However, the observed effect (gastric irritation) is likely due to the fluoride concentration rather than a daily dose (expressed as mg/kg/day). It is not known whether the gastric mucosa would adapt to repeated exposure to this concentration of fluoride. An acute-duration oral MRL for fluorides was not derived due to the previously mentioned uncertainties in basing the MRL on a study that administered a single bolus dose of sodium fluoride and because the resultant MRL would be lower than the chronic-duration oral MRL.

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 lowest-observed-adverse-effect levels (LOAELs) are 0.5 mg fluoride/kg/day for thyroid effects in rats exposed to sodium fluoride in drinking water for 2 months (Bobek et al. 1976) and 0.80 mg fluoride/kg/day for increased bone formation in mice exposed to sodium fluoride in drinking water for 4 weeks (Marie and Hott 1986). Neither study identified a no-observed-adverse-effect level (NOAEL). Derivation of an intermediate-duration MRL from either study would result in an MRL that is lower than the chronic-duration oral MRL.

- A chronic-duration oral MRL of 0.05 mg fluoride/kg/day was derived for fluoride.

A number of studies have examined the possible association between exposure to fluoridated water and the risk of increased bone fractures, particularly hip fractures. In general, the studies involved comparing the incidence of hip fractures among residents aged 55 years and older living in a community with fluoridated water (around 1 ppm) with the incidence in a comparable community with lower levels of fluoride in the water. Inconsistent results have been found, with studies finding decreases (Lehmann et al. 1998; Phipps et al. 2000; Simonen and Laittinen 1985), increases (Cooper et al. 1990, 1991; Danielson et al. 1992; Jacobsen et al. 1990, 1992; Kurttio et al. 1999), or no effect (Arnala et al. 1986; Cauley et al. 1995; Goggin et al. 1965; Jacobsen et al. 1993; Karagas et al. 1996; Kröger et al 1994; Suarez-Almazor et al. 1993) on hip fracture risk. Studies by Li et al. (2001) and Sowers et al. (1986) have examined communities with higher levels of naturally occurring fluoride in the water. Both studies found increases in the incidence of hip fractures in residents exposed to 4 ppm fluoride and higher (Li et al. 2001; Sowers et al. 1986, 1991); the hip fracture incidence in the highly exposed community was compared to the rates in communities with approximately 1 ppm fluoride in the water. Significant increases in the occurrence of nonvertebral fractures were also observed in postmenopausal women ingesting sodium fluoride (34 mg fluoride/day; 0.56 mg fluoride/kg/day) for the treatment of osteoporosis (Riggs et al. 1990, 1994). This result was not found in another study of postmenopausal women with spinal osteoporosis treated with 34 mg fluoride/day as sodium fluoride (Kleerekoper et al. 1991). 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 (Haguenauer et al. 2000). The Li et al. (2001) study was selected as the basis for the chronic-duration oral MRL. This study was selected because other potential sources of fluoride were considered (the Riggs et al. [1990] study did not provide information on the level of fluoride in the drinking water or other sources of fluoride) and calcium levels were similar among the different communities (the Sowers et al. [1986] study did not control for calcium intake). The Li et al. (2001) study identified a NOAEL of 2.62–3.56 ppm (0.15 mg fluoride/kg/day) and LOAEL of 4.32–7.97 ppm (0.25 mg fluoride/kg/day). An MRL of 0.05 mg fluoride/kg/day is calculated by dividing the NOAEL of 0.15 mg/kg/day by an uncertainty factor of 3 to account for human variability; a partial uncertainty factor was used because the most sensitive subpopulation, elderly men and women, was examined.

Hydrogen Fluoride/Hydrofluoric Acid

Inhalation MRLs

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

The respiratory tract appears to be the primary target of hydrogen fluoride toxicity. Upper respiratory tract irritation and inflammation and lower respiratory tract inflammation have been observed in several human studies. Nasal irritation was reported by one subject exposed to 3.22 ppm fluoride as hydrogen fluoride 6 hours/day for 10 days (Largent 1960). Very mild to moderate upper respiratory symptoms were reported by healthy men exposed to 0.5 ppm fluoride as hydrogen fluoride for 1 hour (Lund et al. 1997). At higher concentrations, 4.2–4.5 ppm fluoride as hydrogen fluoride for 1 hour, more severe symptoms of upper respiratory irritation were noted (Lund et al. 1997, 2002). In subjects exposed to 4.2 ppm for 1 hour, analysis of nasal lavage fluid provided suggestive evidence that hydrogen fluoride induces an inflammatory response in the nasal cavity (Lund et al. 2002). Similarly, bronchoalveolar lavage fluid analysis revealed suggestive evidence of bronchial inflammation in another study of subjects exposed to 1.9 ppm fluoride as hydrogen fluoride for 1 hour (Lund et al. 1999); no alterations were observed at 0.5 ppm. Respiratory effects have also been reported in rats acutely exposed to hydrogen fluoride. Mild nasal irritation was observed during a 60-minute exposure to 120 ppm fluoride (Rosenholtz et al. 1963), and respiratory distress was observed at 2,310, 1,339, 1,308, and 465 ppm fluoride for 5, 15, 30, or 60 minutes, respectively (Rosenholtz et al. 1963). 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 (Dalbey et al. 1998a, 1998b). These effects were not observed when the tracheal cannula was not used.

The Lund et al. (1997, 1999) study was selected as the basis of the acute-duration inhalation MRL for hydrogen fluoride. As reported in the 1997 publication, a trend ($p=0.06$) toward increased upper respiratory tract symptom score, as compared to pre-exposure symptom scores, was observed at the lowest concentration tested (0.5 ppm). A significant increase in the total symptom score was also observed at this concentration. No significant alterations in symptom scores were observed at the mid concentration (1.9 ppm), and increases in upper respiratory and total symptom scores were observed at the high concentration (4.5 ppm). Suggestive evidence of bronchial inflammation was also observed at ≥1.9 ppm fluoride (Lund et al. 1999), although no alterations in lower respiratory tract symptoms (Lund et al. 1997) or lung function (Lund et al. 1997) were observed at any of the tested concentrations. The MRL is based on the minimal LOAEL of 0.5 ppm fluoride for upper respiratory tract irritation. Data on nasal irritation from the Largent (1960) report, the Lund et al. (2002) study, and the intermediate-duration study by Largent (1960) provide suggestive evidence that the severity of nasal irritation does not increase with increasing exposure duration. These three studies identified similar LOAEL values for different exposure durations: 3.22 ppm 6 hours/day for 10 days (Largent 1960), 3.8 ppm 1 hour/day for 1 day (Lund et al. 2002), and 2.98 ppm 6 hours/day, 6 days/week for 15–50 days (Largent 1960). Thus, time scaling was not used to derive the acute MRL. The MRL of 0.02 ppm was calculated by dividing the minimal LOAEL of 0.5 ppm by an uncertainty factor of 30 (3 for the use of a minimal LOAEL and 10 to account for human variability).

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 (Largent 1960). 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 (Stokinger 1949). An intermediate-duration inhalation MRL was not derived for hydrogen fluoride because an MRL based on the Largent (1960) study is higher than the acute-duration inhalation MRL derived from the Lund et al. (1997, 1999) study.

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

Oral MRLs

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.

Fluorine

Inhalation MRLs

- 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 ≥10 ppm for 0.5–15 minutes (Keplinger and Suissa 1968) and dyspnea and lung congestion in rats and mice exposed to 47–175 ppm fluorine for 5–60 minutes (Keplinger and Suissa 1968). 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 NOAEL and LOAEL values for nasal irritation identified in the human study by Keplinger and Suissa (1968) were selected as the basis of an acute-duration inhalation MRL for fluorine. Subjects did not report nasal or eye irritation following a 3-, 5-, or 15-minute exposure to 10 ppm. Eye irritation was observed at ≥23 ppm; nose irritation at ≥50 ppm, and skin irritation at ≥78 ppm. 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. The NOAEL of 10 ppm was adjusted for intermittent exposure (0.25 hour/24 hours) and divided by an uncertainty factor of 10 to account for human variability to derive an acute-duration inhalation MRL of 0.01 ppm fluorine.

Longer-duration exposure studies are limited to a multi-species intermediate-duration study (Stokinger 1949) and an occupational exposure study (Lyon 1962). As with acute-duration exposure, the primary effect of intermediate-duration exposure to fluorine was eye, nose, and mouth irritation, which was observed in rats and dogs (Stokinger 1949). Evidence of pulmonary damage (bronchitis, hemorrhage, and edema) was also observed in rats, rabbits, and dogs. The study author noted that there was some difficulty in measuring the exposure concentrations and considered the measurements of exposure concentrations to be questionable. The chronic-duration study of workers exposed to fluorine (Lyon 1962) was not considered for MRL derivation because it used a relatively insensitive measure of

respiratory effects (absences from work and visits to the medical department with respiratory complaints) and the workers and the controls were exposed to uranium hexafluoride and hydrogen fluoride.

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 fluorides, hydrogen fluoride, and fluorine. 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.

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.

Hydrogen fluoride is also a gas and is very water soluble. It dissolves readily in any water present in the air or other media. When hydrogen fluoride is dissolved in water, it is called hydrofluoric acid. 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.

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.

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 fluoride, hydrogen fluoride/hydrofluoric acid, and fluorine. Toxic effects of occupational exposure in aluminum reduction plants, where exposures 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 the amount of fluoride ion.

The primary routes and durations of concern vary with the different fluorine compounds. In general, the more soluble the fluoride, 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 oral 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.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for fluorides, hydrogen fluoride, and fluorine. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. 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 within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

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

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 fluoride or fluorine, these substances are also discussed.

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.

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.

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 hydrogen fluoride and fluorine 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.

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 to 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). In a study (Dalbey et al. 1998a) comparing the toxicity of hydrogen fluoride in rats using mouth-breathing (rats fitted with a tracheal cannula) and nose-breathing models, dramatic differences in lethality were observed. In the mouth-breathing rats, 50 and 80% of the animals died within 2 weeks of a 10-minute mouth breathing exposure to 3,655 or 6,663 ppm fluoride, respectively. In contrast, no deaths were noted following exposure to these concentrations using the nose-breathing model. The difference in lethality between the two models is probably due to the higher dose of hydrogen fluoride reaching the lower airways in the mouth-breathing model.

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.

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. Increases in survival time were observed in rabbits exposed to 50 ppm fluorine for 30 minutes, 1 day/week for 4 weeks prior to exposure to a lethal concentration of fluorine (400 ppm for 30 minutes) (Keplinger 1969). Survival time in the rabbits was 48 hours, as compared to 18 hours or less in similarly exposed rabbits not preexposed to fluorine. In mice, slight increases in LC_{50} values were found in animals receiving a single exposure to 30–45 ppm fluorine prior to exposure to lethal concentrations. However, slight decreases in LC_{50} values were seen in mice preexposed to 25 ppm fluorine (Keplinger 1969). 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.

The LC_{50} values for each species and duration category of exposure to hydrogen fluoride 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 fluorine are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.1.2 Systemic Effects

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 3-1 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 fluorine are recorded in Table 3-2 and plotted in Figure 3-2. The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category of exposure to fluoride are recorded in Table 3-3 and plotted in Figure 3-3.

Respiratory Effects.

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 exposures 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. In another case, a women developed herrhagic alveolitis and adult respiratory disease syndrome following exposure to a presumably high concentration of hydrogen fluoride from a cleaning product (Bennion and Franzblau 1997).

Two human experimental studies have been conducted to assess the ability of hydrogen fluoride to induce respiratory tract inflammation. In the first study, increases in upper airway symptoms were observed in

Table 3-1 Levels of Significant Exposure to Hydrogen Fluoride - Inhalation

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat	1 d 5-60 min/d				2890 (30-minute LC50) 6620 (15-minute LC50) 14600 (5-minute LC50) 1610 (60-minute LC50)	Haskell Laboratory 1988 hydrogen fluoride
2	Rat (Wistar)	1 d 5-60 min/day				1940 (30-minute LC50) 2555 (15-minute LC50) 4722 (5-minute LC50) 1242 (60-minute LC50)	Rosenholtz et al. 1963 hydrogen fluoride
3	Rat	1 d 60 min/d				1325 (60-minuteLC50)	Wohlslagel et al. 1976 hydrogen fluoride
4	Mouse	1 d 60min/d				325 (60-minute LC50)	Wohlslagel et al. 1976 hydrogen fluoride
5	Gn Pig (Hartley)	1 d 5-60 min/d				4327 (15-minute LC50)	Rosenholtz et al. 1963 hydrogen fluoride
	Systemic						
6	Human	1 hour	Resp		1.9 M (lower respiratory inflammation) 0.5 M[b] (upper respiratory irritation)		Lund et al. 1999; Lund et al. 1997 hydrogen fluoride

Table 3-1 Levels of Significant Exposure to Hydrogen Fluoride - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form
7	Human	1 hour	Resp		4.2 M	(upper airway irritation and inflammation)			Lund et al. 2002 hydrogen fluoride
8	Human	1 to sev minutes see comments	Dermal		122	(smarting of the skin)			Machle et al. 1934 hydrogen fluoride
			Ocular		122	(conjunctival irritation)			
9	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)			
10	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					
11	Rat	1 d 5 min/d	Resp		712	(mild nasal irritation)	2310	(temporary respiratory distress and nasal discharge)	Rosenholtz et al. 1963 hydrogen fluoride
			Ocular		712	(moderate lacrimation)			

Table 3-1 Levels of Significant Exposure to Hydrogen Fluoride - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form
12	Rat	1 d 15min/d	Resp	292	357	(nasal irritation)	1339	(temporary respiratory distress and nasal discharge)	Rosenholtz et al. 1963 hydrogen fluoride
			Ocular	292	357	(lacrimation)			
13	Rat	1 d 60min/d	Resp	98	120	(nasal irritation)	465	(temporary respiratory distress and nasal discharge)	Rosenholtz et al. 1963 hydrogen fluoride
			Ocular	98	120	(lacrimation)			
14	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								
15	Rat (NS)	5 wks 6d/wk 6hr/d					31	(100% mortality)	Stokinger 1949 hydrogen fluoride
16	Mouse (NS)	5 wks 6d/wk 6hr/d					31	(100% mortality)	Stokinger 1949 hydrogen fluoride
	Systemic								
17	Human	15-50 d 6 hr/d	Resp		2.98	(slight nasal irritation)			Largent 1960 hydrogen fluoride
			Dermal		2.98	(stinging sensation on skin)			
			Ocular		2.98	(stinging sensation in eyes)			

Table 3-1 Levels of Significant Exposure to Hydrogen Fluoride - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
18	Rat (NS)	5 wks 6hr/d	Resp	8.2	31 (pulmonary hemorrhage)		Stokinger 1949 hydrogen fluoride
			Hemato	31			
			Renal	8.2	31 (cortical necrosis)		
			Ocular		8.2 (subcutaneous hemorrhage around the eyes and on the feet)		
19	Mouse (NS)	5 wks 6d/wk 6hr/d	Dermal		8.2 (subcutaneous hemorrhage around the eyes and on the feet)		Stokinger 1949 hydrogen fluoride
20	Dog (NS)	5 wks 6d/wk 6hr/d	Resp		31 (pulmonary hemorrhage)		Stokinger 1949 hydrogen fluoride
			Hemato	31			
21	Rabbit (NS)	5 wks 6d/wk 6hr/d	Resp	8.2	31 (pulmonary hemorrhage)		Stokinger 1949 hydrogen fluoride
			Hemato	31			
	Neurological						
22	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 3-1.

b Used to derive an acute-duration inhalation minimal risk level (MRL) of 0.02 ppm; the concentration was divided by an uncertainty factor of 30 (3 for use of a minimal LOAEL and 10 to account for human variability).

Bd = body weight; d = day(s); Hemato = hematological; hr = hour(s); incr = increase; LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; min = minute(s); mo = month(s); NOAEL = no-observed-adverse-effect level; ppm = parts per million; RBC = red blood cell; Resp = respiratory; wk = week(s)

Figure 3-1. Levels of Significant Exposure to Hydrogen Fluoride - Inhalation

Acute (≤14 days)

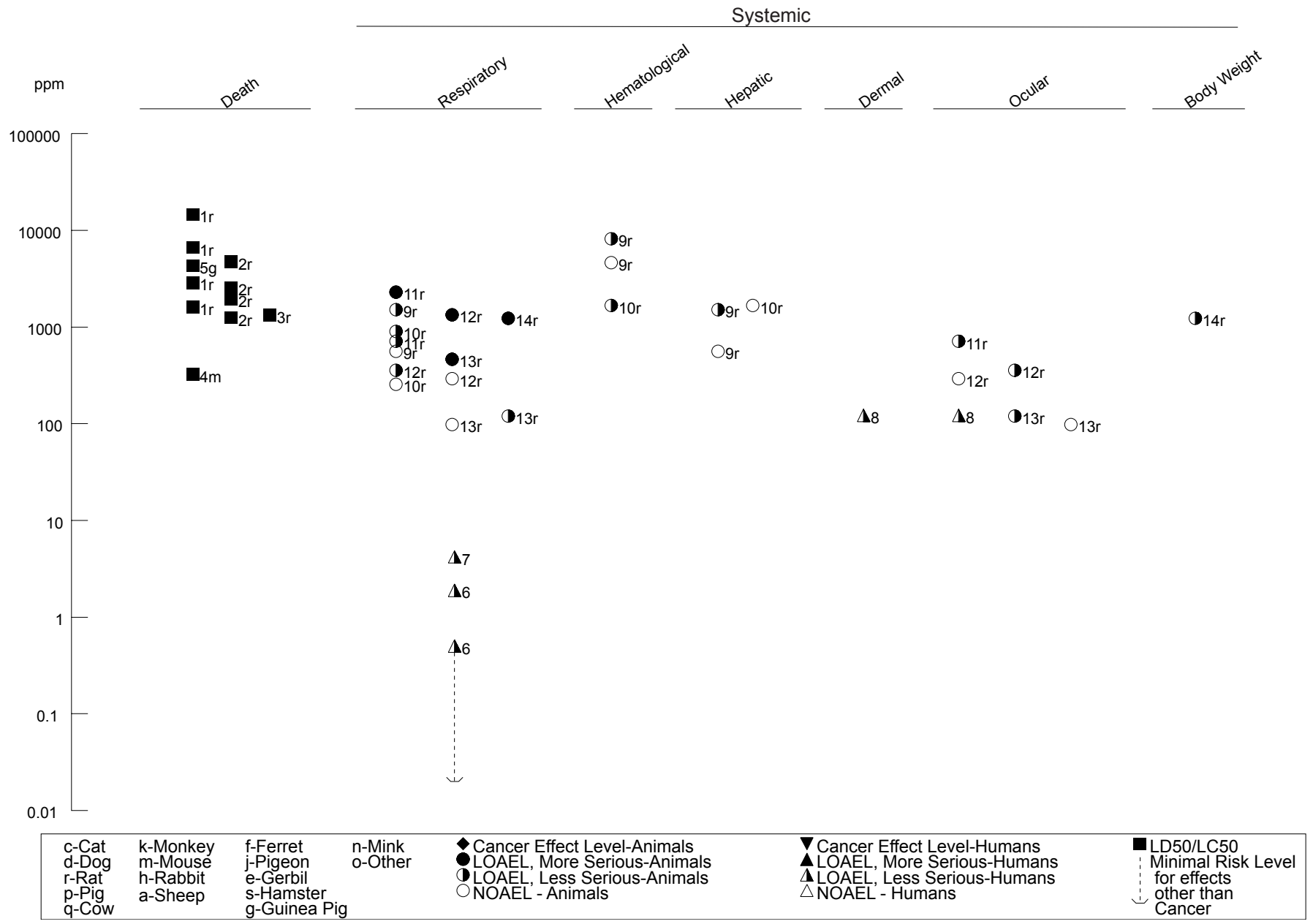


Figure 3-1. Levels of Significant Exposure to Hydrogen Fluoride - Inhalation (*Continued*)

Intermediate (15-364 days)

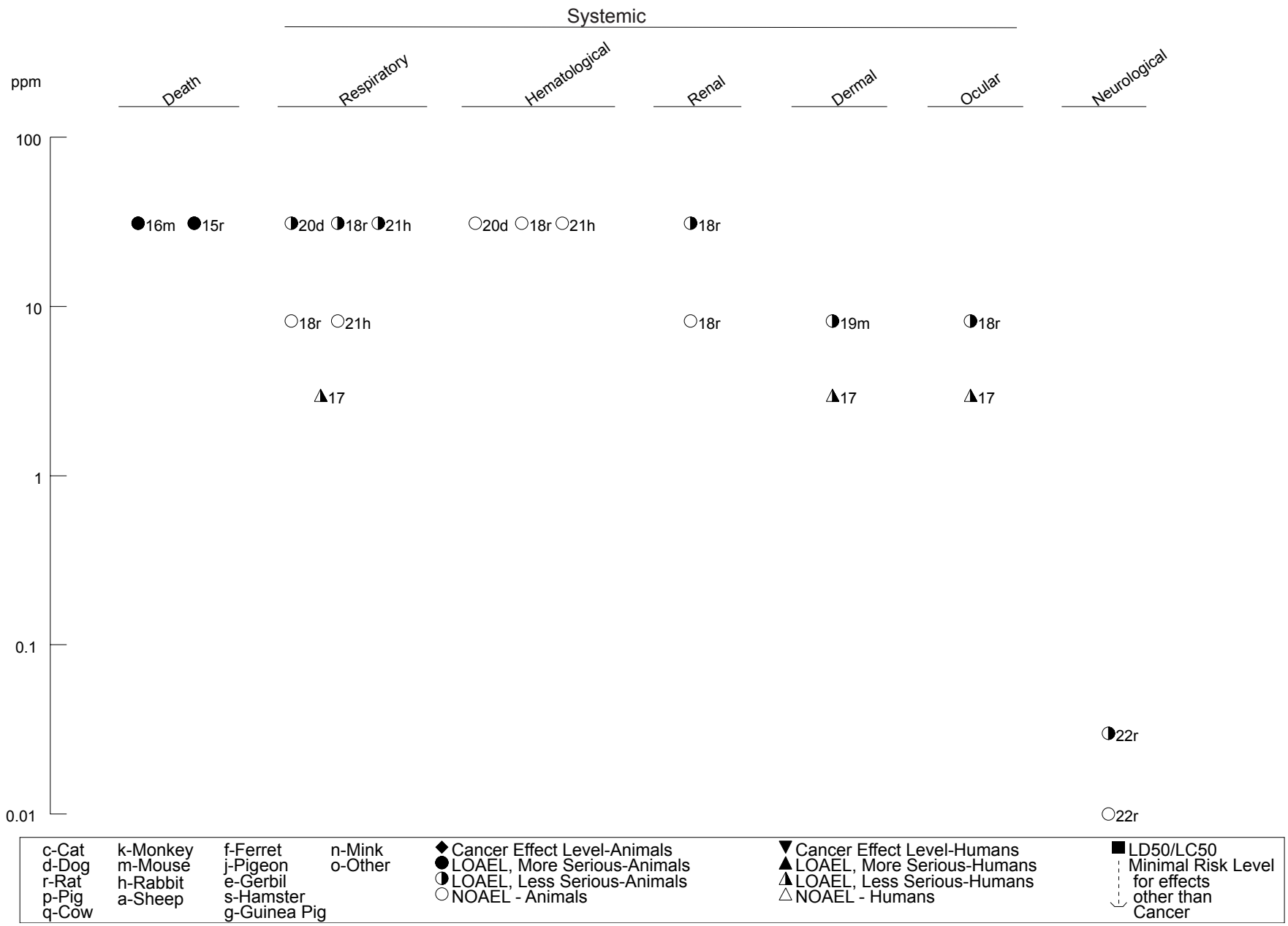


Table 3-2 Levels of Significant Exposure to Fluorine - Inhalation

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat (Osborne-Mendel)	1d 5-60min/d				270 (30-minute LC50) 390 (15-minute LC50) 700 (5-minute LC50) 185 (60-minute LC50)	Keplinger and Suissa 1968 fluorine
2	Mouse (Swiss-Webster)	1d 15-60min/d				225 (30-minute LC50) 375 (15-minute LC50) 600 (5-minute LC50) 150 (60-minute LC50)	Keplinger and Suissa 1968 fluorine
3	Gn Pig (New England)	1d 15-60min/d				395 (15-minute LC50) 170 (60-minute LC50)	Keplinger and Suissa 1968 fluorine
4	Rabbit (New Zealand)	1d 5-30min/d				820 (5-minute LC50) 270 (30-minute LC50)	Keplinger and Suissa 1968 fluorine
	Systemic						
5	Human	2-3 days 3-5 minutes every 15 minutes	Dermal		10 (slight skin irritation)		Keplinger and Suissa 1968 fluorine
			Ocular		10 (slight eye irritation)		

Table 3-2 Levels of Significant Exposure to Fluorine - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
6	Human	15 minutes	Resp	10[b]			Keplinger and Suissa 1968 fluorine
			Dermal	10			
			Ocular	10			
7	Human	1d 0.5min/d	Resp		100 (nasal irritation)		Keplinger and Suissa 1968 fluorine
			Ocular		100 (eye irritation)		
8	Human	1d 1min/d	Resp		67 (nasal irritation)		Keplinger and Suissa 1968 fluorine
			Dermal	67	67 (skin irritation)		
			Ocular		67 (eye irritation)		
9	Human	1d 3min/d	Resp	10	50 (slight nasal irritation)		Keplinger and Suissa 1968 fluorine
			Ocular	10	50 (eye irritation)		
10	Human	1d 5min/d	Resp	23			Keplinger and Suissa 1968 fluorine
			Dermal	23			
			Ocular	10	23 (slight eye irritation)		

Table 3-2 Levels of Significant Exposure to Fluorine - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form
11	Rat (Osborne-Mendel)	1d 5min/d	Resp	88	350	(irritation)			Keplinger and Suissa 1968 fluorine
					175	(dyspnea; mild lung congestion)			
			Ocular	88	175	(eye irritation)			
12	Rat (Osborne-Mendel)	1d 15min/d	Resp	49	195	(irritation)			Keplinger and Suissa 1968 fluorine
					98	(very mild lung congestion)			
			Ocular	195					
13	Rat (Osborne-Mendel)	1d 30min/d	Resp	35	140	(nasal irritation)			Keplinger and Suissa 1968 fluorine
					70	(very mild lung congestion)			
			Ocular	70	140	(eye irritation)			
14	Rat (Osborne-Mendel)	1d 60min/d	Resp	28	93	(nasal irritation)			Keplinger and Suissa 1968 fluorine
					47	(very mild lung congestion)			
			Ocular	93					
15	Mouse (Swiss-Webster)	1d 5min/d	Resp	79			174	(dyspnea; nasal irritation; diffuse lung congestion; alveolar necrosis)	Keplinger and Suissa 1968 fluorine
			Hepatic	174	195	(necrosis and cloudy swelling)			
			Renal	79	114	(necrosis)			
			Ocular	300	467	(eye irritation)			

Table 3-2 Levels of Significant Exposure to Fluorine - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)		LOAEL Serious (ppm)	Reference Chemical Form
16	Mouse (Swiss-Webster)	1d 15min/d	Resp	65	188	(irritation)		Keplinger and Suissa 1968 fluorine
					87	(very mild lung congestion)		
			Ocular	188				
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	67	113	(irritation)		Keplinger and Suissa 1968 fluorine
				32	67	(very mild lung congestion)		
			Ocular	113				
20	Mouse (Swiss-Webster)	1d 60min/d	Resp	30	150	(nasal irritation)		Keplinger and Suissa 1968 fluorine
					50	(very mild lung congestion)		

Table 3-2 Levels of Significant Exposure to Fluorine - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	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	198	(irritation)		Keplinger and Suissa 1968 fluorine
					100	(very mild lung congestion)		
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
			Ocular	39	93	(eye irritation)		
25	Dog (NS)	1d 60min/d	Resp	68	93	(irritation, cough, and slight dyspnea)		Keplinger and Suissa 1968 fluorine
			Ocular	38	68	(eye irritation)		
26	Rabbit (New Zealand)	1d 5min/d	Resp	79	410	(irritation)		Keplinger and Suissa 1968 fluorine
					134	(slight dyspnea)		

Table 3-2 Levels of Significant Exposure to Fluorine - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form
27	Rabbit (New Zealand)	1d 30min/d	Resp	32	135	(irritation)			Keplinger and Suissa 1968 fluorine
					71	(very mild lung congestion)			
	INTERMEDIATE EXPOSURE								
	Death								
28	Rat (NS)	5 wks 6d/wk 6hr/d					18	(100% mortality)	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 3-2 Levels of Significant Exposure to Fluorine - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	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 3-2.

b Used to derive an acute inhalation minimal risk level of 0.01 ppm; the concentration was adjusted for intermittent exposure (0.25 hours/24 hours) and divided by an uncertainty factor of 10 to account for human variability.

d = day(s); Gn Pig = Guinea pig; LC50 = 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 3-2. Levels of Significant Exposure to Fluorine - Inhalation

Acute (≤14 days)

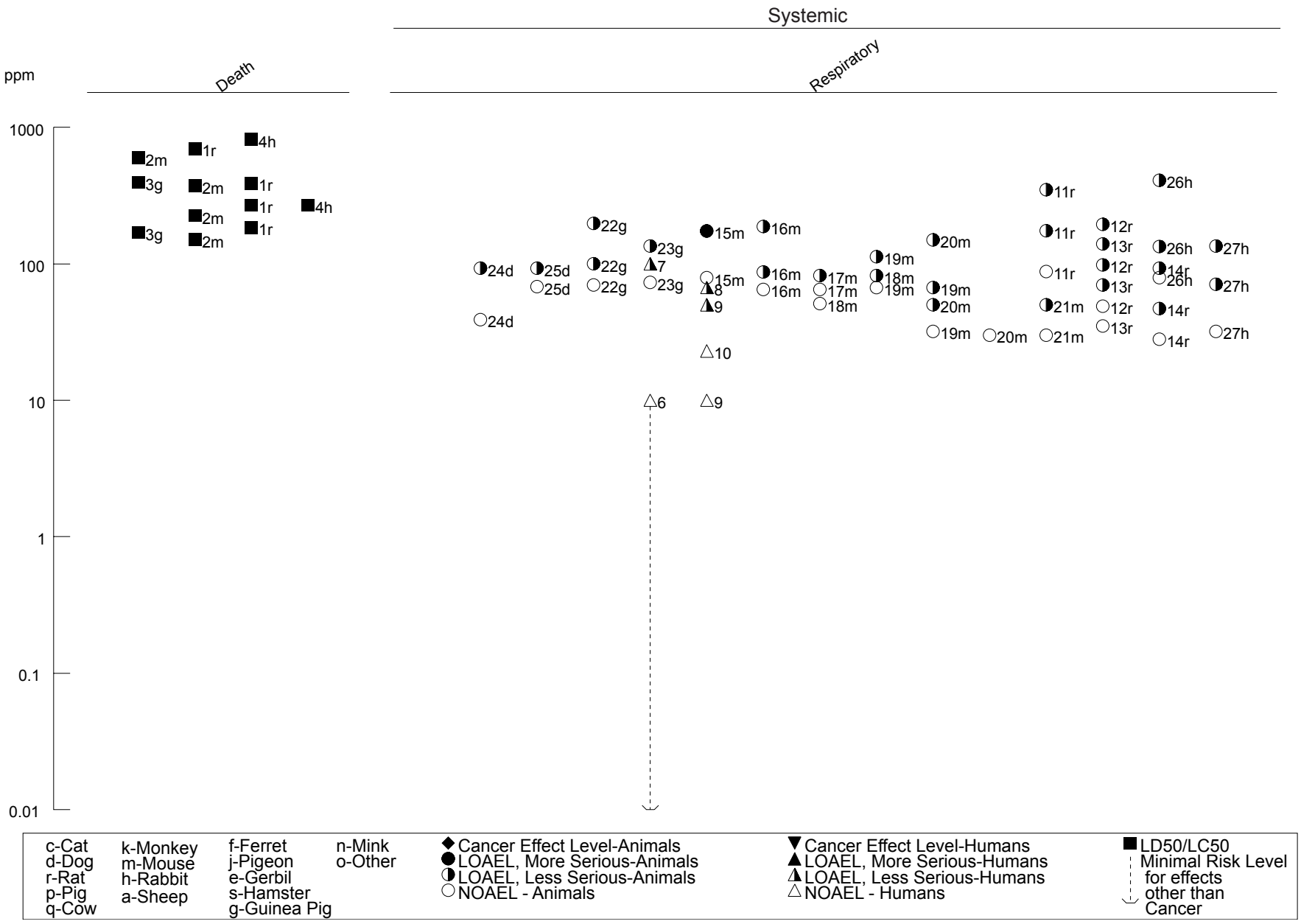


Figure 3-2. Levels of Significant Exposure to Fluorine - Inhalation (*Continued*)

Acute (≤14 days)

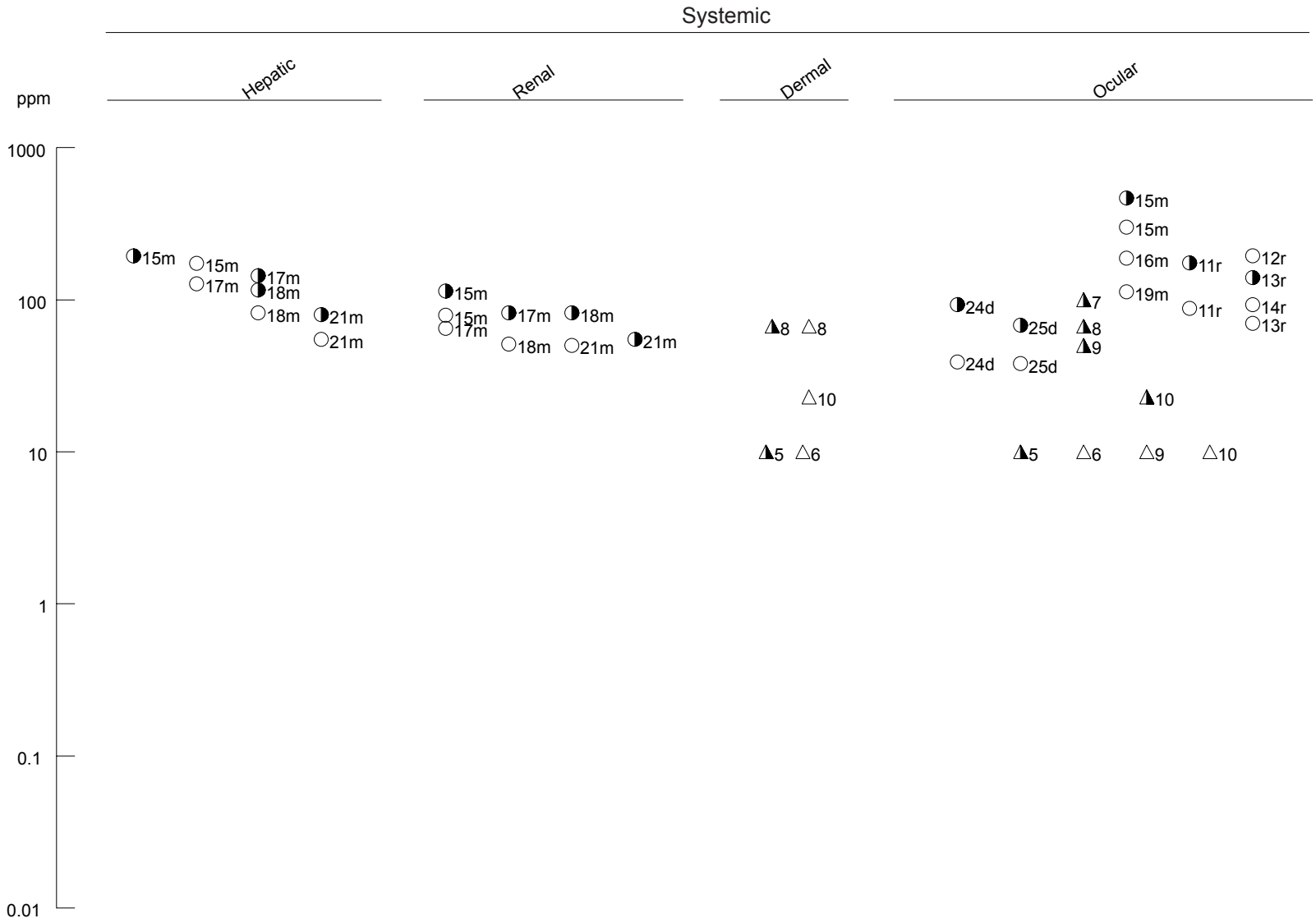


Figure 3-2. Levels of Significant Exposure to Fluorine - Inhalation (*Continued*)

Intermediate (15-364 days)

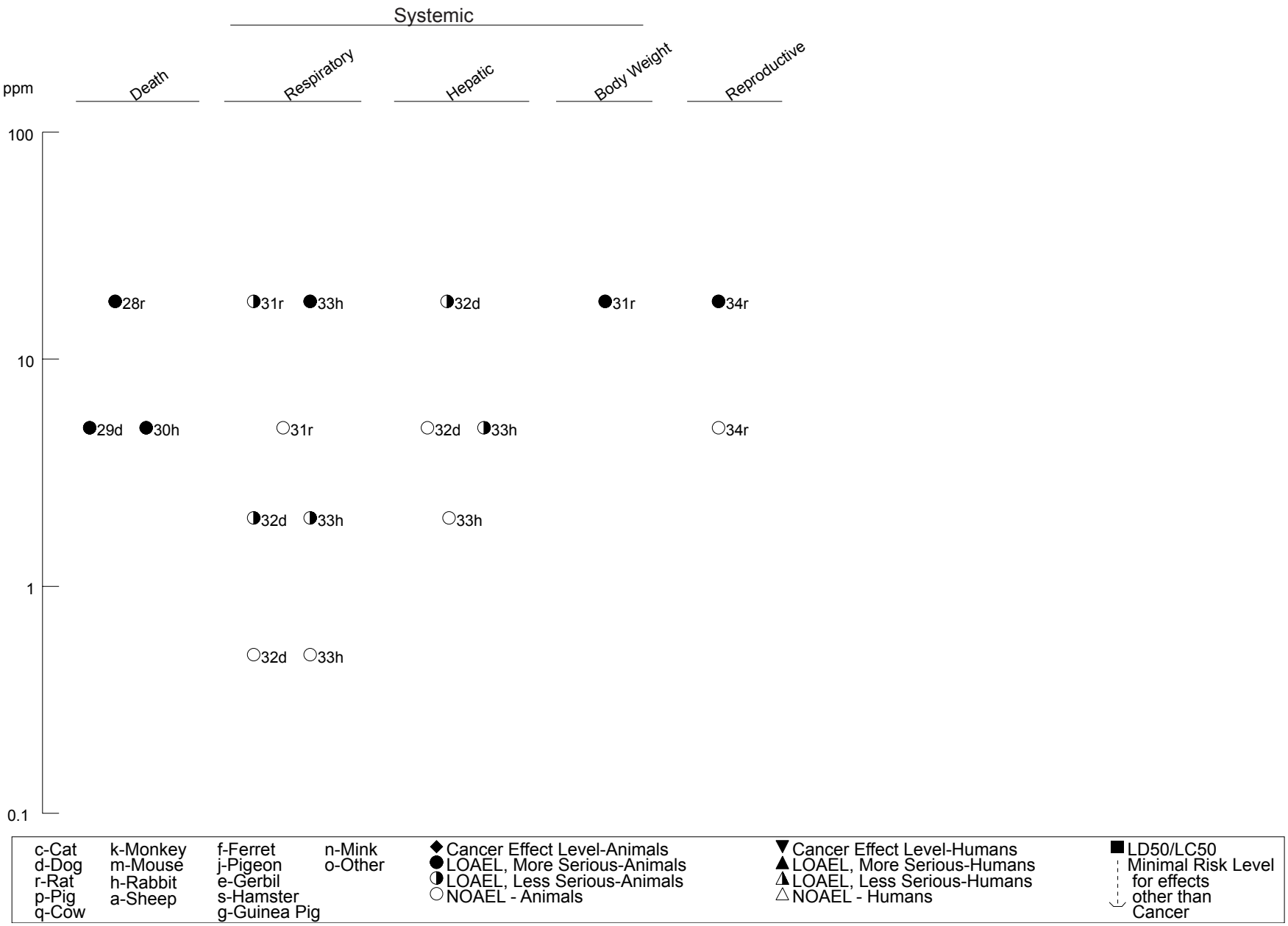


Table 3-3 Levels of Significant Exposure to Fluoride - Inhalation

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m^3)	LOAEL: Less Serious (mg/m^3)	LOAEL: Serious (mg/m^3)	Reference Chemical Form
	ACUTE EXPOSURE						
	Systemic						
1	Mouse (ICR)	4 hours/day 10 days	Resp		13.3 M (increased relative lung weight)		Chen et al. 1999 sodium fluoride
2	Mouse (BALB/c)	4 hour/day 14 days	Resp	2 M		10 M (pulmonary edema)	Yamamoto et al. 2001 sodium fluoride
	Immuno/ Lymphoret						
3	Mouse (BALB/c)	4 hour/day 14 days		2 M	5 M (decreased pulmonary bactericidal activity)		Yamamoto et al. 2001 sodium fluoride
	INTERMEDIATE EXPOSURE						
	Systemic						
4	Mouse (ICR)	4 hours/day 20-30 days	Resp		13.3 M (increased relative lung weight)		Chen et al. 1999 sodium fluoride

a The number corresponds to entries in Figure 3-3.

LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; Resp = respiratory

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

Acute (≤14 days)

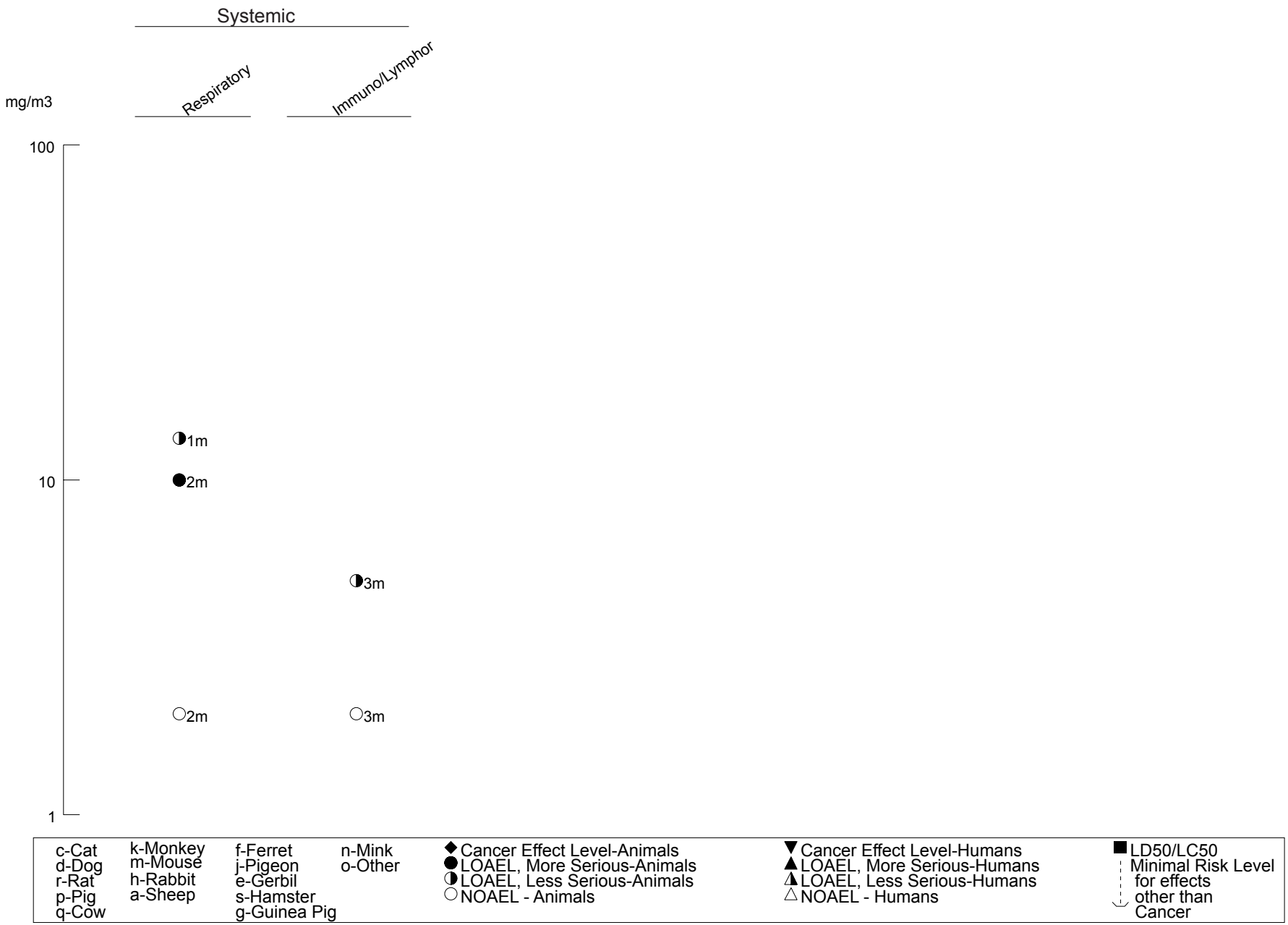
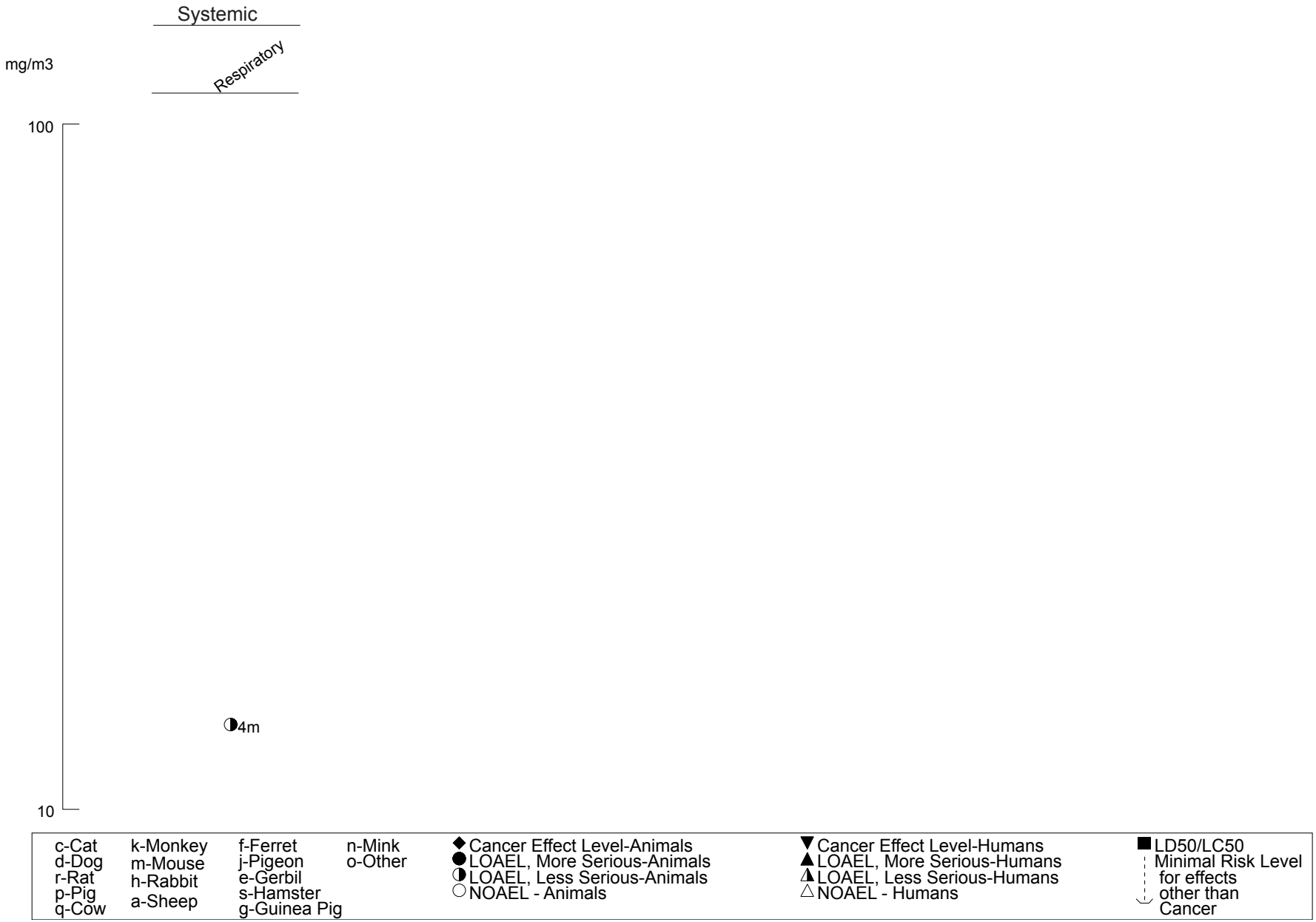


Figure 3-3. Levels of Significant Exposure to Fluoride - Inhalation (*Continued*)

Intermediate (15-364 days)



individuals exposed to 0.5 or 4.5 ppm hydrogen fluoride for 1 hour (Lund et al. 1997). Significant increases in the percentage of CD3-positive cells and lymphocytes in the bronchial portion of the lower respiratory tract, as assessed via bronchoalveolar lavage performed 3 weeks prior to exposure and 24 hours after exposure, was also observed at 4.5 ppm, but not at 0.5 ppm (Lund et al. 1999). However, no significant alterations in lung function or lower airway symptoms were observed (Lund et al. 1997). The second study with a similar study design assessed upper airway inflammation via nasal lavage (Lund et al. 2002). An inflammatory response in the nasal mucosa was observed following a 1-hour exposure to 3.8–4.5 ppm hydrogen fluoride. Seven of the 10 tested subjects also reported upper airway symptoms (specific symptoms were not presented); most of the subjects scored the severity of the symptoms as very mild to mild.

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 (FEV1) 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 2 years after the accident (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 was 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 prevalence 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. Although this study (Dayal et al. 1992) provides suggestive evidence that acute exposure to hydrogen fluoride can result in long-term damage to the respiratory tract, the study results should be interpreted with caution. The

symptom survey was administered 2 years after the accident, there was no medical confirmation of the effects, and the study authors did not provide a definition for severe symptoms.

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 cannula 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.

Fluoride Particulates. There is limited information on the respiratory toxicity of fluorides. Significant increases in relative lung weight were observed in mice exposed to 13.3 mg F/m^3 as sodium fluoride 4 hours/day for 10, 20, or 30 days (Chen et al. 1999). The toxicological significance of this effect is not known because histopathology was not conducted. In another study of mice (Yamamoto et al. 2001), lung damage, as evidenced by significant decreases in total cells and alveolar macrophages and increases in polymorphocytic neutrophils and lymphocytes in the bronchoalveolar lavage fluid, was found in mice exposed to 10 mg F/m^3 as sodium fluoride 4 hours/day for 14 days. An increase in polymorphocytic neutrophils was also observed at 5 mg/m^3.

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.

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 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.

Cardiovascular Effects.

Hydrogen Fluoride. Cardiac arrhythmias have been seen in humans following hydrofluoric acid splashes in the face region, where both dermal and inhalation exposures 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.

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/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 leukocyte 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.

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.

Musculoskeletal Effects.

Fluoride. There are several case reports of radiological alterations (primarily thickening of the bone) in workers exposed to sodium fluoride (McGarvey and Ernstene 1947), rock phosphate dust containing 3.88% fluoride (Wolff and Kerr 1938), or cryolite (Roholm 1937). In the two cryolite workers, the fluorine content of the costa bone was 10-fold higher than in non-exposed individuals. Roholm (1937) also examined 68 cryolite workers exposed to high levels (35 mg/m^3) of cryolite dust. Approximately 35% of the workers complained of "rheumatic attacks, pains, or feeling of stiffness" and reduced mobility was found in approximately 21% of the workers. Radiological examinations revealed diffuse osteosclerosis in approximately 84% of the workers.

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

Hydrogen Fluoride. Human data on the musculoskeletal effects of hydrogen fluoride (in the absence of concomitant exposure to fluoride dusts) are limited to a case report of a worker employed at an alkylation unit of an oil company (Waldbott and Lee 1978). The worker complained of back pains, leg pains, and loss of memory and was diagnosed with advanced osteoarthritis of the spine. The data presented in this report are inadequate to assess whether the back and leg pains were related to hydrogen fluoride exposure, the osteoarthritis, or a petroleum product.

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 post-shift 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 post-shift 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. Indications of early skeletal fluorosis (advanced painful symptoms, advanced limitation of motion in at least two joints or spine, marked ossifications on two or more x-rays, initial osteosclerosis, slight periosteal reaction, and thickening of long bone cortices) were found in 5.12% of the workers and definite fluorosis (stage I) was found in 1.0% of the workers. 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

(mild increase in bone density, periosteal changes, calcifications of ligaments) in a few pot room workers employed for >10 years. The study authors noted that there was poor agreement on early signs of fluorosis among the two radiologists reading the x-ray films. No effects 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).

Skeletal fluorosis was also observed in workers involved in study the crushing and refining of cryolite (Moller and Gudjonsson 1932). Thirty-nine of the 78 examined 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. 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.

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 was exposed to other chemicals, and some of the musculoskeletal symptoms may have actually been due to heavy physical labor.

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.

Hepatic Effects.

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.

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).

Renal Effects.

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

Degeneration and necrosis of the renal cortex was reported in 27/30 rats exposed to 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.

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.

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

Dermal Effects.

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. "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.

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.

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.

Ocular Effects.

Hydrogen Fluoride. Marked conjunctival irritation was noted 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. At 61 ppm fluoride, conjunctival and nasal irritations were still marked, and tickling and discomfort of the nasal passages were reported. A concentration of 32 ppm fluoride 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.

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.

Mild eye irritation was observed in five volunteers exposed 6 hours/day for 15–50 days, to hydrogen fluoride at concentrations averaging from approximately 0.85 to 7.7 ppm fluoride; the mean of the average concentrations was 2.98 ppm (Largent 1960). This study is limited by the inadequacy of both the experimental details and the description of effects observed.

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). Eye irritation, evidenced 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 (Keplinger and Suissa 1968).

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 10 or 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.

Body Weight Effects.

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).

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.

3.2.1.3 Immunological and Lymphoreticular Effects

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

Fluoride Particulates. A significant decrease in pulmonary bactericidal activity was observed in mice challenged for 30 minutes with aerosol inhalation of *Staphylococcus aureus* following a 14-day exposure (4 hours/day) to 5 or 10 mg F/m^3 as sodium fluoride (Yamamoto et al. 2001). Bactericidal activity was not significantly altered in mice exposed to 2 mg/m^3. The highest NOAEL values and all reliable LOAEL values for immunologic effects in each species and duration category of inhalation exposure to fluoride are recorded in Table 3-3 and plotted in Figure 3-3.

3.2.1.4 Neurological Effects

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. The toxicological significance of a change in light adaptive reflex is not known.

Exposure to concentrations at about 50% of the LC_{50} values was reported to cause general weakness and decreased activity in Wistar rats (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 3-1 and plotted in Figure 3-1.

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.

3.2.1.5 Reproductive Effects

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

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.

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.

3.2.1.6 Developmental Effects

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

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 [SMR] of 2.52, 95% confidence interval of 1.40–4.12, Standardized Incidence Ratio of 2.5 , 95% confidence interval of 1.6–3.5) (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 (standardized incidence ratio of 1.5, 95% confidence interval of 1.0–2.1). No apparent relationship between incidence of all cancers and the length of employment or latency period was found. Significant increases in cancer mortality, particularly respiratory cancer, were also found in a follow-up study of this cohort (Grandjean et al. 1992). The SMR for all cancer was 1.34 (95% confidence interval of 1.2–1.50) compared to Danish national rates and the standardized incidence ratio for lung cancer was 1.40 (95% confidence interval of 1.01–1.90) compared with rates for Copenhagen. Additionally, a significant increase in bladder cancer

incidence was seen (standardized incidence ratio of 1.84, 95% confidence interval of 1.08–2.96). The investigators noted that smoking habits may have accounted for some of the lung cancer risk.

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 fluoride, hydrogen fluoride, or fluorine.

3.2.2 Oral Exposure

Because hydrogen fluoride and fluorine 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.

The oral toxicity of fluoride has been investigated in humans and animals. The human database mostly consists of epidemiology studies designed to assess whether consumption of fluoridated water is

associated with adverse health effects, particularly skeletal effects and cancer. Most of these studies are community-based and do not provide data on individual exposure levels or the particular fluoride compound. Fluorosilicic acid and sodium hexafluorosilicate are the primary fluoride compounds used in water fluoridation programs, although exposure to other fluoride compounds, such as monofluorophosphate, used in dental products also contribute to total fluoride exposure. Additional information on the toxicity of fluoride in humans comes from studies of communities with naturally high levels of fluoride in the drinking water and experimental studies typically involving exposure to sodium fluoride. Animal studies have primarily involved exposure to sodium fluoride in drinking water or the diet. A few animal studies also examined the toxicity of fluoride following exposure to calcium fluoride, cryolite, and fluoride from rock phosphate. For all forms of fluoride discussed, doses are reported as amount of the fluoride ion.

Conflicting results have been obtained from animal 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. 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.

Several organizations consider fluoride to be an important dietary element for humans. The Institute of Medicine (IOM 1997) 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. Using body weight data reported by IOM (2000), these dietary intakes are equivalent to doses of approximately 0.05 mg/kg/day for ages 6 months to >18 years; the dose in infants 0–6 months is 0.0014 mg/kg/day. The World Health Organization (WHO) considers fluoride to be "essential" because it considered "resistance to dental caries to be a physiologically important function" (WHO 2002).

3.2.2.1 Death

Fluoride. 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. Based on numerous incidents of fatal fluoride poisoning, Hodge and Smith (1965) estimated the certainly lethal dose to be 5–10 g sodium fluoride (32–64 mg fluoride/kg) in adults.

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.

Erickson (1978) examined the possible relationship between water fluoridation and increased death rate among residents of 24 cities with fluoridation and 22 cities without water fluoridation. Although there was a difference in crude death rates for all causes between the two study populations (1,109.9 and 1,053.6/100,000 person-years for the fluoridation and non-fluoridation populations, respectively), similar death rates (1,123.9 and 1,137.1/100,000 person-years, respectively) were found after adjustment for differences in age, sex, race, and analysis of covariance (median education and city population density

In rats, LD_{50} values for sodium fluoride administered by oral gavage range from 31 to 126.3 mg fluoride/kg (DeLopez et al. 1976; Lim et al. 1978; Skare et al. 1986; Whitford et al. 1990). Differences in rat strains, variations in weight (and presumably differences in ages), and gender differences may account for the reported differences in LD_{50} values. LD_{50} values were higher in younger female rats (52–54 mg/kg) than in older female rats (31 mg/kg) (DeLopez et al. 1976). LD_{50} values (84.3–146.3 mg fluoride/kg) were also estimated in rats administered monofluorophosphate (Whitford et al. 1990). These LD_{50} values were similar to the LD_{50} values for sodium fluoride (85.5-126.3 mg fluoride/kg) measured in the same study. An LD_{50} of 44.3 mg fluoride/kg was reported for mice (Lim et al. 1978).

All reliable LD_{50} and LOAEL values for death in each species and duration category are recorded in Table 3-4 and plotted in Figure 3-4.

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.

3.2.2.2 Systemic Effects

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

Table 3-4 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)				52 (LD50 for 150g rats) 54 (LD50 for 80g rats) 31[b] (LD50 for 250g rats)	DeLopez et al. 1976 sodium fluoride
3	Rat (Rochester)	1 d 1x/d (GW)				51.6 (LD50)	Lim et al. 1978 sodium fluoride
4	Rat (Sprague-Dawley)	1 d 1x/d (GW)				101.3 (LD50)	Skare et al. 1986 sodium fluoride
5	Rat (Sprague-Dawley)	once (GW)				126.3 M (LD50)	Whitford et al. 1990 sodium fluoride
6	Rat (Sprague-Dawley)	once (GW)				85.5 M (LD50)	Whitford et al. 1990 sodium fluoride
7	Rat (Sprague-Dawley)	once (GW)				146.3 M (LD50)	Whitford et al. 1990 Monofluorophosphate
8	Rat (Sprague-Dawley)	once (GW)				84.3 M (LD50)	Whitford et al. 1990 Monofluorophosphate

Table 3-4 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
9	Mouse (Swiss)	1 d 1x/d				44.3 (LD50)	Lim et al. 1978 sodium fluoride
	Systemic						
10	Rat	2wk (W)	Musc/skel		9.5 (decreased modulus of elasticity)		Guggenheim et al. 1976 sodium fluoride
	Reproductive						
11	Mouse	5d 1x/d (G)		32			Li et al. 1987a sodium fluoride
	Developmental						
12	Rat (Wistar)	GD 6-19 (GW)			18 F (increased percentage of skeletal and visceral abnormalities)		Guna Sherlin and Verma 2001 sodium fluoride
13	Rat (Sprague-Dawley)	Gd 6-15 daily (W)		13.21			Heindel et al. 1996 sodium fluoride
14	Rabbit (New Zealand)	Gd 6-19 daily (W)		13.72			Heindel et al. 1996 sodium fluoride
	INTERMEDIATE EXPOSURE						
	Death						
15	Mouse (B6C3F1)	6 mo daily (W)				67 (increased mortality)	NTP 1990 sodium fluoride
16	Mouse	6mo ad lib (W)				300[c] M (increased mortality) 600 F (increased mortality)	NTP 1990 sodium fluoride

Table 3-4 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
	Systemic						
17	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
18	Rat (CD)	daily 16-19 weeks (W)	Musc/skel	8.25 F	10.7 F (prominent growth lines on upper incisors)		Collins et al. 2001a sodium fluoride
19	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
20	Rat (Wistar)	5 wk (W)	Musc/skel	13	19 (histological fluorosis; decr bone growth)		Harrison et al. 1984 sodium fluoride
21	Rat (Fischer- 344)	6 mo daily (W)	Gastro		7 (hyperplasia of glandular stomach)		NTP 1990 sodium fluoride
			Hepatic	20			
			Renal	20			
22	Rat (Sprague-Dawley)	daily 16 or 48 weeks (W)	Musc/skel	0.15 M	0.5 M (decreased vertebral strength and bone mineralization)		Turner et al. 2001 sodium fluoride
23	Rat	30d (W)	Musc/skel		14 (delayed healing of broken bones)		Uslu 1983 sodium fluoride

Table 3-4 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
24	Mouse	280 d daily (W)	Hepatic		0.95	(pale, granular hepatocytes with fatty vacuoles)			Greenberg 1982a sodium fluoride
25	Mouse	280d (W)	Renal		1.9	(nephron degeneration)			Greenberg 1986 sodium fluoride
26	Mouse	4 wk 7d/wk daily (W)	Musc/skel		0.8	(incr bone formation rate; slight decr bone calcium)			Marie and Hott 1986 sodium fluoride
27	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)			
28	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)			

Table 3-4 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
29	Mouse (Kunmin)	daily 100-150 days (W)	Musc/skel	0.06 M	3.2 M (incisor fluorosis)		Zhao et al. 1998 sodium fluoride
			Endocr	0.06 M	3.2 M (decreased radiolabelled iodine uptake)		
			Bd Wt	3.2 M			
30	Rabbit (NS)	6 mo daily (F)	Resp		4.5 (congestion, edema fluid, desquamation of respiratory epithelium in lungs)		Purohit et al. 1999 sodium fluoride
	Neurological						
31	Rat (Sprague-Dawley)	6 wk daily (W)			6 F (altered spontaneous behavior)		Mullenix et al. 1995 sodium fluoride
32	Rat (Sprague-Dawley)	6 wk daily (W)		5.5 F	7.5 F (altered spontaneous behavior)		Mullenix et al. 1995 sodium fluoride
33	Rat (Wistar)	60 d daily (GW)			9 (decr spontaneous activity)		Paul et al. 1998 sodium fluoride
	Reproductive						
34	Rat (Sprague-Dawley)	daily 30 days (W)				10.21 F (decreased number of viable fetuses, increased resorptions)	Al-Hiyasat et al. 2000 sodium fluoride
35	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

Table 3-4 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
36	Rat (NS)	daily 30 d (GW)				2.3 (decreased fertility and sperm counts)	Chinoy et al. 1992 sodium fluoride
37	Rat (Charles Foster)	30 or 50 days d (F)				4.5 (decreased sperm motility and count)	Chinoy et al. 1995 sodium fluoride
38	Rat (CD)	daily 16-19 weeks (W)		10.7 F			Collins et al. 2001a sodium fluoride
39	Rat (Wistar)	daily 6 wk (W)		21			Krasowska and Wlostowski 1992 sodium fluoride
40	Rat (Wistar)	daily 16 wk (W)			7.5 (seminiferous tubule atrophy)		Krasowska and Wlostowski 1992 sodium fluoride
41	Rat	3 mo 7d/wk (F)		23			Marks et al. 1984 sodium fluoride
42	Rat Charles Foster	daily 50 d (GW)			4.5 (decr testosterone levels and Leydig cell diameter)		Narayana and Chinoy 1994 sodium fluoride
43	Rat (Sprague-Dawley)	daily (W)		16			Sprando et al. 1997 sodium fluoride

Table 3-4 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
44	Rat (Sprague-Dawley)	daily (W)		16				Sprando et al. 1998 sodium fluoride
45	Mouse (Swiss)	30 d daily (F)				4.5	(decr sperm motility and count and infertility)	Chinoy and Sequeira 1992 sodium fluoride
46	Mouse (Swiss-Webster)	25 wks (W)		9.5		19	(nearly complete infertility)	Messer et al. 1973 sodium fluoride
47	Mouse	35 d 1x/d (GW)		5.2				Pillai et al. 1988 sodium fluoride
48	Gn Pig (NS)	30 d daily (GW)				4.5	(decr sperm motility and viability)	Chinoy et al. 1997 sodium fluoride
	Developmental							
49	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
50	Rat (CD)	daily 16-19 weeks (W)		12.2 F				Collins et al. 2001b sodium fluoride
51	Rat (Sprague-Dawley)	28 wk 7d/wk 24hr/d (W)		21				Ream et al. 1983 sodium fluoride

Table 3-4 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						
52	Human	daily (W)	Musc/skel	0.04			Hillier et al. 2000 sodium fluoride
53	Human	Daily (W)	Musc/skel	0.15[d]	0.25 (Increased prevalence of bone fractures)		Li et al. 2001 sodium fluoride
54	Human	4 yr (C)	Musc/skel		0.56 (increased fracture rate)		Riggs et al. 1990 sodium fluoride
55	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			

Table 3-4 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
56	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					
57	Rabbit	24 mo 1x/d (GW)	Gastro		5	(roughened duodena mucosa)			Susheela and Das 1988 sodium fluoride
58	Rabbit	7-12 mo 1x/d (G)	Hemato		4.52	(decr leukocyte and hemoglobin levels)			Susheela and Jain 1983 sodium fluoride
59	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
	Immuno/ Lymphoret								
60	Rabbit (albino)	18 mo 1x/d (G)			4.5	(decr primary and secondary antibody titers)			Jain and Susheela 1987 sodium fluoride

Table 3-4 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
	Reproductive						
61	Mouse	3 gen (F)		13			Tao and Suttle 1976 sodium fluoride
62	Rabbit (NS)	daily 18 mo (GW)				4.5 M (structural damage of the spermatid and epididymal spermatozoa)	Kumar and Susheela 1994 sodium fluoride
63	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
64	Rabbit (NS)	daily 18 or 29 mo (GW)				4.5 (complete cessation of spermatogenesis)	Susheela and Kumar 1991 sodium fluoride
65	Rabbit (New Zealand)	daily 18 or 23 mo (GW)			4.5 (Leydig cell damage)		Susheela and Kumar 1997 sodium fluoride
66	Mink	382 d daily (F)		9.1			Aulerich et al. 1987 sodium fluoride

Table 3-4 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
	Cancer						
67	Rat (Fischer- 344)	103 wk (W)				2.4 M (osteosarcoma of bone)	NTP 1990 sodium fluoride

a The number corresponds to entries in Figure 3-4.

b Only this dose level, for the most sensitive group, is plotted in Figure 3-4.

c Differences in levels of health effects and cancer effects between males and females are not indicated in Figure 3-4. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

d Used to derive a chronic-duration oral minimal risk level (MRL) of 0.05 mg fluoride/kg/day; the dose was divided by an uncertainty factor of 3 to account for human variability.

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; LD50 = 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 3-4. Levels of Significant Exposure to Fluoride - Oral

Acute (≤14 days)

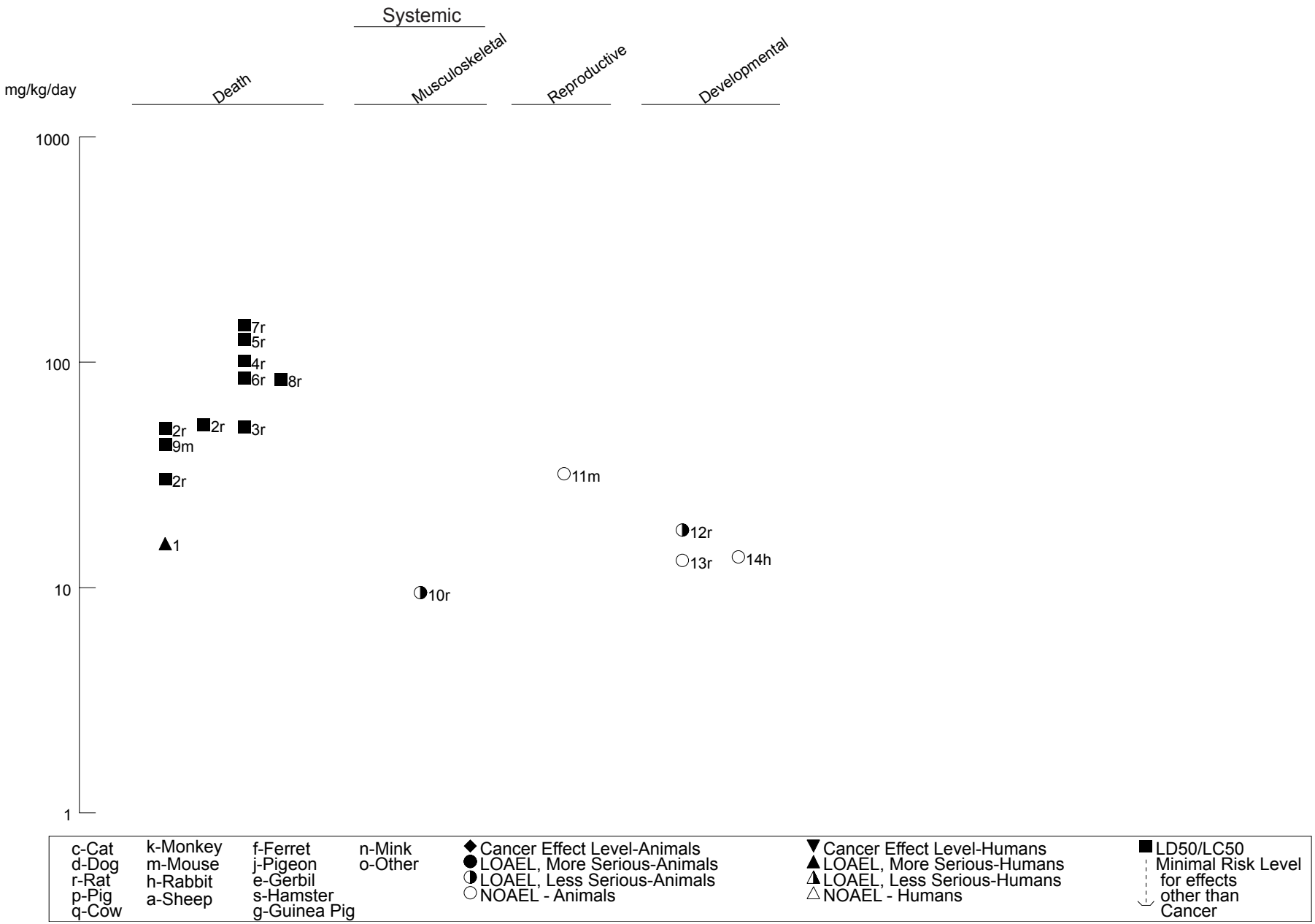


Figure 3-4. Levels of Significant Exposure to Fluoride - Oral (*Continued*)

Intermediate (15-364 days)

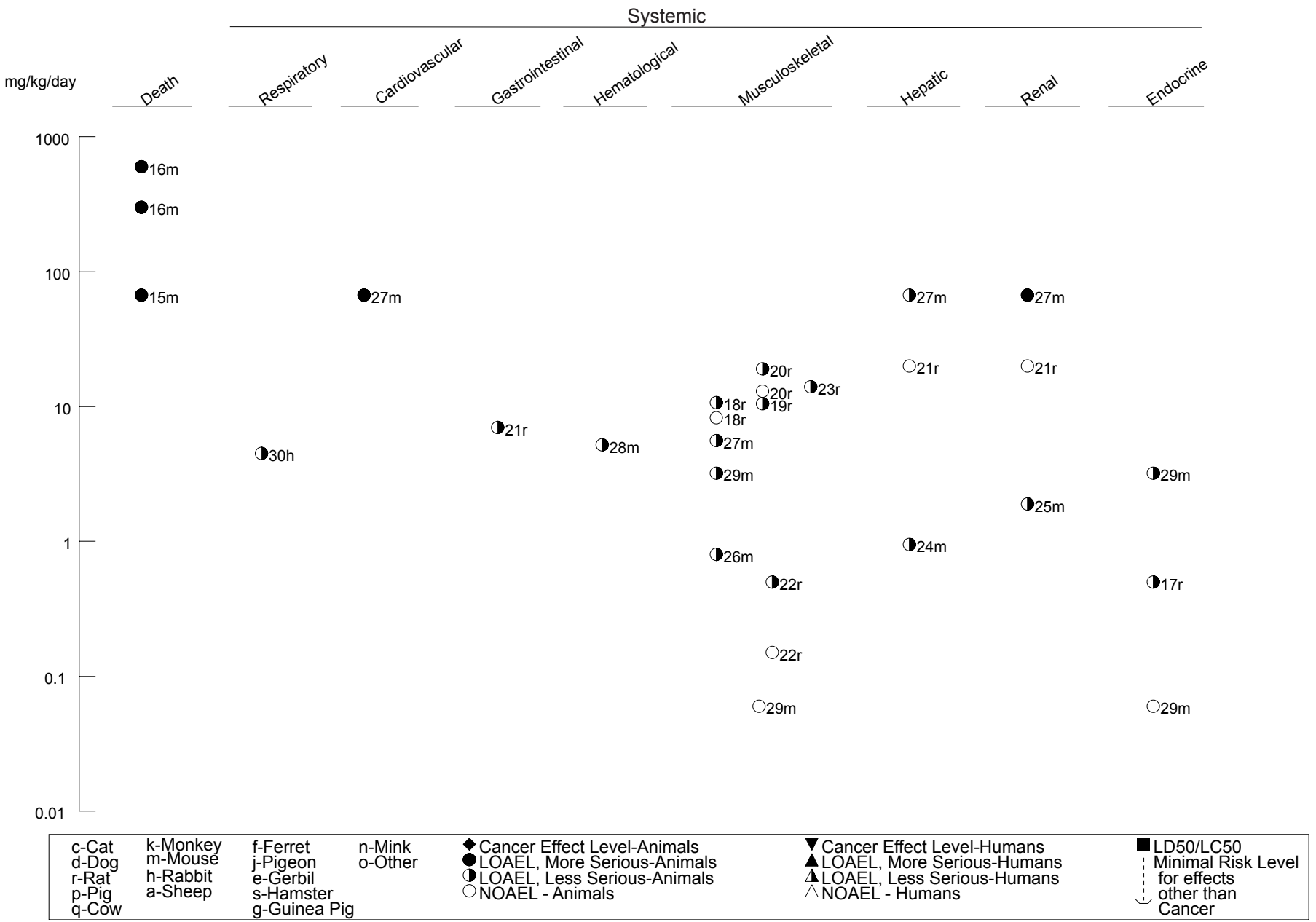


Figure 3-4. Levels of Significant Exposure to Fluoride - Oral (*Continued*)

Intermediate (15-364 days)

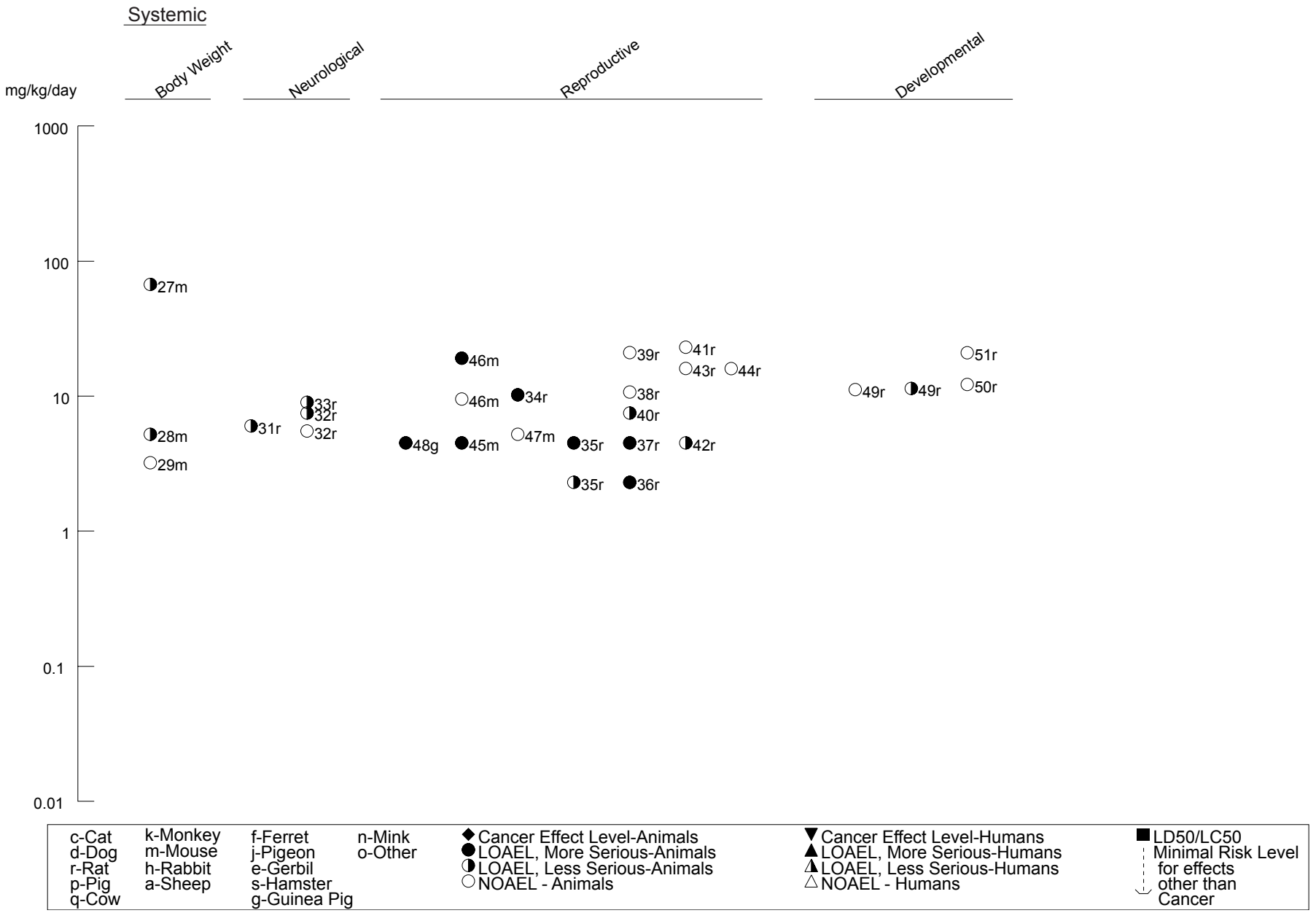
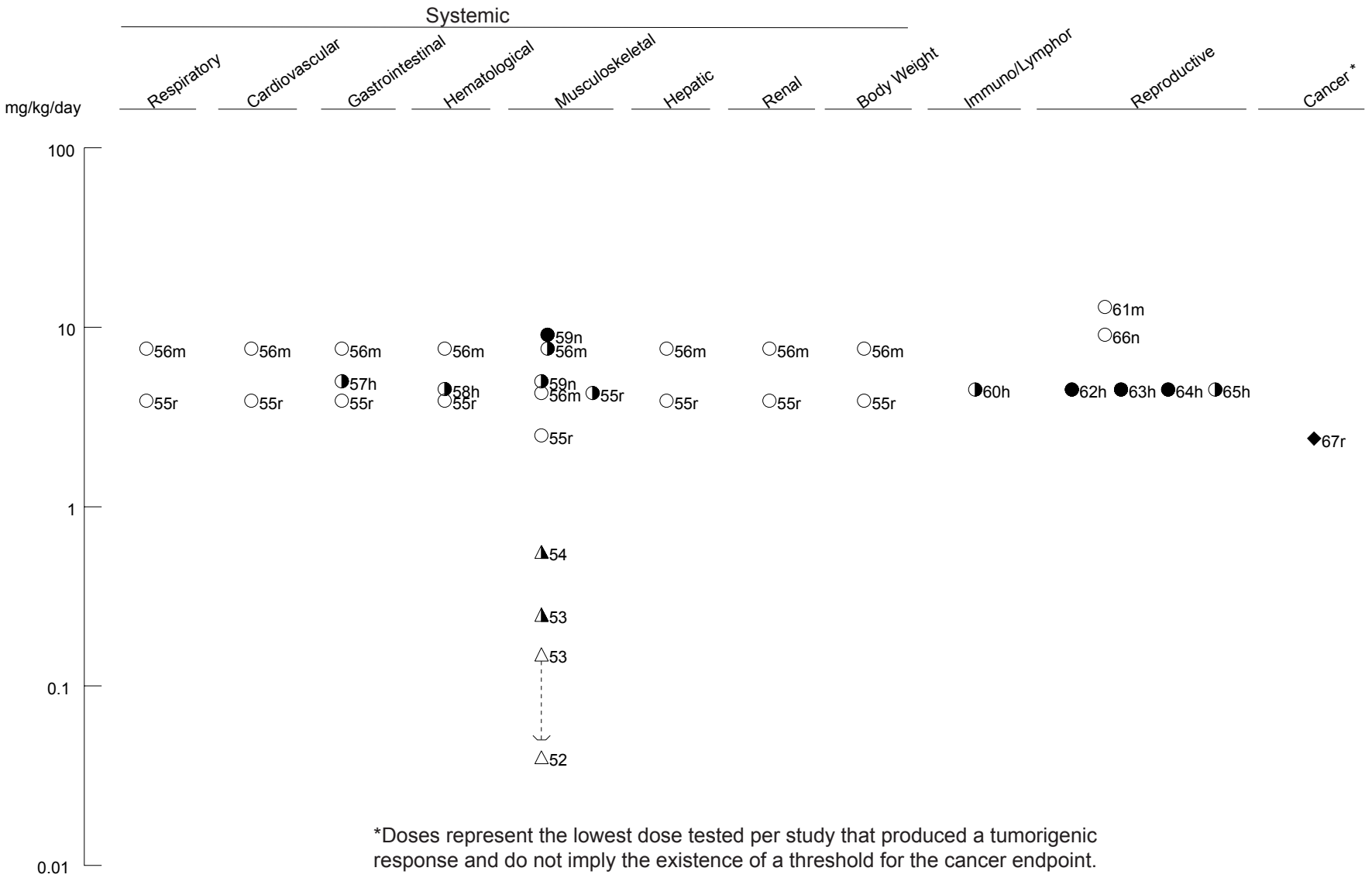


Figure 3-4 Levels of Significant Exposure to Fluoride - Oral (*Continued*)

Chronic (≥365 days)



The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 3-4 and plotted in Figure 3-4.

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

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.

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 a study of adults with skeletal fluorosis living in an area of China with high levels of fluoride in the drinking water (4.1–8.6 ppm) (Xu and Xu 1997), a higher percentage of electrocardiogram abnormalities was observed in individuals with skeletal fluorosis (50.73%), as compared to a control group (0.1–0.6 ppm fluoride in water) (20.0%).

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.

Similarly, no significant alterations in the rate of cardiovascular system abnormalities were observed in a community with 8 ppm fluoride in the water supply, as compared to a community with 0.4 ppm (Leone et al. 1954).

The results of other studies have suggested a role for fluoride in reducing cardiovascular disease. 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. 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. Electrocardiogram alterations and

histological alterations in the myocardium were observed in rabbits exposed to sodium fluoride (Okushi 1971).

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 where it dissociates to release both fluoride and hydrogen ions.

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 two other cases, individuals 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) or sodium fluorosilicate (Dadej et al. 1987).

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 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), or application of 0.42% fluoride dental gel (5.1 mg fluoride ingested) (Spak et al. 1990). Fluoride treatment resulted in petechiae (minute hemorrhages) or erosions in most of the subjects. Histological examination of biopsied stomach tissue revealed signs of irritation. Nausea was present in one-third of the subjects drinking the sodium fluoride solution, suggesting that nausea may not be the first sign of fluoride irritation of the gastric mucosa.

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 20 non-ulcer dyspepsia patients at an outpatient clinic in India and 10 volunteers without gastrointestinal problems from the surgical clinic (Susheela et al. 1992). While 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 were 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 a community with high levels of naturally occurring fluoride (8 ppm) as compared to a community with low levels of fluoride (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. No significant alterations in hemoglobin, erythrocyte, and total leukocyte levels were found in children living in a community with fluoridated water (1.2 ppm), as compared to children living in a community with nonfluoridated water (Schlesinger et al. 1956).

As part of the 2-year National Toxicology Program (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 high levels of fluoride.

Musculoskeletal Effects. The skeletal system is the primary site of fluoride deposition in the body resulting in both beneficial and adverse effects. Oral exposure to fluoride has been shown to decrease the

prevalence of dental caries in children (the relationship between fluoride and dental caries is discussed in greater detail in Appendix D); however, at higher doses, fluoride can also result in non-beneficial effects on the teeth, dental fluorosis. Dental or enamel fluorosis occurs when excess amounts of fluoride are ingested during tooth development (1–8 years of age). It is characterized by increased porosity (or hypomineralization) of the subsurface enamel and well mineralized surface layer of enamel. Mildly fluorosed enamel is full functional (denBesten and Thariani 1992), but may be cosmetically objectionable. As the severity of dental fluorosis increases, the depth of the enamel involvement and the degree of porosity increases (Fejerskov et al. 1990). More severely fluorosed enamel is more porous, pitted, and discolored and is prone to fracture and wear because the well mineralized zone is very fragile to mechanical stress (denBesten and Thariani 1992; Fejerskov et al. 1990). Not all teeth are similarly affected by elevated fluoride levels. Teeth that develop earlier in life appear to be less affected than those that develop later (Fejerskov et al. 1990). Several methods have been developed for quantifying dental fluorosis. The most commonly used method is Dean's index (Dean 1934), which classifies fluorosis as a scale of from 0 to 4 as follows: class 0, no fluorosis; class 1, very mild fluorosis (opaque white areas irregularly covering ≤25% of the tooth surface); class 2, mild fluorosis (white areas covering 25–50% of the tooth surface); class 3, moderate fluorosis (all surfaces affected, with some brown spots and marked wear on surfaces subject to attrition); and class 4, severe fluorosis (widespread brown stains and pitting). The average score of the two most severely affected teeth is used to derive the classification. Other commonly used methods to rate dental fluorosis include the Thylstrup-Fejerskov (TF) index (Thylstrup and Fejerskov 1978) and the tooth surface index of fluorosis (TSIF) (Horowitz et al. 1984). Unlike the Dean's index, the TF and TSIF indexes use all tooth surfaces to develop the final index score.

The development and severity of dental fluorosis is dependent on the amount of fluoride ingested, the duration of exposure, and the stage of amelogenesis at the time of exposure. The relationship between fluoride exposure levels and the prevalence and severity of dental fluorosis was first established in the 1930s and 1940s. There is an extensive amount of literature on the relationship between the prevalence of dental fluorosis and the concentration of fluoride in municipal water (e.g., Alarcón-Herrera et al. 2001; DHHS 1991; Eklund et al. 1987; Heifetz et al. 1988; Jackson et al. 1995; Selwitz et al. 1995; Teotia and Teotia 1994) and the use of fluoridated dentifrices (as reviewed by Warren and Levy 1999). Studies examining children living in communities with different fluoride levels found that the severity of dental fluorosis is directly related to fluoride exposure levels. Higher fluorosis severity scores were found in children living in communities with 4 ppm fluoride in drinking water compared to children living in communities with 1 ppm fluoride in drinking water (Heifetz et al. 1988; Jackson et al. 1995; Selwitz et al. 1995). No signs of dental fluorosis (using the TSIF scoring method) were found in 81.8, 54.7, and 7.9%

of the children aged 7–14 years living in communities with 0.2, 1, or 4 ppm, fluoride in drinking water, respectively (Jackson et al. 1995). Moderate dental fluorosis (TSIF score of 3) was observed in 0, 0.9, and 25.7%, respectively, of the children. The maximum TSIF score was 2 (3.2% of the children received this score) in the 0.2 ppm community, 4 (0.9% of children) in the 1 ppm community, and 7 (6.9% of children) in the 4 ppm community. Studies in adults have not always found a direct relationship between severity of dental fluorosis and prevalence of dental caries (Eklund et al. 1987). A recent meta-analysis of 88 studies on dental fluorosis (McDonagh et al. 2000) found a dose-related response relationship between the levels of fluoride in drinking water and the prevalence of dental fluorosis. At a water fluoride concentration of 1 ppm, the estimated prevalence of dental fluorosis is 48% (95% confidence interval of 40–57%) and the prevalence of fluorosis of aesthetic concern would be 12.5% (95% confidence interval of 7.0–21.5%). Another meta-analysis found a significant association between dental fluorosis and use of fluoride supplements (Ismail and Bandekar 1999).

There is also evidence that the prevalence of dental fluorosis has increased over time due to the multiple, widespread sources of fluoride in food processed with fluoridated water and dentifrices containing fluoride, which has resulted in higher fluoride exposure levels. The DHHS (1991) compared the prevalence of dental fluorosis in three cities (Kingston, New York, Kewanee, Illinois, and Newburgh, New York) measured in 1939 or 1955 with prevalence in those cities in 1980 or 1985. In Kingston, which had a municipal fluoride level of 0 ppm, the prevalence of dental fluorosis (using the Dean's index) increased from 0.0 to 7.3%, primarily in the very mild (4.4% received this score) category. In the other two cities (0.9 or 1.0 ppm fluoride in water), there was only a slight change in the overall prevalence (12.2 versus 14.6% for Kewanee and 7.3 versus 7.7% in Newburgh) of dental fluorosis. However, there was a shift toward higher severity scores. For example in Kewanee, the prevalence in the very mild, mild, moderate, and severe categories was 10.6, 1.6, 0.0, and 0.0%, respectively, in 1939 and 7.4, 4.8, 1.8, and 0.6%, respectively, in 1980. In another comparison conducted by DHHS (1991), the prevalence and severity of dental fluorosis measured in children living in 21 cities in the 1940s were compared with the prevalence and severity of dental fluorosis measured in 28 cities in the 1980s. During the 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 by children at risk has increased since the 1940s, because fluorosis levels increased for all water fluoride levels. Another series of studies compared the prevalence and severity of dental fluorosis in 8–10 and 13–15-year-old children living in communities with 1, 2, 3, or 4 ppm fluoride in drinking water in 1980 to the prevalence in 1985 (Heifetz et al. 1988) and 1990 (Selwitz et al. 1995). 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 (this group of children also participated in the 1980 study). 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 exposure groups. The increased levels of fluorosis were attributed to increased fluoride exposure from multiple sources. However, the apparent increase in fluorosis did not continue from 1985 to 1990 (Selwitz et al. 1995); in many cases, the severity of the fluorosis declined in the period of 1985–1990 compared to the 1985 levels.

There is some evidence to suggest that exposure to very high levels of fluoride can increase the susceptibility to dental caries. Studies in children and adolescents aged 8–16 years (Driscoll et al. 1986; Mann et al. 1987) found higher incidences of dental caries in individuals with severe dental fluorosis than in individuals with less severe dental fluorosis. However, for children with very mild, mild, or moderate fluorosis, no significant associations were found. Driscoll et al. (1986) reported a mean decayed, missing, and filled surface (DMFS) score of 2.96 for children with severe fluorosis (TSIF score of 4) compared to 1.40 for children with very mild dental fluorosis (TSIF score of 0.5) or 1.58 for children with mild to moderate fluorosis (TSIF score of 1–3). It is possible that the higher prevalence of filled teeth was due to the increased rate of fracture and wear in severely fluorosed teeth rather than a higher risk of tooth decay.

As with the dental effects, fluoride has both beneficial and adverse effects on bone. Because fluoride stimulates bone formation, and increases bone mass, especially in cancellous bone, and inhibit bone resorption, fluoride has been used as a treatment for osteoporosis. However, the effect of fluoride on the bone varies in different parts of the body. It increases bone formation earlier and to a larger extent in trabecular bone than in cortical bone (Gruber and Baylink 1991). There is an excellent response in the spine, slight response in the hip, and poor response in the wrist as a result of fluoride treatment. Studies examining the efficiency of fluoride treatment for osteoporosis have found an increased risk of hip fractures; the prevailing view is that the beneficial increase in spinal bone mass is at the expense of an increasing risk of hip fractures. There is some evidence that exposure to low doses of slow released

sodium fluoride can significantly reduce the occurrence of spinal fractures in individuals with osteoporosis (Pak et al. 1995). A large number of studies have examined the adverse skeletal effects of fluoride; the human studies primarily consist of clinical trials of elderly subjects administered fluoride for the treatment of osteoporosis and community-based studies of populations exposed to fluoride in drinking water. The observed effects include increases in bone density, increased risk of bone non-vertebral fractures, and skeletal fluorosis.

Skeletal fluorosis is a condition associated with an accumulation of fluoride in the bone resulting in brittle bones and decreased tensile strength. In severe cases (crippling skeletal fluorosis), complete rigidity of the spine, often accompanied by kyphosis (humpbacked) or lordosis (arched back), is observed. Skeletal fluorosis is associated with long-term exposure to very high oral doses of fluoride or occupational exposure to cryolite (AlF_6Na_2) dust (which would involve inhalation and oral exposure to fluoride). Cases of skeletal fluorosis are predominantly found in developing countries, particularly India and China, and are associated with high fluoride intakes coupled with malnutrition (WHO 2002). High tea consumption and increased consumption of water with high levels of naturally occurring fluoride are the primary contributors to the elevated fluoride intake; in China, the indoor burning of fluoride-rich coal also contributes to the overall fluoride intake. Most reports of skeletal fluorosis are inadequate for establishing dose-response relationships. Choubisa et al. (1997) examined the prevalence of skeletal fluorosis in residents of 15 villages in India. At 1.4 ppm fluoride in drinking water, the prevalence of skeletal fluorosis was 4.4%; at 6.0 ppm fluoride, the prevalence was 63.0%. Another investigator found that skeletal fluorosis occurred 10 years after the initiation of increased fluoride consumption; the average water concentration was 9.2 ppm fluoride and daily water consumption was 4.6 L/day (42 mg fluoride/day) (Saralakumari and Ramakrishna Rao 1993); after 20 years of exposure, the prevalence of skeletal fluorosis was 100%. A limited number of cases of skeletal fluorosis have been reported in the United States (Bruns and Tytle 1988; Fisher et al. 1981; Goldman et al. 1971; Sauerbrunn et al. 1965); where doses are known, they are generally 15–20 mg fluoride/day for over 20 years. In 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, a 10–15% incidence of fluoride-related bone changes was observed (Leone et al. 1955). Coarsened trabeculation and thickened bone were observed, but no exostoses were evident, and the subjects were asymptomatic. The severity of the skeletal fluorosis appears to be related to bone fluoride levels. Among persons whose drinking water contains about 1 ppm fluoride, bone ash fluoride concentrations trypically range from 500 to 1,500 ppm. The higher values are generally found among older persons since the concentrations tend to increase gradually throughout life. 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).

Studies of individuals undergoing fluoride treatment for osteoporosis, epidemiology studies of communities with high levels of fluoride in drinking water, and community-based studies of populations with different fluoride levels in the water have examined the possible relationship between exposure to fluoride and alterations in bone mineral density and/or the risk of bone fractures. The effect of fluoride on bone fracture rate and mineralization has alos been investigated in children.

A prospective, randomized of 135 women with postmenopausal osteoporosis ascertained the effect of administering 34 mg fluoride/day as sodium fluoride (0.56 mg fluoride/kg/day) for 4 years (Riggs et al. 1990). The fluoride treated and the placebo control groups received 1,500 mg calcium/day. 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 additional 2 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 radius 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 postmenopausal 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 were used, fluoride treatment for 2–4 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.

Conflicting findings on whether fluoride exposure in drinking water results in increased bone mineral density have been reported, with studies finding increases in spine and femur bone mineral density (Kröger et al. 1994; Phipps et al. 1998, 2000), decreases in radius mineral density (Phipps et al. 1998), or no effect on bone mineral density (Cauley et al. 1995; Lehmann et al. 1998; Sowers et al. 1991). Lumbar spine, proximal femur, and forearm bone mineral densities were measured in men and women 60 years and older living in one of three cities with different levels of naturally occurring fluoride in drinking water (Phipps et al. 1998). After adjusting for a number of non-fluoride related risk factors, significant elevations in bone mineral density of the lumbar spine (men and women) and proximal femur (women only) were observed in residents with the highest levels of fluoride (2.5 mg/L), as compared to densities in residents with the lowest fluoride concentration (0.03 mg/L); no significant differences in bone mineral density were found between residents with the mid-level fluoride concentration (0.7 mg/L) and the lowest concentration. In contrast to this finding, a negative correlation between bone mineral density of the forearm and an individual's fluoride intake from drinking water and toothpaste was found. Significant

increases in bone mineral density were also reported in another study by this group (Phipps et al. 2000). Adjusted (age, weight, education, knee/grip strength, surgical menopause, calcium intake, alcohol consumption, estrogen use, thiazide use, diabetes, thyroid hormone levels, exercise, and smoking) mineral densities were higher in the lumbar spine and femur and lower in the radius in women aged 65 years and older exposed to fluoridated drinking water, as compared to women with no reported exposure to fluoridated water. Kröger et al. (1994) also found significant increases in bone mineral density (adjusted for confounding factors such as age, weight, menopausal status, calcium intake, physical activity) of the femoral neck and lumbar spine among women aged 47–56 years exposed to fluoridated drinking water (1.2 mg/L) for >10 years (mean exposure duration was 25.9 years), as compared to women exposed to fluoridated drinking water for <10 years.

In a study of women aged 65 years and older, no significant alterations in bone mineral density of the radius, calcaneus, hip, or lumbar spine were found between women with no exposure to fluoridated water (n=1,248), 1–10 years of exposure (n=438), 11–20 years of exposure (n=198), or greater than 20 years of exposure (n=192) (Cauley et al. 1995). Total calcium intake was significantly higher in the >20-year group and lower in the 11–20-year group. Lehmann et al. (1998) also found no difference in age- and weight-adjusted bone mineral density of the spine and femur of women aged 20–69 years living in an area with fluoridated water (1 mg/L). In the men living in the fluoridated water a community, there was a significant increase in age- and weight-adjusted bone mineral density of the Ward's triangle portion of the femur, but no effect on neck or trochanter portions of the femur or the spine. The lack of adjustment for other risk factors limits the interpretation of this study; significantly higher alcohol consumption and lower calcium intakes were found in the fluoride-exposed group. Sowers et al. (1991) also found no significant alterations in bone mass in women aged 20–80 years living in a community with naturally high fluoride levels (4 mg/L) as compared to women living in a community with fluoridated water (1 mg/L). However, radius bone mass was significantly lower in the high fluoride group.

As with bone mineral density, conflicting results have been found on the effect of low levels of fluoride on the risk of fractures, particularly hip fractures. 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. 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 among women ≥65 years old. Fewer spine, hip, and humerus fractures were observed in this group. However, a nonsignificant trend toward higher incidences of wrist fractures was observed in the continuous exposure group. Lehmann et al. (1998) also found a significant decrease in the occurrence of hip fractures (adjusted for age) in men and women living in an area with fluoridated water (approximately 1 ppm), as compared to residents living in a city with low levels of fluoride in the water.

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) found a higher incidence of hip fractures among women aged 55–80 years living in a community with high levels of naturally occurring fluoride (4 ppm) in the water, as compared to women living in an area with fluoridated water (1 ppm). The lower calcium intake in the high fluoride group may have influenced these results. 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). Another study by this group (Jacobsen et al. 1992) also found a significantly elevated risk of hip fractures in residents living in counties with fluoridated water. The relative risks were 1.17 (95% CI=1.13–1.22) and 1.08 (95% CI=1.06–1.10) for men and women aged 65 years and older. The highest prevalence of hip fractures was found in counties that began a fluoridation program within the last 5 years. 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. county 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. An increase in the risk of hip fractures (age, sex, and quatelet index-adjusted odds ratio of 1.86, 95% CI=1.02–3.36) was also observed in adults aged 65 years and older living in areas

with drinking water fluoride levels ranging from 0.11 to 1.83 ppm (Jacqmin-Gadda et al. 1995); these data were reported as a letter to the editor and limited study details were provided.

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 to –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). The age-adjusted rate was significantly elevated in both women (relative risk 1.27, 95% CI=1.08–1.46) and men (relative risk 1.41, 95% CI=1.00–1.81). In men, the rates in the fluoridated and nonfluoridated communities were similar until age 70. After age 75, 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.

A study by Li et al. (2001) found a U-shaped pattern for the prevalence of overall bone fractures and the level of fluoride in the drinking water of six communities in rural China. The prevalence of bone fractures (adjusted for age and gender) was significantly elevated in the communities with 0.25–0.34 ppm fluoride (7.41%) or 4.32–7.97 ppm fluoride (7.40%), as compared to the prevalence (5.11%) in the community with 1.00–1.06 ppm fluoride in the water. When only hip fractures since age 20 years were examined, the age- and body mass index (BMI)-adjusted prevalence was only significantly higher in the 4.32–7.97 ppm group; prevalence of 1.20% compared to 0.37% in the 1.00–1.06 ppm group. A similar pattern was found for overall fractures since age of 50 years; the age-adjusted prevalences were 4.80 and 3.28% in the 4.32–7.97 and 1.00–1.06 ppm groups, respectively.

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). 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). Similarly, Avorn and Niessen (1986) found no statistically significant alteration in the occurrence of long bone fractures among women aged 65 years and older living in counties with fluoridated water (fluoride concentrations were not reported) as compared to residents living in counties without fluoridated water. No alteration in the occurrence of hip or ankle fractures were observed in men and women aged 65 years or older residents living in communities with fluoridated water, as compared to residents living in communities without a water fluoridation program (Karagas et al. 1996). In men, the risk of proximal humerus fracture (relative risk 1.23, 95% CI=1.06–1.43) and distal forearm fractures (relative risk of 1.16, 95% CI=1.02–1.33) were higher in the fluoridated water areas; the relative risks of these fractures in women living in fluoridated areas were not significantly altered. Cauley et al. (1995) found no effect on the risk of vertebral or nonvertebral fractures among women aged 65 years and older exposed to fluoridated water for 13 years (mean exposure duration).

Jacobsen et al. (1993) compared hip fractures rates in the 10-year period prior to fluoridation to the rates in the 10-year period after fluoridation of a city's water source (fluoride concentration of 1.1 ppm). No

significant differences in the risk of hip fractures were found in men or women aged 50 years and older; the relative risks, after adjusting for other risk factors, were 0.78 (95% CI=0.37–1.66) and 0.60 (95% CI=0.42–0.85) for men and women, respectively. No significant alterations in the risk of hip fracture were found among male and female residents aged 45 and older living in a city with fluoridated water (Suarez-Almazor et al. 1993). However, when male residents were considered separately, the relative risk of hip fracture was statistically significant in the 65 years and older age bracket (risk ratio of 1.13, 95% CI=1.00–1.24) and all men combined (risk ratio of 1.12, 95% CI=1.01–1.24).

With the exception of studies examining skeletal fluorosis, most of the studies on the skeletal effects of fluoride involved older adult populations. There is also some limited evidence that fluoride may affect bone mineralization in children. Increased trabecular height and area were observed in the distal radial metaphysis of boys (11–12 years of age) with dental fluorosis living in an area with 2.7 ppm fluoride in water (Chlebna-Sokol and Czerwinski 1993). No alterations were observed in similarly aged girls or older (13.5–15 years) boys and girls. The trabecular changes were correlated with lower serum calcium levels and higher alkaline phosphatase activity levels. Alarcón-Herrera et al. (2001) found a significant correlation between bone fracture incidence and Dean's index of dental fluorosis among children aged 6–12 years and adults aged 13–60 years.

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 fluoride/kg/day), 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 fluoride/kg/day as sodium fluoride 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 fluoride/kg/day (Harrison et al. 1984). 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 >1,000 ppm bone strength started to decrease. 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. An increase in the diameter of the femur bone and decreased breaking strength was observed in pigs administered sodium fluoride or rock phosphate in the diet (Kick et al. 1933).

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

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). Significant increases in water consumption and apparent (based on qualitative descriptions) increases in acid phosphatase activity in the glomeruli were observed in monkeys exposed to 0.46 mg fluoride/kg/day as hydrofluosilicic acid for 180 days (Manocha et al. 1975). The toxicological significance of these changes is not known.

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. In another study conducted in India, a positive dose-response relationship between parathyroid hormone and fluoride intake from drinking water was observed in children aged 6–12 years (Gupta et al. 2001). It is unclear if nutritional deficiencies played a contributing role to the observed endocrine effects. Jooste et al. (1999) found a higher goiter prevalence among children (6–15 years of age) living in two towns in South Africa with high levels of fluoride in the water (1.7 or 2.6 ppm), as compared to children living in towns with low (0.3 or 0.5 ppm) or optimal (0.9 or 1.1 ppm) fluoride levels in the water. The prevalence of goiter was also elevated in three of the other four towns, although the prevalence was lower

than in the high fluoride towns; suggesting that the children were exposed to other goitrogens. Iodine deficiency was not the likely etiological agent because the median urinary iodine levels were higher than iodine sufficiency standards. These data are inadequate to assess the relationship between elevated fluoride intake and goiter formation.

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. In contrast, Zhao et al. (1998) did not find any alterations in serum T_3 or T_4 levels in mice exposed to 3.2 mg fluoride/kg/day as sodium fluoride in drinking water for 100 or 150 days. However, a decrease in thyroid radiolabelled iodine uptake was observed at 3.2 mg fluoride/kg/day, but not at 0.06 mg fluoride/kg/day.

No significant alterations in parathyroid hormone levels or morphological alterations in the parathyroid gland were observed in rats exposed to 3.3 mg fluoride/kg in drinking water for 46 weeks (Rosenquist et al. 1983).

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 months) 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. An increase in the cellularity of Peyer's patches and mesenteric lymph nodes was observed in rats administered sodium fluoride (Butler et al. 1990).

3.2.2.4 Neurological Effects

There are limited data on the neurological toxicity of fluoride in humans. Exposure to very high doses of fluoride can result in neuromuscular symptoms (e.g., tetany, paresthesia, paresis, convulsions). These effects are probably due to 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. Using dental fluorosis as a surrogate for high fluoride intake, Morgan et al. (1998)

examined the possible correlation between dental fluorosis and behavioral problems in children aged 7–11 years. No significant correlations were found.

There are limited animal data on the neurotoxicity of fluoride. Significant decreases in spontaneous motor activity were 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. 1995a) 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. In a recent study only available as an abstract (Whitford et al. 2003), no significant alterations in performance on operant behavior tests were observed in female rats exposed to 2.9–11.5 mg fluoride/kg/day in drinking water for 7 months. Varner et al. (1998) 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. This study did not assess neurofunction; thus, it is difficult to assess 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 calculated using a reference water intake of 2 L/day and body weight of 70 kg), 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. The ecologic nature of this study design does not allow an evaluation of the nature of the total fertility rate and fluoride association. 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.

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 offspring 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 females, 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). Significant decreases in the number of viable fetuses and increases in the resorption rate were observed in female Sprague-Dawley rats exposed to 10.21 mg fluoride/kg/day as sodium fluoride in drinking water for 30 days prior to mating with unexposed males (Al-Hiyasat et al. 2000); it is not known if these effects were directly related to fluoride exposure or were secondary to the severe decreases in body weight (31% lower than controls) and water consumption. In contrast, a two-generation study by Collins et al. (2001a) did not find any significant alterations in reproductive performance in CD rats exposed to 10.7 mg fluoride/kg/day as sodium fluoride in drinking water for 10 weeks prior to mating with similarly exposed males. This study only found a

small decrease in body weight gain (approximately 6%) in the rats exposed to a similar sodium fluoride concentration as used by Al-Hiyasat et al. (2000). Decreased estrus rate and increased incidence of missed pregnancies was observed in Sheltie dogs fed dog food 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 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 3-4 and plotted in Figure 3-4.

3.2.2.6 Developmental Effects

Fluoride readily crosses the placenta and is found in fetal and placental tissue (Armstrong et al. 1970; Gupta et al. 1993; Malhotra et al. 1993; Shen and Taves 1974). A number of human and animal studies have examined the potential of fluoride to induce developmental effects.

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 6 (12%) of the 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.

Three studies (Li et al. 1995a; Lu et al. 2000; Zhao et al. 1996) conducted in China have found significant decreases in intelligence score in children living in areas with high endemic levels of fluoride in the

water. As noted below, these studies have a number of design limitations, which restrict the interpretation of the results. A fourth study did not find significant alterations in IQ scores in Mexican children (Calderon et al. 2000). The 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. Zhao et al. (1996) found significantly lower IQ scores in children living in a village with high levels of fluoride in drinking water (4.12 ppm) as compared to children living in a village with 0.91 ppm fluoride in water. The study authors noted that IQ levels in children were correlated with the educational levels of the parents; however, the educational level of parents in the village with low fluoride levels was higher than those in the high fluoride village.

No significant alterations in IQ scores were found in Mexican children (6–8 years of age) exposed to 1.2–3 ppm fluoride in drinking water (Calderon et al. 2000; only available as an abstract). However, increases in reaction time and decreases in visuospatial organization were found; the scores on these tests were correlated with urinary fluoride levels.

Rapaport (1956) reported an increased prevalence of Down's syndrome in areas with fluoridated water. However, this finding has 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. Takahashi (1998) criticized the methods used by Erickson et al. (1976) to analyze the data. Using the same dataset and combining Down's syndrome prevalence for the three youngest maternal ages, Takahashi (1998) found a significant association between water fluoridation and Down's syndrome. Similar to Erickson et al. (1976), Needleman et al. (1974) found no maternal age-specific increases in Down's syndrome; ascertainment was nearly complete in this study of over 80,000 children in fluoride areas and over 1,700,000 children in low-fluoride areas. 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).

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 13.21 or 13.72 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) or in the offspring of F0 or F1 rats exposed to 12.2 mg fluoride/kg/day as sodium fluoride in drinking water for 10 weeks prior to mating and during gestation (Collins et al. 2001b). 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. Significant increases in the percentage of fetuses with skeletal or visceral abnormalities were also observed in the fetuses of rats receiving gavage doses of 18 mg fluoride/kg/day as sodium fluoride on gestational days 6–19 (Guna Sherlin and Verma 2001). As with the Collins et al. (1995) study, significant decreases in maternal body weight and food consumption were also observed in the dams.

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 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. Most studies have not found significant increases in cancer mortality (Erickson 1978; Hoover et al. 1976; Rogot et al. 1978; Taves 1977) or site-specific cancer incidence (Freni and Gaylor 1992; Gelberg et al. 1995; Hoover et al. 1976; Mahoney et al. 1991; McGuire et al. 1991). However, a couple of studies have reported significant fluoridation-related increases in cancer mortality (Yiamouyiannis and Burk 1977) or incidence (Takahashi et al. 2001). The lack of control for potential confounding variables (i.e., age, race) limits the interpretation of these study results. Most of the investigations were community-based studies, and the sensitivity limit of even the most sensitive analysis in these studies appears to be a 10–20% increase.

Yiamouyiannis and Burk (1977) were the first investigators to suggest a relationship between water fluoridation and increased cancer risk. In their study, cancer death rates for 1940–1950 were compared to rates for 1953–1969 for residents of the 10 largest cities in the United States with fluoridated water. Similar comparisons were made in 10 cities without fluoridated water. The investigators noted that prior

to fluoridation (1940–1950) the crude cancer deaths were similar in the two groups of cities. After fluoridation (1953–1969), a sharp increase in cancer deaths was observed in the cities with fluoridated water. The increases in cancer deaths among residents aged 45–64 years and ≥65 years living in cities with fluoridated water were significantly higher than in residents of cities with nonfluoridated water. Yiamouyiannis and Burk (1977) noted that there was a greater increase in nonwhites in the fluoridated cities than in the nonfluoridated cities. Because they found no correlation between the increase in age-adjusted cancer death rate and the increase in the number of nonwhites living in each city, they concluded that the change in racial composition did not contribute to the fluoridation-related increase in cancer death rates.

A number of investigators have criticized the methods used by Yiamouyiannis and Burk and have re-analyzed the data (Chilvers 1982, 1983; Doll and Kinlen 1977; Hoover et al. 1976; Kinlen and Doll 1981; Oldham and Newell 1977; Smith 1980; Taves 1977). The study was primarily criticized for the dissimilarity of the age, sex, and race distribution between the fluoridated and nonfluoridated cities and the rather short cancer latency period. Chilvers (1983) and Smith (1980) noted that the divergence in crude cancer deaths began almost immediately after fluoridation was initiated. The latency period (the period of time between first exposure and the discovery of cancer) is usually >5 years and the period between first exposure and death from cancer is typically >15 years. Thus, Chilvers (1983) and Smith (1980) suggested that exposure to fluoridated water was not the likely cause of the divergence in cancer mortality between the two groups of cities that began shortly after initiation of a water fluoridation program. Smith (1980) noted that using age bands of 20 years is problematic for cancer studies because cancer mortality dramatically increases with age so that small differences in the age distribution between two populations can result in apparently significant differences in cancer mortality.

Smith (1980) also criticized Yiamouyiannis and Burk's dismissal of the potential confounding variable of race based on the lack of significant correlation relationships. Additionally, he noted that the appropriate analytical method should account for race, age, and sex differences at the same time. Between 1950 and 1970, the proportion of nonwhites and individuals over the age of 65 years increased more rapidly in the fluoridated cities than in the nonfluoridated cities (Doll and Kinlen 1977). This change in demographics would have likely resulted in increased cancer deaths independent of fluoridation. Oldham and Newell (1977) noted that although the crude cancer rates in the two groups of cities were similar, the 1950 excess cancer rate (which accounts for race, sex, and age differences) in the fluoridated cities was 10.3 per 100,000 higher than in the nonfluoridated cities. The higher excess cancer rate in the fluoridated cities was attributed to the smaller number of white elderly women and greater number of elderly white males.

Oldham and Newell (1977) estimated that in 1970, the excess cancer rate increased by 1% in the fluoridated cities and 4% in the nonfluoridated cities; the increases in absolute deaths were 8.8 per 100,000 and 7.7 per 100,000 in the fluoridated and nonfluoridated cities, respectively. In re-examining the data used by Yiamouyiannis and Burk (1977), Hoover et al. (1976) noted that when fluoride was the only variable used in the regression analysis, it was a significant predictor of cancer mortality rate. However, when other demographic variables (population density, education level, race, employment in manufacturing, and geographic section of the country) were also entered into the equation, fluoride only statistically predicted stomach cancer mortality rate. Re-analysis of stomach cancer data with adjustment for high-risk ethnic groups resulted in a nonsignificant association for females and a significant association for males.

Yiamouyiannis and Burk's selection of nonfluoridated cities has also been criticized because they did not select the 10 largest cities (the criteria used for selecting fluoridated cities), rather they selected the 10 largest cities with a crude cancer death rate exceeding 155 per 100,000 (the average in fluoridated cities). Comparison of the SMRs for 1950, 1960, and 1970 and the change from 1950 to 1970 using cancer mortality analysis of data from the original 10 largest fluoridated cities and the 10 largest nonfluoridated cities did not result in any relevant changes in cancer mortality (Kinlen and Doll 1981). Similarly, Taves (1977) calculated SMRs for three 2-year periods (1949–1951, 1959–1961, and 1969–1971) for all cancers in the fluoridated and nonfluoridated cities examined by Yiamouyiannis and Burk and for the next 10 largest fluoridated cities and 5 nonfluoridated cities. The SMRs for the 20 fluoridated cities, as well as the SMRs for the 15 nonfluoridated cities, were relatively constant for the three time periods, suggesting that water fluoridation did not increase the cancer risk.

A number of other population studies have examined the possible association between water fluoridation and increased risk of all cancers or site-specific cancers. Hoover et al. (1976) examined cancer mortality data for counties in Texas with varying levels of naturally occurring fluoride. For white males and females, no significant increases in SMRs for all cancers combined or site-specific cancers were found in the three groups of counties with high levels of fluoride (0.7–1.2 ppm, 1.3–1.9 ppm, and ≥2.0 ppm) as compared to counties with very low fluoride levels in the drinking water. Hoover et al. (1976) also examined the effect of artificial fluoridation on cancer mortality. SMRs were calculated for residents of counties in the United States that were 67% urban. No significant differences in the SMRs for all cancer combined between the fluoridated and nonfluoridated counties were seen prior to fluoridation or 5, 10, or 15 years after fluoridation. Similarly, no significant differences in SMRs were seen for individual cancer sites. A third study conducted by Hoover et al. (1976) examined cancer incidence data from Birmingham,

Alabama (nonfluoridated) and Denver, Colorado (fluoridated after 1947–1948). No fluoridation-related increases in age-adjusted, site-specific cancer incidence rates were found prior to fluoridation (1947–1948) or after fluoridation (1969–1971).

Using mortality data from 22 nonfluoridated and 24 fluoridated cities with populations greater than 250,000, Erickson (1978) calculated crude and adjusted death rates for all malignant neoplasms and several site-specific cancers (digestive, respiratory, breast, genital, urinary, leukemia). Slightly higher crude mortality rates were seen in the fluoridated cities (206.6 versus 183.0); however, when the mortality rates were adjusted for age, sex, and race, and demographic, social, and economic variables, no significant differences were found. Rogot et al. (1978) also found no association between fluoridation and cancer mortality among cities with populations of 25,000 or more in 1950. Mortality rates for 1950, 1960, and 1970 and the change from 1950 to 1970 were compared for fluoridated and nonfluoridated cities. In a study of cancer mortality rates in three counties in Kansas with fluoridated water, and one county with nonfluoridated water, no consistent fluoridation-related increases in age-adjusted mortality from all cancers were found (Neuberger 1982). In one fluoridated county, there was a significant increase in mortality; however, in another county, cancer mortality was significantly lower than in the nonfluoridated county and in the third county, there were no significant differences. Examination of cancer mortality data for individual tumor sites revealed slightly higher rates of rectum cancer in females, higher rates of pancreatic cancer in females living in the county with the longest history of fluoridation, and bone cancer in males with the longest history of fluoridation exposure; the statistical significance of these findings was not reported. Using data from the NCI Surveillance, Epidemiology and End Result (SEER) program, Hoover et al. (1991a) evaluated cancer mortality data for 36 years and incidence data for 15 years. No consistent evidence of a relationship between site-specific cancer mortality or incidence and the pattern of fluoridation was found. A suggestive relationship between renal cancer incidence and duration of fluoridation was found. However, when the incidence data were divided into two time periods (1973–1980, 1981–1987), no relationship between renal cancer incidence and duration of fluoridation was found.

A more recent study has also examined cancer incidence in populations with fluoridated water. Using data from three states (Connecticut, Iowa, and Utah) and six cities (Atlanta, Detroit, New Orleans, Seattle, San Francisco, and Los Angeles), Takahashi et al. (2001) conducted regression analysis of site-specific cancers. Statistically significant positive associations between fluoridation index (percentage of population with naturally or artificially fluoridated water) and cancer at a number of sites including the oral cavity, esophagus, colon, liver, pancreas, bronchus, lungs, kidney, urinary bladder, and bone were

found. However, interpretation of these data is limited by the lack of control for potential confounding variables (particularly age and race) between the fluoridated and nonfluoridated communities.

In the early 1990s, two population-based studies found increases in the incidence of bone and joint cancer or osteosarcoma among males under the age of 20 living in areas with fluoridated water (Cohn 1992; Hoover et al. 1991b). Based on the NCI SEER program data, Hoover et al. (1991b) found 47 and 79% increases in the incidences of bone and joint cancer and osteosarcoma, respectively, among males and females living in areas with fluoridated water. In contrast, 34 and 4% declines in bone and joint cancer and osteosarcoma, respectively, were found in the nonfluoridated areas. The investigators questioned the biological significance of this finding because no relationship between the increased incidence and the initiation of fluoridation was found (Hoover et al. 1991b). In the Cohn (1992) study of the New Jersey cancer registry data, significant increases in the osteosarcoma incidence risk ratios were found among males under the age of 20 years living in areas with fluoridated water. The investigator cautioned that these results were based on a small number of cases. Other population-based studies (Freni and Gaylor 1992; Mahoney et al. 1991) did not find significant associations between fluoridation and bone cancer. Freni and Gaylor (1992) reported significant increases in the cumulative risk of bone cancer among young men aged 10–29 years in 40 cancer registry areas in the United States, Canada, and Europe for the period of 1958–1987. However, when registry data for areas with known fluoridation status were examined, no consistent pattern was observed; both increases and decreases in cumulative risk were found in areas with fluoridated water. Similarly, Mahoney et al. (1991) reported a significant trend for increasing incidence of bone cancer among young men (<30 years of age) living in New York State, exclusive of New York City. A significant trend was not observed in young females or for osteosarcomas. Comparisons between bone cancer and osteosarcoma incidence rates among residents of counties with fluoridated water and residents of counties with nonfluoridated water did not reveal any statistically significant associations. A case-control study of New York residents, excluding New York City, also failed to show an association between fluoridated water and increased risk of osteosarcoma (Gelberg et al. 1995). A significant protective trend (odds ratio decreased with increased fluoride intake) was observed for males, although the authors noted that this may be due to good health practices rather than fluoride because a significant trend was not observed when only fluoridated water was considered. A small-scale case-control study (22 cases examined) also failed to find a significant association between fluoridated water and osteosarcoma occurrence (McGuire et al. 1991).

The NTP conducted two chronic oral bioassays of fluoride administered as sodium fluoride (0, 25, 100, or 175 ppm) in drinking water for 103 weeks, 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 specially formulated diet used in the second study contained 8.6 ppm fluoride; daily fluoride amounts administered in the food for control and experimental groups were 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 Sikivuev 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. Hepatocholangiocarcinomas, which are rare liver neoplasms, were identified in the original pathology examination in five treated male mice, four treated female mice, and one control female mouse. The Pathology Working Group reclassified all of the neoplasms (except one in a high-dose female mouse and one in a control female mouse) as hepatoblastomas, because they contained well-defined populations of cells that resembled embryonal liver cells more closely than they did biliary cells. The dose levels at which the reclassified hepatocholangiocarcinomas were found were not reported.

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

Based on the finding of a rare tumor in a tissue known to accumulate fluoride, but not at the usual site for chemically-associated osteosarcomas, a weakly significant dose-related trend, and the lack of supporting data in female rats and mice of either gender, the NTP concluded that there was "equivocal evidence of carcinogenic activity of sodium fluoride in male F344/N rats." NTP defined equivocal evidence of carcinogenic activity to be a situation where the results show "a marginal increase in neoplasms that may be chemically related." NTP further concluded that there was no evidence that fluoride was carcinogenic at doses up to 4.73 mg/kg/day in female F344/N rats, or at doses up to 17.8 and 19.9 mg/kg/day in male and female $B6C3F_1$ mice, respectively.

The first chronic study in this series conducted by NTP was a 2-year cancer study in $B6C3F_1$ mice and F344/N rats using a semisynthetic diet containing 2.1 ppm fluoride and fluoride provided in drinking water as sodium fluoride at 0, 10, 30, or 100 ppm. Several 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 B12 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 in female rats (male mice were not mentioned).

A study sponsored by Procter 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. Fluoride-related toxicity 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 hydrogen fluoride or fluorine 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 fluoride, hydrofluoric acid, or fluorine.

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 fluoride, hydrofluoric acid, or fluorine.

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category of exposure to 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 fluoride or fluorine, and no studies were located regarding respiratory effects in animals after dermal exposure to fluoride, hydrofluoric acid, or fluorine.

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.

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

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL				Reference Chemical Form
				Less Serious		Serious		
ACUTE EXPOSURE								
Systemic								
Rabbit	1 d 1-4hr/d	Dermal	2 Percent (%)			2 Percent (%)	(necrotic lesions)	Derelanko et al. 1985 hydrogen fluoride
INTERMEDIATE EXPOSURE								
Systemic								
Rat (NS)	5 wks 6d/wk 6hr/d	Dermal		8.2 ppm	(subcutaneous hemorrhage around the eyes and on the feet)			Stokinger 1949 hydrogen fluoride
Reproductive								
Dog (NS)	5 wks 6d/wk 6hr/d		8.2 ppm	31 ppm	(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		
ACUTE EXPOSURE								
Systemic								
Rat (Sprague- Dawley)	1 d 24hr/d	Dermal		0.5 Percent (%)	(superficial necrosis, moderate edema, PMN infiltration)	1 Percent (%)	(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

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

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. Skin irritation and damage has been observed in humans and/or animals exposed to fluoride, hydrogen fluoride, hydrofluoric acid, or fluorine. Dermal effects related to exposure to hydrogen fluoride or fluorine are discussed under Inhalation Exposure (Section 3.2.1.2).

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.

Hydrofluoric Acid. 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. 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.

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.

Ocular Effects. Ocular irritation and damage has been observed in humans and animals exposed to hydrogen fluoride, hydrofluoric acid, and fluorine. The ocular effects resulting from exposure to hydrogen fluoride or fluorine are discussed under inhalation exposure (Section 3.2.1.2).

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.

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.

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

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

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

Species (test system)	End point	Results		Reference	Form
		With activation	Without activation		
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	–	Slameňová et al. 1992	NaF
Mouse lymphoma cells	Gene mutation	No data	(+)	Cole et al. 1986	NaF
Mouse lymphoma cells	Gene mutation	+	+	Caspary et al. 1987, 1988; NTP 1990	NaF

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

Species (test system)	End point	Results		Reference	Form
		With activation	Without activation		
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

negative for dominant lethal mutations following inhalation exposure to hydrogen fluoride in C57B1 mice (Voroshilin et al. 1975). In 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%.

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).

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

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

Hydrogen Fluoride. Increases in plasma fluoride levels were observed in humans inhaling 0.8–2.8 or 2.9–6.0 ppm fluoride as hydrogen fluoride of 60 minutes (Lund et al. 1997); maximum plasma concentrations were observed 60–90 minutes after exposure initiation. 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 has been demonstrated in several studies. In a study by Collings et al. (1952), two workers were exposed to approximately 5 mg fluoride/m^3 for 6 hours with 15-minute breaks every 2 hours. 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. Two studies of aluminum potroom workers found elevated plasma fluoride levels (Ehrnebo and Ekstrand 1986; Søyseth et al. 1994). In workers exposed to 0.910 mg fluoride/m^3 total fluoride (34% of which was gasous fluoride) during an 8-hour workshift, elevated plasma fluoride concentrations and urinary fluoride levels were observed (Ehrnebo and Ekstrand 1986). Although these studies demonstrate absorption of fluoride, none measure the extent of fluoride absorption.

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.

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

Fluoride. In humans and animals, fluoride is rapidly and efficiently absorbed from the gastrointestinal tract. Elevated plasma fluoride levels are seen shortly after exposure to sodium fluoride; peak plasma levels are typically seen within 30–60 minutes of ingestion (Carlson et al. 1960a; Ekstrand et al. 1977, 1978). Fluoride is absorbed from both the stomach and small intestine via passive diffusion. Nopakun et al. (1989) estimated that in rats, approximately 20% of total absorbed fluoride was absorbed from the stomach. Absorption of fluoride from the stomach is inversely proportional to pH (Messer and Ophaug 1993; Whitford and Pashley 1984), suggesting that fluoride is absorbed from the stomach as the undissociated hydrogen fluoride rather than the fluoride ion (Whitford and Pashley 1984). After gastric emptying, fluoride was rapidly absorbed from the small intestine (Messer and Ophaug 1993). An *in vitro* study suggests that in the small intestine, fluoride is primarily absorbed as the fluoride ion (Nopakun and Messer 1990). The absorption of fluoride does not appear to be homeostatically regulated. A linear correlation between fluoride (as sodium fluoride) intake and the area under the plasma fluoride concentration curve was found in humans ingesting 2–10 mg doses of sodium fluoride (Trautner and Seibert 1986).

A number of dietary factors can influence the absorption of fluoride. Delayed gastric emptying slows the rate of fluoride absorption, but does not appear to affect the total amount of fluoride absorbed (Messer and Ophaug 1993). Ingestion of sodium fluoride with food delayed the peak plasma level but did not significantly alter the total amount of fluoride absorbed, as compared to values when the subjects ingested sodium fluoride after an 8-hour fast (Shulman and Vallejo 1990; Trautner and Einwag 1987). In contrast, ingestion of calcium fluoride with a meal dramatically increased (33.5 versus 2.8%) the absorption of fluoride, as compared to absorption after an 8-hour fast; similar results were found for the fluoride in bone meal tablets (Trautner and Einwag 1987). It is likely that the increased residence time in the upper gastrointestinal tract increased absorption. Ingestion of sodium fluoride with milk decreased fluoride absorption by 13–50% (Ekstrand and Ehrnebo 1979; Shulman and Vallejo 1990; Trautner and Seibert 1986). Other studies have also shown that co-exposure to calcium carbonate or a diet high in calcium decreases fluoride absorption (Jowsey and Riggs 1978; Whitford 1994). Increased exposure to magnesium (Stookey et al. 1964; Weddle and Muhler 1954) or aluminum (Stookey et al. 1964; Weddle and Muhler 1954) also resulted in decreases in fluoride absorption.

Soluble fluoride compounds, such as sodium fluoride, hydrogen fluoride, and fluorosilic acid, are readily absorbed from the gastrointestinal tract. Studies in humans and animals have found that >80% of an oral

dose of soluble fluoride compound is absorbed (Ericsson 1958; McClure et al. 1950, 1945; Zipkin and Likins 1957); several studies have reported 99–100% absorption efficiencies (Ekstrand et al. 1978; Trautner and Einwag 1987). Poorly soluble fluoride compounds, such as calcium fluoride, magnesium fluoride, and aluminum fluoride, do not appear to be well absorbed. Very little (<10%) fluoride was absorbed in fasting subjects ingesting calcium fluoride (Afseth et al. 1987; Trautner and Einwag 1987). Compared to sodium fluoride, the fluoride from bone meal (McClure et al. 1945; Trautner and Einwag 1987) and cryolite (McClure et al. 1945) was poorly absorbed.

The absorption of fluoride in infants, children, and adults appears to be similar. A study of four infants (mean age 8 months) reported mean absorption rates of 88.9–96.0% when a sodium fluoride solution was administered along with infant formula (Ekstrand et al. 1994b). As discussed previously, the absorption efficiency in adults usually exceeds 90% (Ekstrand et al. 1978; Trautner and Einwag 1987). As with adults, peak plasma levels usually occurred in 30–60 minutes (mean of 39 minutes) in infants (Ekstrand et al. 1994a) and young children aged 3–4 years (Ekstrand et al. 1983). One observed difference between fluoride absorption in infants and adults is that administration of fluoride with a high calcium diet did not result in a significant decrease in fluoride absorption (88.9 versus 96.0%) in infants (Ekstrand et al. 1994b); a decrease in absorption has been reported in adults (Ekstrand and Ehrnebo 1979; Shulman and Vallejo 1990; Trautner and Einwag 1987).

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.

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 [14C]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.

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.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

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).

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 remodeling. 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).

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).

3.4.2.2 Oral Exposure

Fluoride. Once absorbed, fluoride is rapidly distributed throughout the body via the blood. Fluoride is distributed between the plasma and blood cells, with plasma levels being twice as high as blood cell levels (Whitford 1990). After ingestion of sodium fluoride, the plasma fluoride does not appear to be bound to proteins (Ekstrand et al. 1977a; Rigalli et al. 1996). However, there is evidence that following ingestion of sodium monofluorophosphate, the plasma contains diffusible fluoride and protein-bound fluoride

(Rigalli et al. 1996). The elimination of fluoride from plasma following short-term exposure to sodium fluoride has been fit to a two-compartment model (Ekstrand et al. 1977a). The half-life of the terminal phase ranged from 2 to 9 hours. The rapid phase of fluoride distribution represents distribution in soft tissues, with fluoride being more rapidly distributed to well-perfused tissues. In pigs, the plasma clearance half-time of fluoride was 0.88 hours (Richards et al. 1982). Fluoride does not accumulate in most soft tissue; the ratio between tissue fluoride levels and plasma fluoride levels is typically between 0.4 and 0.9 (Whitford et al. 1979a). It is likely that fluoride enters the intracellular fluid of soft tissues as hydrogen fluoride (Whitford et al. 1979a). Studies in rats and ewes suggest that the blood brain barrier is effective in preventing fluoride migration into the central nervous system (Spak et al. 1986; Whitford et al. 1979a); brain fluoride concentrations typically do not exceed 10% of plasma concentrations (Whitford et al. 1979a). Higher fluoride concentrations are found in the renal tubules, the concentration often exceeding plasma concentrations.

The largest concentration of fluoride in the body is found in calcified tissues. Approximately 99% of the fluoride in the body is found in bones and teeth (Hamilton 1990; Kaminsky et al. 1990). The pineal gland which contains hydroxyapatite also accumulates fluoride (Luke 2001). Fluoride is incorporated into bone by replacing the hydroxyl ion in hydroxyapatite to form hydroxyfluroapatite (McCann and Bullock 1957; Neuman et al. 1950). Fluoride is not irreversibly bound to bone and is mobilized from bone through the continuous process of bone remodeling and to a lesser extent from ionic flux between interstitial fluoride and the crystalline bone surface (Turner et al. 1993; Whitford 1990). The biological half-life of fluoride was estimated to be 58.5 days in pigs orally exposed 2 mg fluoride/kg/day as sodium fluoride for 6 months (Richards et al. 1985). A comparison between the retention of sodium fluoride, fluorosilicic acid, and sodium fluorosilicate did not find significant differences in the percentage of intake retained in the body of female rats exposed to 24 ppm fluoride in the diet for 5 months; fluoride retentions were 66.2, 68.1, and 64.8, respectively (Whitford and Johnson 2003; only available as an abstract).

Tissue fluoride levels are not homeostatically regulated. In adults, plasma fluoride levels appear to be directly related to fluoride intake. At higher fluoride intakes, a wide fluctuation of plasma fluoride levels were found in two adults and three children consuming 9.6 ppm fluoride in water (Ekstrand 1978); the fluctuation in plasma fluoride levels was smaller in the children, as compared to the adults. Mean plasma levels in individuals living in areas with a water fluoride concentration of <0.1 ppm was 0.4 µmol/L, compared to a mean plasma fluoride level of 1 µmol/L in individuals with a water fluoride content of 0.9–1.0 ppm (Guy et al. 1976). The level of fluoride in bone is influenced by several factors including age, past and present fluoride intake, and the rate of bone turnover. In adults (mean age, 47–60 years),

fluoride levels in the iliac crest ranged from 0.06 to 0.10% of bone ash (Boivin et al. 1988). In contrast, in subjects undergoing sodium fluoride treatment for osteoporosis for 5–6 years, the fluoride content of the iliac crest was 0.67% bone ash. Termination of high fluoride exposure can result in a decrease in bone fluoride levels. In aluminum workers diagnosed with skeletal fluorosis, there was a significant and progressive decrease in bone fluoride levels (Boivin et al. 1988).

Age strongly influences the distribution of fluoride. The amount of fluoride taken up by bone is inversely related to age (Lawrenz et al. 1940; Miller and Phillips 1956; Suttie and Phillips 1959; Zipkin and McClure 1952; Zipkin et al. 1956). In a study of dogs (Ekstrand and Whitford 1984; Whitford 1990), the fractional uptake of fluoride by bone steadily declined during the first year of life. At weaning, 90% of an administered dose was taken up by bone compared to 50% at 1 year of age. Similar findings have been reported in human studies. In infants aged 37–410 days exposed to 0.25 mg fluoride supplement, the mean retention (bone uptake) of fluoride ranged from 68.1 to 83.4% (Ekstrand et al. 1994a, 1994b). In contrast, retention in adults receiving a fluoride supplement was 55.3% (Ekstrand et al. 1979).

Human and animal studies have shown that fluoride is readily transferred across the placenta. There appears to be a direct relationship between maternal blood fluoride levels and cord blood fluoride levels (Armstrong et al. 1970; Gupta et al. 1993; Malhotra et al. 1993; Shen and Taves 1974). At relatively low maternal blood levels, the cord blood levels were at least 60% of that of maternal blood (Brambilla et al. 1994; Gupta et al. 1993). Although cord fluoride levels were typically lower than maternal levels, one study found no statistical difference between maternal and newborn (1 day old) serum fluoride levels (Shimonovitz et al. 1995). However, a partial placental barrier may exist at high maternal fluoride levels. At higher maternal blood levels, the cord to maternal fluoride ratio is lower than at lower maternal fluoride levels (Gupta et al. 1993). Another study found that the use of fluoride supplements markedly increased placental fluoride levels, while fluoride levels in fetal blood remained relatively constant, suggesting that the placenta can regulate the transfer of fluoride from maternal blood to fetal blood (Gedalia 1970). Animal studies also demonstrate that maternal fluoride exposure also results in increased levels of fluoride in fetal teeth and bones (Bawden et al. 1992b; Nedeljković and Matović 1991; Theuer et al. 1971).

In humans, fluoride is poorly transferred from plasma to milk (Ekstrand et al. 1981c, 1984b; Esala et al. 1982; Spak et al. 1983). A single dose of 1.5 mg sodium fluoride did not result in a significant rise in fluoride breast milk concentrations within 3 hours of the exposure (Ekstrand et al. 1981c). Although no linear correlation between fluoride levels in tap water and fluoride levels in breast milk has been found,

significantly higher breast milk fluoride concentrations were found in women living in an area with high levels of naturally occurring fluoride (1–7 ppm) as compared to women in areas with low fluoride levels in tap water (0.2 ppm) (Esala et al. 1982). Fluoride levels in human milk of 5–10 µg/L have been measured (Fomon and Ekstrand 1999).

3.4.2.3 Dermal Exposure

No information was located in humans or animals regarding the distribution of fluoride, hydrogen fluoride, or fluorine 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 radiolabelled fluoride (^{18}F) is taken up by bone; 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 most of the remainder is excreted in the urine, with smaller amounts in feces, and sweat, and saliva within 24 hours (Dinman et al. 1976a, 1976b; McClure et al. 1945). Urinary excretion is markedly decreased in the presence of decreased renal function (Kono et al. 1984; Spak et al. 1985).

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 (100–1,000 times) higher than concentrations that would be normally found in human tissues.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

Hydrogen Fluoride. 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.

Hydrogen Fluoride and Fluoride Dusts. Studies in humans indicate that fluoride absorbed from inhaled hydrogen fluoride and fluoride dusts 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). A significant correlation between urinary fluoride excretion and the area under the plasma concentration-time curve was found in aluminum

workers (Ehrnebo and Ekstrand 1986). A significant correlation between urinary fluoride excretion and exposure levels of gaseous fluoride, but not particulate fluoride, was also found.

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.

3.4.4.2 Oral Exposure

Fluoride. The primary pathway for fluoride excretion is via the kidneys and urine; to a lesser extent, fluoride is also excreted in the feces, sweat, and saliva. A study in rats suggests that the source of the small amount fecal fluoride may be fluoride that has re-entered the more distal portion of the intestine and became associated with unabsorbed cations (Whitford 1994). It has been estimated that approximately 1% or less of an ingested dose is excreted in saliva (Carlson et al. 1960a; Oliveby et al. 1989), because saliva is swallowed, this amount does not enter mass balance calculations. The concentration of fluoride in the saliva appears to mirror plasma fluoride levels (Ekstrand 1977; Oliveby et al. 1989, 1990) and the ratio of saliva fluoride to plasma fluoride is about 0.5–0.64 (Ekstrand 1977; Oliveby et al. 1989). There are limited data on fluoride excretion via sweat. An older study (McClure et al. 1945) estimated that 19% of an ingested fluoride dose (3.7 mg) was excreted in sweat under comfortable conditions. Excretion of fluoride increased to 42% under hot-moist conditions. However, this study appears to have grossly overestimated fluoride excretion in sweat. A more recent study (Henschler et al. 1975), reported low levels of fluoride in sweat, approximately 20% of plasma levels, 2 hours after administration of sodium fluoride.

Renal excretion is the major route of fluoride removal from the body; it typically equals 35–70% of intake in adults (Ekstrand et al. 1978; Machle and Largent 1943;). The fluoride ion is filtered from the plasma as it passes through the glomerular capillaries followed by a varying degree (10–70%) of tubular reabsorption; there is no evidence of tubular secretion of fluoride (Schiffl and Binswanger 1982; Whitford 1990). Renal clearance rates in humans can range from 12.4 to 71.4 mL/minute with average values of 36.4–41.8 mL/minute (Schiffl and Binswanger 1982; Waterhouse et al. 1980). A number of factors, including urinary pH, urinary flow, and glomerular filtration rate, can influence urinary fluoride excretion. Urinary pH appears to be the major determining factor for fluoride reabsorption from the renal

tubules (Ekstrand et al. 1980a, 1982; Järnberg et al. 1980, 1981, 1983; Whitford et al. 1976). At lower pH levels, more fluoride exists in the undissociated form (hydrogen fluoride) than in the ion form; the uncharged hydrogen fluoride more readily diffuses through the tubular epithelium to the interstitial fluid than the free charged fluoride ion. In the neutral interstitial fluid, the hydrogen fluoride would rapidly dissociate and the fluoride ions would be returned to the systemic circulation (Whitford et al. 1976). Thus, renal clearance of fluoride is directly related to urinary pH. A significant correlation between urinary flow and urinary fluoride excretion has been reported in humans (Ekstrand et al. 1978, 1982). Ekstrand et al. (1982) noted that a high flow rate in the renal tubules would likely increase the renal clearance of a substance that is reabsorbed at a slow rate. Similarly, a decrease in glomerular filtration rate would result in a decrease in urinary fluoride excretion (Jeandel et al. 1992).

Most of the data on renal clearance of fluoride in humans come from studies of health adults; however, several studies have examined renal clearance of fluoride at different age levels (Ekstrand et al. 1994a; Jeandel et al. 1992; Spak et al. 1985; Villa et al. 2000). Whitford (1999) compared the results of many of these studies in infants and children with those in adults and concluded that there are no apparent age-related differences in renal clearance rates (adjusted for body weight or surface area) between children and adults. However, in older adults (>65 years), a significant decline in renal clearance of fluoride has been reported (Jeandel et al. 1992). This is consistent with the decline in glomerular filtration rate and renal clearance of many substances that are also observed in the elderly (Whitford 1999).

3.4.4.3 Dermal Exposure

No studies were located regarding excretion of fluoride, hydrogen fluoride, or fluorine 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).

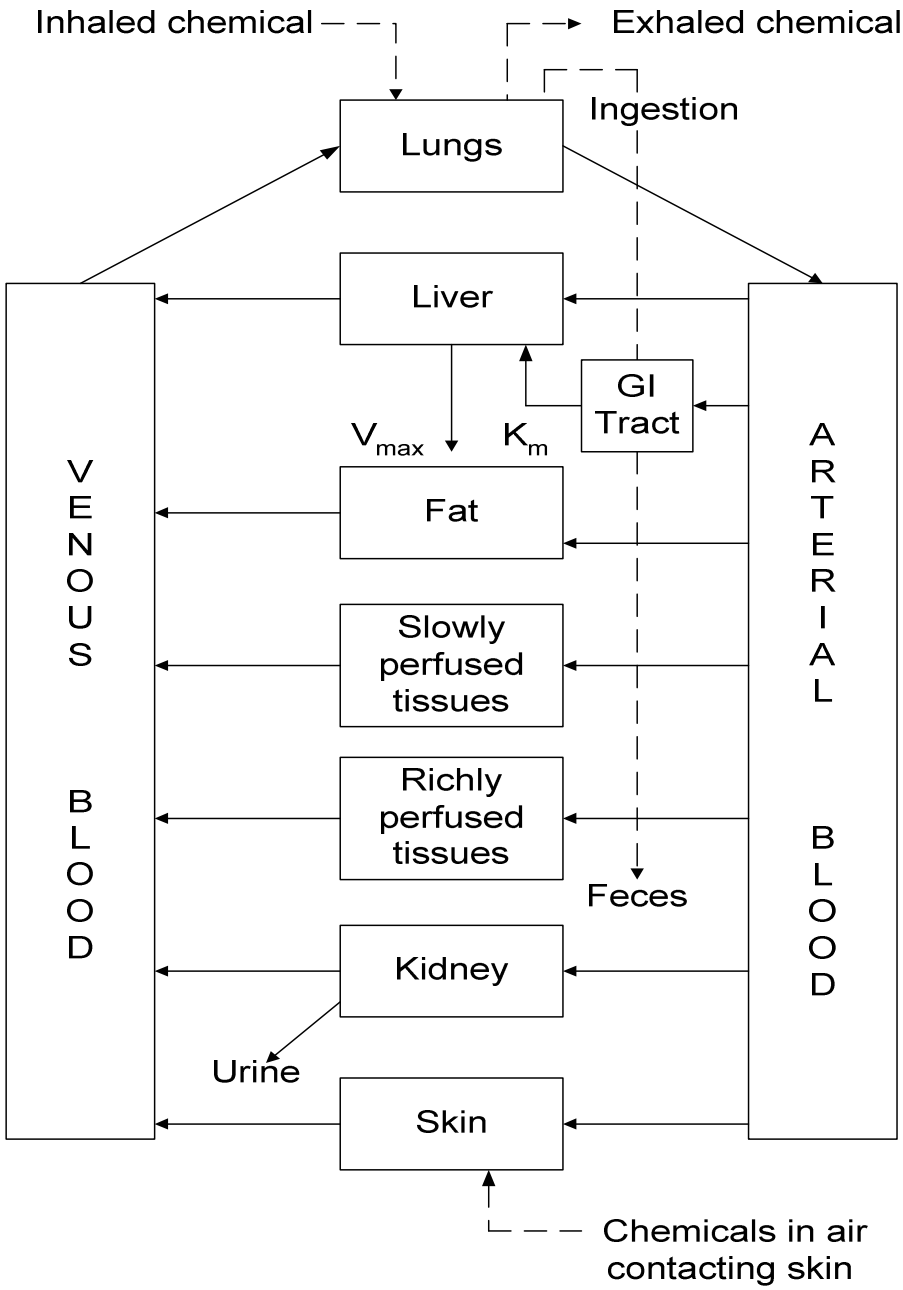
PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-5 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; Ekstrand et al. 1977a; Hall et al. 1977; Richards et al. 1982, 1985) 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. (1995) 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

Figure 3-5. 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.

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.

3.5 MECHANISMS OF ACTION

Skeletal Effects. 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 high-dose 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 as well 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 with long-term, high-dose administration of fluoride (Chachra 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. Further,, 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.

Dental Fluorosis. Numerous human and animal studies have demonstrated that exposure to elevated fluoride levels during tooth development can result in dental fluorosis. As described previously, fluorosed enamel is composed of hypomineralized subsurface enamel covered by well-mineralized enamel. The exact mechanisms of dental fluorosis development have not been fully elucidated. Although there are a number of proposed mechanisms, most of the recent research has focused on the theory that dental fluorosis results from a fluoride-induced delay in the hydrolysis and removal of amelogenin matrix proteins during enamel maturation and subsequent effects on crystal growth (as reviewed by Aoba 1997; Bawden et al. 1995; DenBesten and Thariani 1992; Whitford 1997). Amelogenins, proteins secreted by ameloblasts, comprise >90% of the enamel matrix proteins and are involved in the regulation of the form and size of hydroxapatite crystallites; large molecular weight amelogenins inhibit the growth of enamel crystallites. In the early maturation phase of tooth development, the amelogenins are removed from the enamel matrix by amelogeninases, and crystallite growth dramatically increases. This phase of enamel maturation appears to be the most sensitive to elevated fluoride levels. The current evidence strongly suggests that fluoride inhibits amelogeninase activity. In one proposed mechanism, fluoride indirectly

inhibits amelogeninase, a calcium-dependent metalloenzyme, by binding to calcium in the mineralizing milieu and thereby decreasing the calcium concentration (or its activities) and the activation of amelogeninases (Aoba 1997; DenBesten and Thariani 1992; Whitford 1997). Another proposed mechanism is that amelogeninases are activated by a metalloproteinase and that calcium is required for this activation (Bawden et al. 1995; DenBesten and Thariani 1992); fluoride thus interferes with the proteolytic cascade necessary for hydrolysis of amelogenins. The fluoride-calcium interaction is supported by the findings that the enzymatic cleavage of amelogenins occurs at a slow rate during the secretory phase when calcium transport is low and dramatically increase during the early maturation phase (in the absence of excess fluoride) when calcium transport is high (Aoba 1997).

An alternative theory on the mechanism of dental fluorosis is related to the effects of fluoride on maturation-stage ameloblasts (Bawden et al. 1995; DenBesten and Thariani 1992). Elevated fluoride exposure results in a decrease in the number of ameloblast modulations, which in turn could reduce the number of zone refinement cycles. As defined by Bawden et al. (1995), zone refinement is the process by which impurities (such as magnesium) that have been incorporated into forming crystals are reduced, resulting in an improvement of the structural characteristics of the crystal. Thus, a reduction in zone refinement cycles could result in inferior apatite crystalline structure. This theory is not incompatible with the theory that fluoride interferes with the hydrolysis of amelogenins. The fluoride-induced inhibition of amelogeninases results in an enamel matrix with a higher organic content, which could influence ameloblast modulation rate.

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 Clement (1992), 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 1998c). 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, was 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, IOM 1997; WHO 1973) advocate the use of fluoride supplementation in children. However, there is a delicate balance between prevention of dental caries and the occurrence of dental fluorosis. Dental fluorosis, which is an increased porosity or hypomineralization of the tooth enamel, results from excess exposure to fluoride during tooth development (ages 1–8 years). The development and severity of dental fluorosis are dependent on the amount of fluoride ingested, the duration of exposure, and the stage of enamel development at the time of exposure. In the more severe cases, the tooth enamel is discolored, pitted, and prone to fracture and wear. Severe dental fluorosis is not commonly found in the United States; one study found prevalences of 0.9 and 6.9% in children living in communities with 1 or 4 ppm fluoride in drinking water, respectively (Jackson et al. 1995). 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. In mild dental fluorosis, the tooth enamel is fully functional; the opaque spots are considered a cosmetic effect. A recent meta-analysis (McDonagh et al. 2000) estimated the prevalence of dental fluorosis in children consuming 1 ppm fluoride in water to be 48%; in 12.5% of the children, the fluorosis would be of aesthetic concern. Most of the community-based studies used for the meta-analysis did not consider other sources of fluoride, such as dental products, manufactured beverages, or food.

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; although on a body weight basis, clearance is about the same in children and 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 excretion rate is 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. Fluoride is poorly transferred from maternal blood to breast milk (Ekstrand et al. 1981c; 1984b; Escala et al. 1982; Spak et al. 1983).

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 fluorides, hydrogen fluoride, and fluorine 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 fluorides, hydrogen fluoride, and fluorine 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 Fluorides, Hydrogen Fluoride, and Fluorine

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 and Ehrnebo 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). Villa et al. (2000) found that measurement of fractional urinary fluoride excretion

in children is a good predictor of total daily fluoride intake. 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 described 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), ductal saliva (Oliveby et al. 1990; Whitford et al. 1999b), nails (Whitford et al. 1999a), and tooth enamel (McClure and Likins 1951). When using plasma or saliva as a biomarker, the samples 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). A wide range of plasma fluoride levels have been reported for the general population; the daily intake of fluoride appears to be one of the major contributors to plasma fluoride levels (Ikenishi et al. 1988; NAS 1971a). One study (Guy et al. 1976) found a mean plasma fluoride concentration of 0.4 µmol/L (7.5 µg/L) in individuals consuming drinking water containing <0.1 ppm fluoride and an average plasma fluoride level of 1 µmol/L (19 µg/L) in individuals consuming 0.9–1.0 ppm fluoride in drinking water. Much higher plasma fluoride levels

have been reported in poisoning cases. For example, a plasma fluoride level of 2,000 µg/L was reported in a case of severe oral poisoning with 53 g fluoride as sodium fluoride (Abukurah et al. 1972). Chronic exposure to high levels of fluoride can result in wide fluctuations in plasma fluoride levels during the day (Ekstrand 1978).

Urine, plasma, or saliva can be used as biomarkers of 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. 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 taken up by bone again or excreted in urine. Furthermore, background tissue/fluid levels may affect these measurements since fluoride is prevalent in the environment from dietary sources. An important factor in biological fluid fluoride concentration is urinary pH (Whitford 1990). 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 Fluorides, Hydrogen Fluoride, and Fluorine

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 teeth or skeletal system. Chronic oral fluoride exposure

can produce dental fluorosis (denBesten and Thariani 1992; DHHS 1991; Eklund et al. 1987; Fejerskov et al. 1990; Heifetz et al. 1988; Ismail and Bandekar 1999; Jackson et al. 1995; McDonagh et al. 2000; Selwitz et al. 1995; Teotia and Teotia 1994; Warren and Levy 1999), and higher levels of oral or inhalation exposure can lead to skeletal effects (Kaltreider et al. 1972; Leone et al. 1955). Evidence of moderate or severe dental fluorosis (pitting, staining, and/or excessive wear) are possible markers of effect for fluoride exposure (Walton 1988). However, dental fluorosis is reflective of fluoride exposure during tooth development (typically during ages 1–8 years), rather than current fluoride exposure.

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 elements 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 severe cases of skeletal 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 markers 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.

Teotia and Teotia (1994) found that deficient calcium intake and elevated fluoride intake (1.1–4.0 ppm) resulted in a significant increase in the occurrence of dental fluorosis (100%) and dental caries (74%), as compared to children with normal calcium intakes and excess fluoride intakes (prevalences of dental fluorosis and caries were 14.2 and 31.4%, respectively).

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to fluorides, hydrogen fluoride, and fluorine than will most persons exposed to the same level of fluorides, hydrogen fluoride, and fluorine 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 fluorides, hydrogen fluoride, and fluorine, or compromised function of organs affected by fluorides, hydrogen fluoride, and fluorine. Populations who are at greater risk due to their unusually high exposure to fluorides, hydrogen fluoride, and fluorine are discussed in Section 6.7, Populations With Potentially High Exposures.

Some 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 osteoporosis, people with deficiencies of calcium, magnesium, vitamin C, and/or protein (Murray and Wilson 1948;

Pandit et al. 1940; Parker et al. 1979), and people with kidney problems (Kono et al. 1984, 1985; Schiffl and Binswanger 1980; Spak et al. 1985). For most of these populations, there are very limited data to support or refute increased susceptibility to fluoride. Additionally, there are no data to suggest that exposure to typical fluoride drinking water levels would result in adverse effects in these potentially susceptible populations.

The major route of fluoride excretion is via the kidney and the urine; fluoride excretion is influenced by a number of factors, including glomerular filtration rate, urinary flow, and urinary pH (Ekstrand et al. 1978, 1980a, 1982; Järnberg et al. 1980, 1981, 1983; Whitford et al. 1976). In chronic renal failure, there is a decrease in glomerular filtration rate, which would result in a decrease in urinary fluoride excretion (Jeandel et al. 1992; Schiffl and Binswanger 1980). Decreases in fluoride excretion have been seen in adults (Kono et al. 1984; Schiffl and Binswanger 1980) and children (Spak et al. 1985) with impaired renal function. In children with low glomerular filtration rates (<92 mL/minute), renal fluoride clearance was 31.4 mL/minute compared to 45.0 mL/minute in children with normal glomerular filtration rates (Spak et al. 1985). In older adults (>65 years of age), there is a decline in renal function, which results in a decrease in renal clearance of fluoride (Jeandel et al. 1992; Kono et al. 1985).

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. However, administration of low doses of slow release sodium fluoride medications has been effective in treating spinal osteoporosis (Pak et al. 1995).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to fluorides, hydrogen fluoride, and fluorine. 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 fluorides, hydrogen fluoride, and fluorine. 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 fluorides, hydrogen fluoride, and fluorine:

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 fluoride, hydrogen fluoride/hydrofluoric acid, or fluorine, 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

Fluoride. Ingested fluoride is rapidly absorbed from the gastrointestinal tract. However, fluoride absorption is affected by the presence of several minerals including calcium, magnesium, and aluminum which bind to the fluoride to form less soluble complexes (Ekstrand and Ehrnebo 1979; Kuhr et al. 1987; Machle and Largent 1943; McClure et al. 1945; Spencer and Lender 1979; Spencer et al. 1980a, 1981; Whitford 1994). Gastric lavage with solutions of calcium gluconate, calcium carbonate, calcium lactate, calcium chloride, calcium hydroxide, calcium- or magnesium-based antacid, or aluminum hydroxide gel have been used in the treatment of fluoride poisoning (Ellenhorn and Barceloux 1988; Goldfrank et al. 1990; Haddad and Winchester 1990; Morgan 1989). Two treatments that are not recommended are attempting to neutralize the acid with orally administered sodium bicarbonate due to the resulting exothermic reaction (Bronstein and Currance 1988) and emesis due to the formation of hydrofluoric acid in the stomach (Bronstein and Currance 1988; Haddad and Winchester 1990).

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).

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).

3.11.2 Reducing Body Burden

Fluoride. There is limited information on reducing the body burden of fluoride. Whitford (1994) demonstrated that a diet high in calcium resulted in a negative fluoride balance in rats due to a significant increase in fecal excretion of fluoride. Although no significant alterations in plasma fluoride levels were found, the high calcium diet did result in a significant decrease in fluoride levels in the femur epiphysis.

In a study of 10 individuals with clinical manifestations of fluorosis (Susheela and Bhatnagar 2002), a diet with adequate levels of calcium, vitamins C and E, and other antioxidants and access to drinking water with low levels of fluoride (1 ppm or lower) resulted in a decrease in urinary and blood fluoride levels and a decrease in clinical signs were observed. One year after intervention, there was complete recovery of gastrointestinal complaints, muscular weakness, polyuria, polydypsea, and pain and rigidity in the joints. 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.

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.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

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 was 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 1998). 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). Similarly, Guna Sherlin and Verma (2001) found that co-administration of vitamin D reduced the maternal toxicity (decreased body weight gain and feed intake) and fetal toxicity (increased percentage of fetuses with skeletal or visceral abnormalities) as compared to rats only receiving sodium fluoride.

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.

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 fluorides, hydrogen fluoride, and fluorine 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, hydrogen fluoride, and fluorine.

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.

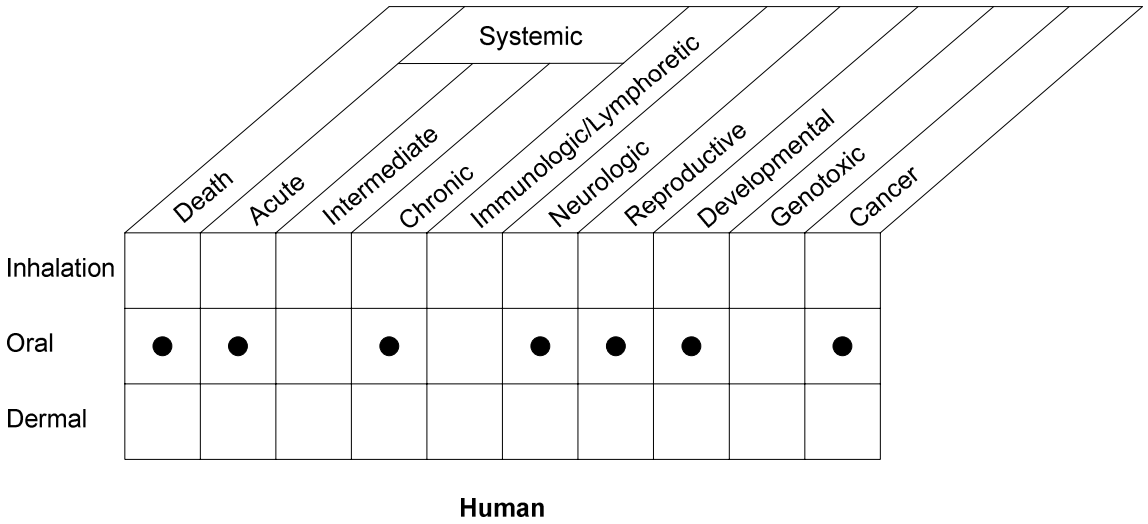
3.12.1 Existing Information on Health Effects of Fluorides, Hydrogen Fluoride, and Fluorine

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to fluorides, hydrogen fluoride, and fluorine are summarized in Figures 3-6, 3-7, and 3-8. The purpose of these figures is to illustrate the existing information concerning the health effects of fluorides, hydrogen fluoride, and fluorine. 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 (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

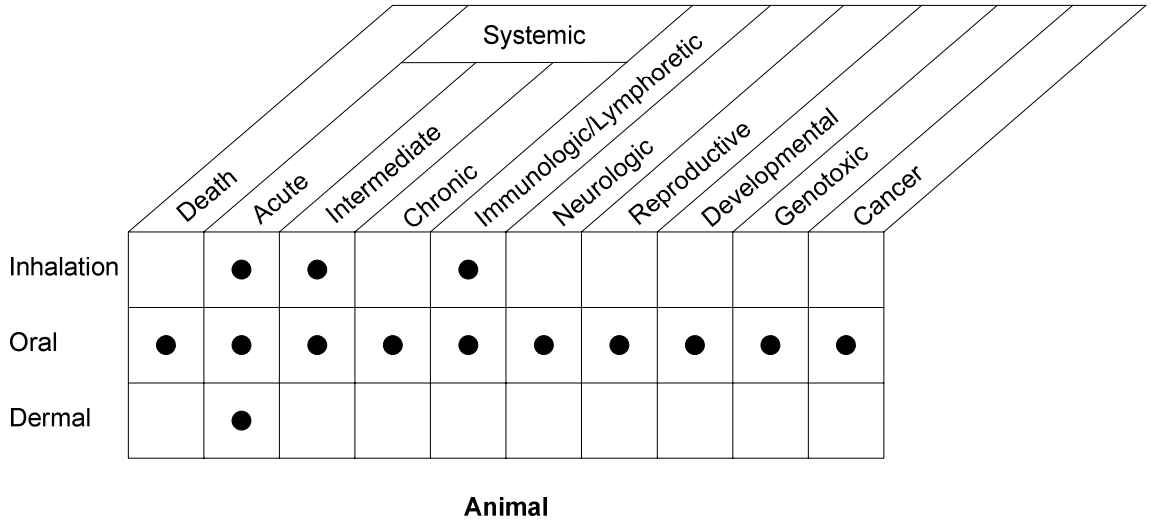
There are many case reports and epidemiological studies investigating the health effects of hydrogen fluoride in humans by the inhalation and dermal routes, and the health effects of fluoride compounds by the inhalation and oral routes. There are also limited data from experimental human exposure to fluorine. Most human studies of the health effects of oral exposure to fluoride are community-based studies of populations ingesting drinking water with various levels of fluoride and case reports of acute and chronic oral exposure to sodium fluoride. There are also some 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.

Figure 3-6. Existing Information on Health Effects of Fluoride



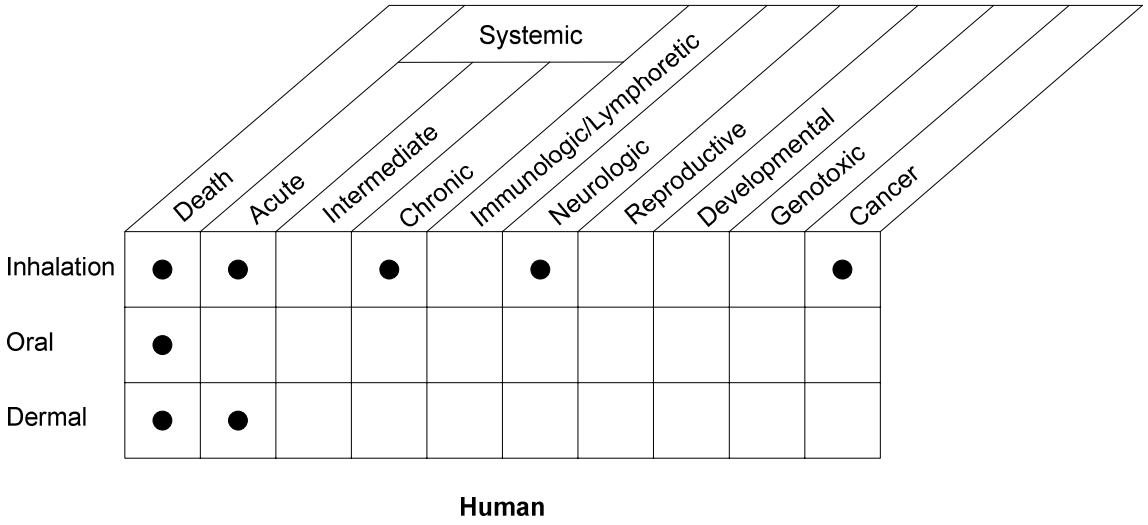
Human



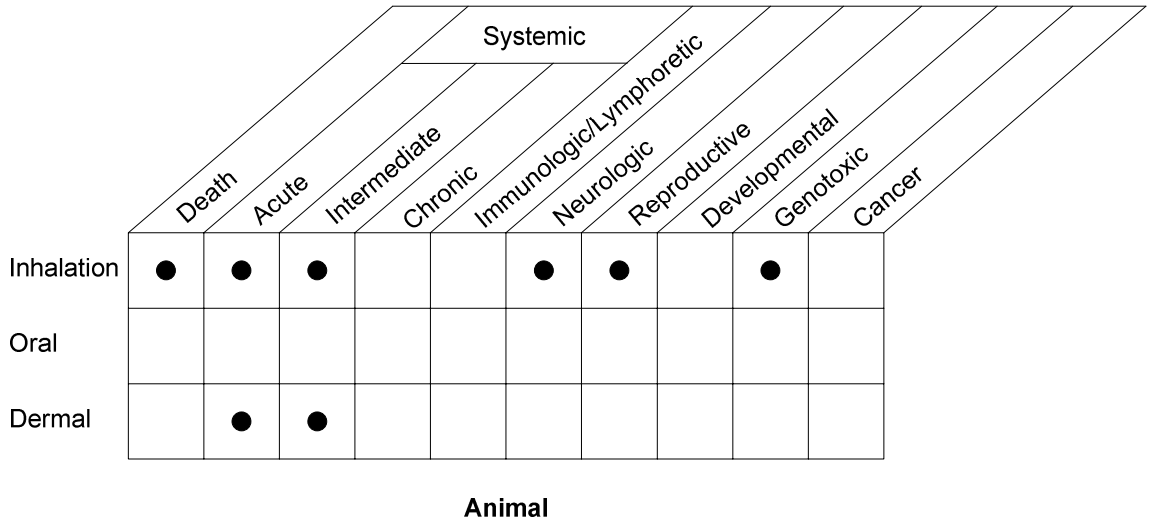
Animal

● Existing Studies

Figure 3-7. Existing Information on Health Effects of Hydrogen Fluoride/Hydrofluoric Acid



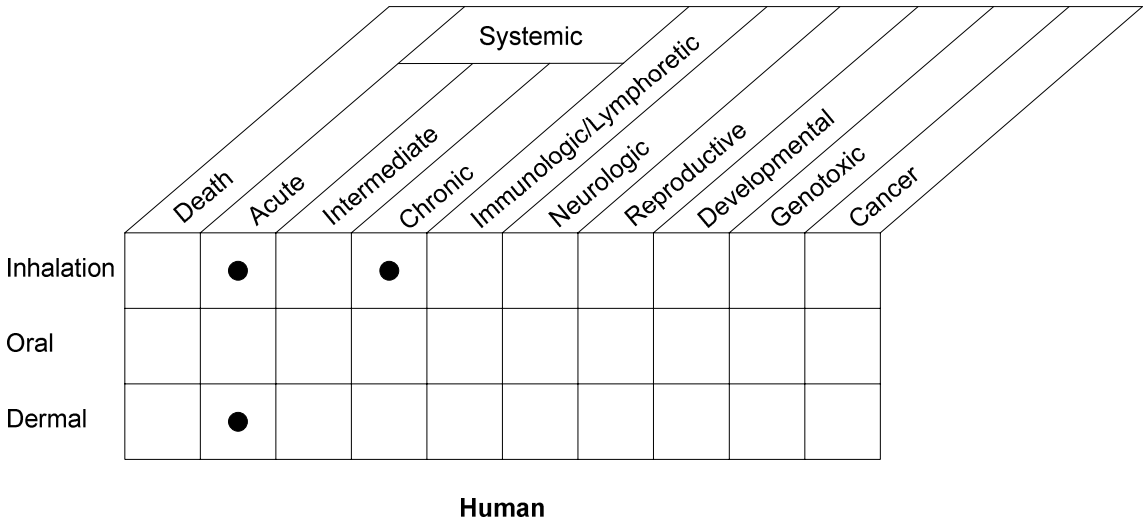
Human



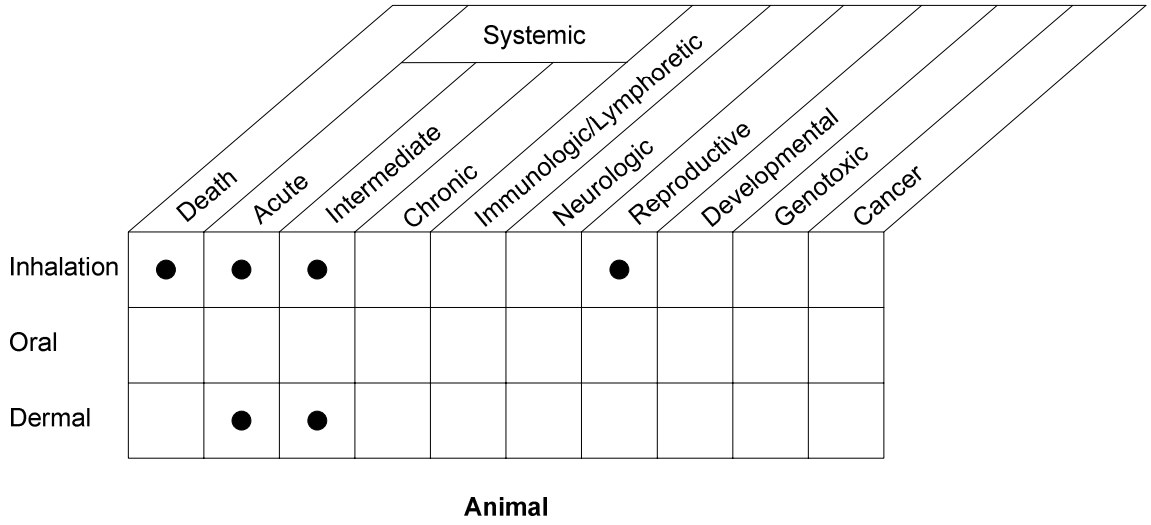
Animal

● Existing Studies

Figure 3-8. Existing Information on Health Effects of Fluorine



Human



Animal

● Existing Studies

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

Acute-Duration Exposure.

Fluoride. Information on the acute toxicity of inhaled fluoride dust is limited to two animal studies that found respiratory tract damage and impaired immune response in mice exposed to sodium fluoride for 4 hours/day for 10–14 days (Chen et al. 1999; Yamamoto et al. 2001). These data were not considered adequate for derivation of an acute-duration inhalation MRL because the upper respiratory tract, a potentially sensitive target of toxicity, was not examined in either study. Studies examining a wide range of end points, including the upper respiratory tract, and using a number of exposure concentrations would be useful for establishing concentration-response relationships and deriving an acute-duration inhalation MRL for fluorides. The acute toxicity of ingested fluorides has been investigated in human and animal studies. Most of the available human (Eichler et al. 1982; Hodge and Smith 1965; Sharkey and Simpson 1933) and animal (DeLopez et al. 1976; Lim et al. 1978; Skare et al. 1986; Whitford et al. 1990) acute studies reported lethal doses and effects resulting from exposure to a lethal dose of sodium fluoride. The gastrointestinal tract (Hoffman et al. 1980; Kessabi et al. 1985; Spak et al. 1989, 1990; Spoerke et al. 1980) and bone (Guggenheim et al. 1976) have been identified as targets of toxicity following a nonlethal exposure to fluorides in human and rat studies, respectively. The potential of sodium fluoride to induce reproductive (Li et al. 1987a) and developmental (Guna Sherlin and Verma 2001; Heindel et al. 1996) effects has also been investigated in laboratory animals. An acute-duration oral MRL was not derived for fluoride; the available data suggest that gastric irritation is the most sensitive end point of acute fluoride toxicity; however, additional studies are needed to establish a concentration-response curve and to assess whether the gastric mucosa would adapt to repeated exposure to fluoride. These studies should also examine other potentially sensitive targets. Data on the dermal toxicity of fluoride is limited to a study that found epidermal necrosis and marked edema of the dermis following application of sodium fluoride to the abraded skin of rats (Essman et al. 1981). Additional dermal exposure studies would be useful for establishing concentration-response relationships for fluoride.

Hydrogen Fluoride/Hydrofluoric Acid. A number of studies have examined the acute toxicity of hydrogen fluoride in humans under accidental exposure conditions (Dayal et al. 1992; Wing et al. 1991) or experimental conditions (Lund et al. 1997, 1999, 2002; Machle et al. 1934) and in laboratory animals (Dalbey et al. 1998a, 1998b; Rosenholtz et al. 1963; Stavert et al. 1991). These studies demonstrate that the respiratory tract is the most sensitive target of toxicity; at slightly higher concentrations, skin and eye irritation are also observed. Hematological (increased red blood cell and hemoglobin levels) and liver (increased aspartate aminotransferase activity) alterations have also been observed in laboratory animals exposed to much higher concentrations (Dalbey et al. 1998a, 1998b). An acute duration inhalation MRL based on lower respiratory tract irritation in humans (Lund et al. 1997) was derived for hydrogen fluoride. Data on the oral toxicity of hydrofluoric acid are limited to a report of six deaths following accidental consumption of a rust remover containing hydrofluoric acid (Menchel and Dunn 1986). These data were not considered adequate for derivation of an acute-duration oral MRL for hydrofluoric acid. It is likely that the most sensitive target following acute oral exposure to hydrofluoric acid would be the gastrointestinal tract; studies are needed to confirm this hypothesis and establish a concentration-response curve. Dermal exposure studies demonstrate that hydrofluoric acid is very caustic, and severe tissue damage can result from direct contact (Chela et al. 1989; Derelanko et al. 1985; Mayer and Gross 1985; Roberts and Merigan 1989). Exposure to a high concentration or prolonged exposure can result in systemic effects that are similar to fluoride (Braun et al. 1984; Mayer and Gross 1985; Mullett et al. 1987). There are limited concentration-response data and additional dermal exposure studies would be useful.

Fluorine. A series of studies conducted by Keplinger and Suissa (1968) have investigated the acute toxicity of fluorine in humans, rats, mice, rabbits, guinea pigs, and dogs. In all species tested, fluorine was irritating to the respiratory tract, skin, and eyes. In addition to these direct contact effects, exposure to fluorine also resulted in liver (necrosis and cloudy swelling) and kidney (necrosis) effects in the laboratory animal species. An acute-duration MRL for fluorine was derived from the Keplinger and Suissa (1968) human study, which identified a NOAEL and LOAEL for nasal irritation. Additional studies are needed to evaluate the concentration-response relationship for skin effects as well as other end points following dermal-only exposure.

Intermediate-Duration Exposure.

Fluoride. The toxicity of inhaled fluoride is limited to an animal study that found lung effects in mice exposed to sodium fluoride for 4 hours/day for 20–30 days (Chen et al. 1999). With the exception of direct contact effects, it is likely that the toxicity of inhaled fluoride would be similar to ingested fluoride.

Additional inhalation studies would be useful for establishing a concentration-response relationship and deriving an intermediate-duration inhalation MRL for fluorides. A number of animal studies have investigated the toxicity of fluoride following intermediate oral exposure; no intermediate-duration human studies were located. These animal studies have reported a number of systemic effects, including alterations in bone and tooth mineralization (Collins et al. 2001a; DenBesten and Crenshaw 1984; Harrison et al. 1984; Marie and Hott 1986; Turner et al. 2001; Uslu 1983; Zhao et al. 1998), hyperplasia of the glandular stomach (NTP 1990), alterations in thyroid function (Bobek et al. 1976; Zhao et al. 1998), and kidney damage (Greenberg 1986; NTP 1990). Additionally, neurological (Mullenix et al. 1995; Paul et al. 1998; Purohit et al. 1999), reproductive (Al-Hiyasat et al. 2000; Araibi et al. 1989; Chinoy and Sequeira 1992; Chinoy et al. 1992, 1997; Krasowska and Wlostowski 1992; Messer et al. 1973; Narayana and Chinoy 1994), and developmental effects in the presence of maternal toxicity (Collins et al. 1995) have been observed. The available studies identify the bones and possibly the thyroid as the most sensitive targets of fluoride toxicity in rodents following intermediate-duration exposure to fluoride. Chronic-duration studies in humans strongly support the identification of bone as a sensitive target of fluoride toxicity. However, bone growth in rats differs from humans, and it is not known whether it is appropriate to extrapolate an adverse effect level from rats to humans. The potential of fluoride to induce thyroid effects in humans has not been adequately assessed; additional studies are needed to determine whether this end point is relevant for humans. The intermediate-duration database was considered inadequate for derivation of an MRL due to the uncertainties associated with the use of rodent data, and derivation of an MRL using the Bobek et al. (1976) or Turner et al. (2001) animal studies that identified the lowest LOAEL values would result in an MRL that is lower than the human-based chronic-duration MRL. No intermediate-duration dermal toxicity studies were identified for fluorides; based on the results of an acute-duration rat study (Essman et al. 1981), it is likely that fluoride exposure would result in damage to the skin. Studies are needed to confirm that this would also be the most sensitive target of toxicity following longer-duration exposure and to assess whether there are other sensitive targets.

Hydrogen Fluoride/Hydrofluoric Acid. Nasal irritation was reported in the only human intermediate-duration study identified for hydrogen fluoride (Largent 1960). A small number of animal studies are available. These inhalation studies found respiratory tract irritation (Machle and Kitzmiller 1935; Stokinger 1949), skin and eye irritation (Stokinger 1949), kidney damage (Machle and Kitzmiller 1935), and neurobehavioral alterations (Sadilova et al. 1965) in laboratory animals. An intermediate-duration inhalation MRL was not derived for hydrogen fluoride because an MRL based on the Largent (1960) study is higher than the acute-duration inhalation MRL derived from the Lund et al. (1997, 1999) study.

Additional studies are needed to identify a NOAEL for respiratory tract effects. No intermediate-duration oral or dermal exposure studies were identified; the gastrointestinal tract and skin, respectively, are the likely targets of toxicity. Studies are needed for establishing concentration-response curves for these exposure routes and identifying other possible targets of toxicity.

Fluorine. The database on the intermediate-duration toxicity of fluorine is limited to a multispecies study that found eye, nose, and mouth irritation in rats and dogs and lung damage in rats, rabbits, and dogs (Stokinger 1949). Because the measurements of exposure concentrations were questionable, this study was not selected as the basis of an intermediate-duration inhalation MRL for fluorine. Additional studies using multiple exposure concentrations are needed to establish the concentration-response relationship for fluorine and derive an MRL. Studies involving dermal-only exposure to fluorine gas would be useful for assessing the dermal toxicity of this element in humans wearing respirators without adequate protective clothing.

Chronic-Duration Exposure and Cancer.

Fluoride. No studies have examined the chronic toxicity of inhaled fluorides; however, several occupational exposure studies have examined workers exposed to hydrogen fluoride and fluoride dusts, and these are discussed under hydrogen fluoride. Thus, a chronic-duration inhalation MRL was not derived for fluorides. Shorter-term inhalation studies and chronic-duration oral studies suggest that the respiratory tract, teeth, and bones are likely to be the principal targets of fluoride. Studies are needed to confirm this hypothesis and to establish concentration-response data. A large number of human and animal studies have investigated the chronic toxicity of ingested fluoride. Most of the human studies are ecological studies examining communities with fluoridated water or naturally high levels of fluoride in water. For the most part, these studies have focused on the occurrence of dental fluorosis (DHHS 1991; Eklund et al. 1987; Heifetz et al. 1988; Ismail and Bandekar 1999; Jackson et al. 1995; McDonagh et al. 2000; Selwitz et al. 1995; Teotia and Teotia 1994; Warren and Levy 1999) and alterations in bone density or increased bone fracture rates (Arnala et al. 1986; Cauley et al. 1995; Cooper et al. 1990, 1991; Danielson et al. 1992; Goggin et al. 1965; Jacobsen et al. 1990, 1992, 1993; Haguenauer et al. 2000; Hillier et al. 2000; Karagas et al. 1996; Kleerekoper et al. 1991; Kröger et al 1994; Kurttio et al. 1999; Lehmann et al. 1998; Li et al. 2001; Phipps et al. 2000; Riggs et al. 1990, 1994; Simonen and Laittinen 1985; Suarez-Almazor et al. 1993). At typical fluoridation levels (0.9–1.0 ppm), increases, decreases, or no effect on bone fracture rates have been found. At higher doses, fluoride has consistently increased bone fracture rates. Other potential targets of toxicity that have been examined in humans include the cardiovascular system (Hagan et al. 1954; Heasman and Martin 1962), gastrointestinal tract (Susheela et

al. 1992), kidneys (Lantz et al. 1987), intelligence and behavior (Li et al. 1995a; Lu et al. 2000; Morgan et al. 1998), reproductive system (Freni 1994; Susheela and Jethanandani 1996), and developing organism (Berry 1958; Erickson et al. 1976; Li et al. 1995a; Lu et al. 2000; Needleman et al. 1974; Rapaport 1956; Takahashi 1998). These studies did not find positive and/or consistent results. Several animal studies have examined the chronic toxicity; the observed effects included bone alterations in rats (NTP 1990), mice (NTP 1990), and mink (Aulerich et al. 1987), intestinal damage in rabbits (Susheela and Das 1988), hematological effects in rabbits (Susheela and Jain 1983), immunological effects in rabbits (Jain and Susheela 1987), and male reproductive effects in rabbits (Kumar and Susheela 1994, 1995; Susheela and Kumar 1991, 1997). One limitation of the animal studies is that the doses used were much higher (>10 times higher) than doses that result in increased fracture rates in humans. Additional animal studies that used lower doses would be useful in determining if there are additional sensitive targets of toxicity following chronic-duration oral exposure to fluoride. A large community-based study by Li et al. (2001) was used to derive a chronic-duration oral MRL for fluoride. No chronic-duration dermal studies were identified. The toxicity of fluoride is not likely to be route-specific, with the exception of direct contact effects. An acute toxicity study (Essman et al. 1981) found skin damage in animals exposed to sodium fluoride; studies are needed to identify the threshold of toxicity of dermal irritation and other potentially sensitive targets such as teeth and bone.

The carcinogenicity of fluoride has been assessed in a number of human studies of communities with fluoridated water or naturally high levels of fluoride in the drinking water (Cohn 1992; Erickson 1978; Freni and Gaylor 1992; Gelberg et al. 1995; Hoover et al. 1976, 1991a, 1991b; Kinlen and Doll 1981; Mahoney et al. 1991; McGuire et al. 1991; Neuberger 1982; Oldham and Newell 1977; Rogot et al. 1978; Takahashi et al. 2001; Taves 1977; Yiamouyiannis and Burk 1977) and chronic-duration oral exposure studies of rats (Maurer et al. 1990; NTP 1990) and mice (NTP 1990). Although some human studies have found positive results, particularly for bone cancer (Cohn 1992; Hoover et al. 1991b; Takahashi et al. 2001; Yiamouyiannis and Burk 1977), the majority of the studies have not found significant increases in cancer risk. The NTP (1990) bioassay 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. Significant increases in cancer risk were found in the Maurer et al. (1990) study. Additional studies are needed to further evaluate the potential of fluoride to induce bone cancers following chronic oral exposure.

Hydrogen Fluoride/Hydrofluoric Acid. The available data on the chronic toxicity are limited to several occupational exposure studies of workers (Carnow and Conibear 1981; Chan-Yeung et al. 1983a, 1983b;

Czerwinski et al. 1988; Derryberry et al. 1963; Dinman et al. 1967c; Kaltreider et al. 1972; Macuch et al. 1963; Moller and Gudjonsson 1932) exposed to hydrogen fluoride and fluoride dusts and an inhalation study in guinea pigs (Rioufol et al. 1982). The occupational exposure studies primarily focused on respiratory tract and skeletal effects and the guinea pig study examined the kidneys. Although the occupational exposure studies examined the primary targets of hydrogen fluoride and fluoride toxicity, they are limited by co-exposure to a number of other chemicals and limited, if any, exposure data. Additional chronic-duration studies are needed to derive a chronic-duration inhalation MRL for hydrogen fluoride. No chronic-duration dermal exposure studies were located for hydrogen fluoride. At high concentrations, the skin is the most sensitive target of toxicity; however, long-term exposure to lower concentrations is likely to result in different targets of toxicity, possibly the same as chronic fluoride toxicity. Additional chronic-duration studies are needed to establish the concentration-response relationships for direct contact effects and other possible targets of toxicity.

Several studies have examined the carcinogenicity of hydrogen fluoride and fluoride dust exposures in cryolite workers (Grandjean et al. 1985, 1992), aluminum industry workers (Andersen et al. 1982; Gibbs and Horowitz 1979; Milham 1979; Rockette and Arena 1983), fluorspar miners (deVilliers and Windish 1964), and individuals residing near or working in the steel industry (Cecilioni 1972). Several studies reported increases in respiratory tract cancer rates (Andersen et al. 1982; deVilliers and Windish 1964; Gibbs and Horowitz 1979; Grandjean et al. 1985, 1992; Milham 1979); however, no adjustments for occupational exposure to other carcinogenic compounds and smoking were made in most of these studies. Well-controlled studies are needed to assess the carcinogenic potential of hydrogen fluoride and fluoride dust exposure.

Fluorine. Data on the chronic toxicity of fluorine is limited to an occupational exposure study in which a relatively insensitive measure of respiratory tract effects (visits to the medical department with respiratory complaints and absences from work) was used and in which the controls and exposed workers were exposed to uranium hexafluoride and hydrogen fluoride (Lyon 1962). This study was considered inadequate for derivation of a chronic-duration inhalation MRL. Additional studies are needed to define the concentration-response relationships following exposure to inhaled fluorine gas and following dermal-only exposure to fluorine. There are no data on the carcinogenicity of fluorine; the carcinogenicity of absorbed fluorine is expected to be similar to fluoride. However, additional studies are needed to assess whether long-term exposure to fluorine would result in portal-of-entry cancers.

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).

Reproductive Toxicity. Hydrogen fluoride and fluorine animal inhalation exposure studies and human and animal fluoride oral exposure studies have assessed reproductive toxicity. No data are available on the reproductive toxicity following dermal exposure in humans or animals. Degenerative testicular changes were observed in rats exposed to high concentrations of hydrogen fluoride (Stokinger 1949) or fluorine (Stokinger 1949); it is possible that these effects were due to direct contact with the gas rather than a systemic effect. Several studies have investigated the reproductive toxicity of fluoride in humans. One study found a significant association between decreasing total fertility rates and increasing fluoride levels in drinking water (Freni 1994) and another study found decreases in serum testosterone levels in men with skeletal fluorosis (Susheela and Jethanandani 1996). Both studies have several limitations that preclude drawing firm conclusions from them about the potential of fluoride to induce reproductive toxicity. Alterations in the male reproductive system have also been observed in rats and rabbits orally exposed to sodium fluoride. The observed effects included alterations in serum testosterone levels (Araibi et al. 1989; Narayana and Chinoy 1994), histological alterations in the testes (Krasowska and Wlostowski 1992; Narayana and Chinoy 1994; Susheela and Kumar 1991), alterations in sperm morphology or spermatogenesis (Chinoy et al. 1992, 1995, 1997; Kumar and Susheela 1994, 1995; Susheela and Kumar 1991), and impaired fertility (Chinoy and Sequeira 1992; Chinoy et al. 1992). However, other studies have not found any effects on male reproduction (Dunipace et al. 1989; Li et al. 1987a; Sprando et al. 1997, 1998). Additional studies are needed to address the conflicting results. As with the male reproductive effects, conflicting results have been found for fluoride-induced female reproductive effects. Infertility was observed in one study (Messer et al. 1973), but not in three others (Collins et al. 2001a; Marks et al. 1984; Tao and Suttie 1973). A decrease in fetus viability and an increase in resorption rate have also been reported at maternally toxic doses (Al-Hiyasat et al. 2000).

Developmental Toxicity. The potential of fluoride, hydrogen fluoride, or fluorine to induce developmental effects following inhalation or dermal exposure has not been investigated in humans or animals. Several community-based studies have examined the possible association between fluoridated water consumption and developmental effects (Berry 1958; Erickson et al. 1976; Needleman et al. 1974;

Rapaport 1956; Takahashi 1998); the overall weight of evidence suggests that low levels of fluoride are not associated with developmental effects. However, higher exposure levels (levels associated with dental or skeletal fluorosis) have been associated with developmental effects in humans (Gupta et al. 1995; Li et al. 1995a; Lu et al. 2000); additional studies are needed to confirm the results of these studies, which do not appear to adjust for potential confounders such as poor nutrition and exposure to other chemicals. Studies in laboratory animals have not found adverse developmental effects in the offspring of rats or rabbits exposed to sodium fluoride in drinking water (Collins et al. 1995, 2001b; Heindel et al. 1996); however, fetal mortality and abnormalities were observed at maternally toxic doses (Collins et al. 1995; Guna Sherlin and Verma 2001). Studies in wild or domestic animals (cattle and mink) (Aulerich et al. 1987; Krook and Maylin 1979; Maylin and Krook 1982) have reported developmental effects; the relevance to humans is not known.

Immunotoxicity. Information of the potential of fluoride, hydrogen fluoride, or fluorine to induce immune effects is limited to an inhalation study in mice that found a decrease in bactericidal activity following exposure to sodium fluoride (Yamamoto et al. 2001) and an oral exposure study in rabbits that found a decrease in antibody titers following an 18-month exposure via gavage to sodium fluoride and immunization with transferrin (Jain and Susheela 1987). These studies provide some suggestive evidence that the immune system is a target of fluoride toxicity. A study utilizing an immune battery of tests would be useful in assessing the immunotoxic potential of fluoride.

Neurotoxicity. Alterations in the light adaptive reflex were found in humans exposed to very low concentrations of hydrogen fluoride (Sadilova et al. 1965). The investigators of this study also found alterations in conditioned responses in rats exposed to relatively low concentrations. This finding has not been supported by other human or animal studies. A decrease in IQ scores has also been observed in children living in areas with high fluoride levels in the water (Li et al. 1995a; Lu et al. 2000; Zhao et al. 1996); however, the lack of control of potential confounding variables limits the interpretation of these studies. Epidemiology studies examining this end point and controlling for potentially confounding variables, such as poor nutrition and exposure to other chemicals, would provide confirming or refuting data. Alterations in spontaneous behavior were found in rats orally exposed to sodium fluoride (Mullenix et al. 1995a; Paul et al. 1998); however, another study did not find this effect (Whitford et al. 2003). Studies utilizing a neurobehavioral test battery would provide valuable information on the neurotoxic potential of fluoride, hydrogen fluoride, and fluorine.

Epidemiological and Human Dosimetry Studies. Available data on the toxicity of inhaled hydrogen fluoride and fluorine come from case reports involving exposure to hydrogen fluoride (Bennion and Franzblau 1997; Braun et al. 1984; Chan et al. 1987; Chela et al. 1989; Dieffenbacher and Thompson 1962; Kleinfeld 1965; Machle et al. 1934; Tepperman 1980; Waldbott and Lee 1978), accidental exposure of a community to hydrogen fluoride (Dayal et al. 1992; Wing et al. 1991), experimental studies of exposure to hydrogen fluoride (Largent 1960; Lund et al. 1997, 1999, 2002; Machle et al. 1934) and fluorine (Keplinger and Suissa 1968), and occupational exposure to hydrogen fluoride and fluoride dusts (Carnow and Conibear 1981; Chan-Yeung et al. 1983a; Czerwinski et al. 1988; Derryberry et al. 1963; Dinman et al. 1976c; Kaltreider et al. 1972; Moller and Gudjonsson 1932), fluorides (McGarvey and Ernstene 1947; Roholm 1937; Wolff and Kerr 1938), or fluorine (Lyon 1962). These studies identify the respiratory tract as the most sensitive target of toxicity, and data are sufficient to derive acute-duration inhalation MRLs for hydrogen fluoride and fluorine using these human data. However, the long-term toxicity of fluorides, hydrogen fluoride, and fluorine has not been adequately investigated. The only consistently reported effect is skeletal fluorosis (Czerwinski et al. 1988; Dinman et al. 1976c; Kaltreider et al. 1972; Moller and Gudjonsson 1932); poor exposure characterization and difficulty assessing the skeletal fluorosis limit these studies.

Many studies have examined the possible association between the long-term exposure to fluoridated water and adverse health effects, particularly effects on bone and teeth. Most of the studies are community-based studies examining the prevalence of dental fluorosis (DHHS 1991; Eklund et al. 1987; Heifetz et al. 1988; Jackson et al. 1995; McDonagh et al. 2000; Selwitz et al. 1995; Teotia and Teotia 1994; Warren and Levy 1999) and bone fracture rates (Arnala et al. 1986; Cauley et al. 1995; Cooper et al. 1990, 1991; Danielson et al. 1992; Goggin et al. 1965; Jacobsen et al. 1990, 1992, 1993; Karagas et al. 1996; Kröger et al 1994; Kurttio et al. 1999; Lehmann et al. 1998; Phipps et al. 2000; Simonen and Laittinen 1985; Suarez-Almazor et al. 1993) in residents living in communities with fluoridated water or water with naturally high levels of fluoride. Overall, the data on dental fluorosis provide strong evidence of increased prevalence and severity of dental fluorosis with increasing fluoride exposure levels. However, a dose-response relationship is difficult to establish because other sources of fluoride (e.g., dentrifices, bottled water) were typically not taken into consideration. The findings on the possible association between exposure to approximately 1 ppm fluoride in water (typical level of fluoride in communities with fluoridated water) and increases in hip fracture rates in the elderly are inconsistent, with studies finding increases, decreases, or no effect. A common limitation of these community-based studies is the lack of individual exposure data; fluoride levels in drinking water were used to estimate intake and other sources of fluoride or water consumption levels were not taken into consideration.

Experimental studies (Haguenauer et al. 2000; Riggs et al. 1990, 1994) and a community study (Li et al. 2001) involving exposure to higher levels of fluoride have consistently found increases in bone fracture rates. Human case reports (Hoffman et al. 1980; Rao et al. 1969; Spoerke et al. 1980) and experimental studies (Spak et al. 1989, 1990) have also identified the gastrointestinal tract as a sensitive target following bolus administration of fluoride; additional studies are needed to establish the dose-response relationship for this end point.

In addition to these effects, human studies have examined reproductive (Freni et al. 1994), neurodevelopmental (Li et al. 1995a; Lu et al. 2000 Zhao et al. 1996), and developmental (Erickson et al. 1976; Gupta et al. 1995) end points; inadequate exposure characterization and adjustments for potentially confounding variables limit the interpretation of these studies. A number of studies have examined the carcinogenicity of fluoride in communities with fluoridated water (or high levels of naturally occurring fluoride) (Cohn 1992; Erickson 1978; Freni and Gaylor 1992; Gelberg et al. 1995; Hoover et al. 1976, 1991a, 1991b; Kinlen and Doll 1981; Mahoney et al. 1991; McGuire et al. 1991; Neuberger 1982; Oldham and Newell 1977; Rogot et al. 1978; Takahashi et al. 2001; Taves 1977; Yiamouyiannis and Burk 1977). Most of these studies have not found a significant association, although some studies have found increased risks (Takahashi et al. 2001; Yiamouyiannis and Burk 1977), particularly for bone cancer in young men (Cohn 1992; Hoover et al. 1991b). Additional studies that control for potentially confounding variables are needed to adequately assess whether there is an increased risk of bone cancer in young males living in communities with fluoridated water.

Biomarkers of Exposure and Effect.

Exposure. Fluoride can be readily detected in biological tissues such as urine (Ekstrand and Ehrnebo 1983; Ekstrand et al. 1983; Zipkin et al. 1956), plasma (Ekstrand et al. 1983), nails (Whitford et al. 1999a), saliva (Oliveby et al. 1990; Whitford et al. 1999b), and tooth enamel (McClure and Likins 1951). Urinary fluoride is most commonly used to assess fluoride exposure and has been shown to be a good predictor of total daily fluoride intake (Villa et al. 2000). Urine, plasma, and saliva can be used as biomarkers for acute exposures; however, measurements should be taken shortly after exposure due to the rapid elimination of fluoride. Bone (Baud et al. 1978; Boivin et al. 1988) and nail (Schamschula et al. 1985; Whitford et al. 1999a) fluoride levels can be used to quantitate long-term fluoride exposure. Additional studies are needed to relate levels of fluoride in these biological tissues to exposure dose.

Effect. Fluoride accumulates in bone, with levels increasing with age. This accumulation of fluoride in bone can lead to adverse effects such as alterations in bone density, which can be detected by radiographs.

However, these are nonspecific changes and other elements can sequester in the skeleton and produce similar changes observed in radiographs. Exposure to elevated levels of fluoride can also result in dental fluorosis in children (Den Besten and Thariani 1992; DHHS 1991; Eklund et al. 1987; Fejerskov et al. 1990; Heifetz et al. 1988; Ismail and Bandekar 1999; Jackson et al. 1995; McDonagh et al. 2000; Selwitz et al. 1995; Teotia and Teotia 1994; Warren and Levy 1999). There is some evidence that dental fluorosis can be used as a reliable biomarker in children younger than 7 years of age (Den Besten 1994). However, additional studies are needed to quantify the effect of several variables including dose, duration of exposure, and timing of exposure.

Absorption, Distribution, Metabolism, and Excretion. The absorption, distribution, metabolism, and excretion of fluoride, hydrogen fluoride, and fluorine have been investigated in humans and animals. Evidence for absorption of fluorine, hydrogen fluoride, and fluoride after exposure via the inhalation and dermal routes is provided by the observation of elevated urine and plasma levels in workers exposed to hydrogen fluoride and fluoride dusts (Collings et al. 1951; Ehrnebo and Ekstrand 1986; Rye 1961; Søyseth et al. 1994), in people accidentally exposured to hydrofluoric acid (Buckingham 1988; Burke et al. 1973), and in subjects experimental exposed to hydrogen fluoride (Lund et al. 1997). A number of human experimental studies provide strong evidence that fluoride is rapidly and completely absorbed following oral exposure to soluble fluoride compounds (Carlson et al. 1960a; Ekstrand et al. 1977, 1978; Shulman and Vallejo 1990; Trautner and Einwag 1987) and insoluble fluoride compounds are poorly absorbed (Afseth et al. 1987; Trautner and Einwag 1987). The results of animal inhalation (Keplinger and Suissa 1968; Morris and Smith 1982; Stokinger 1949), oral (McClure et al. 1945, 1950; Zipkin and Likins 1957), and dermal (Keplinger and Suissa 1968; Watanabe et al. 1975) exposure studies confirm the results of the human studies. Additional studies would be useful in characterizing the absorption of fluoride, hydrogen fluoride, and fluorine following inhalation and dermal exposure.

The distribution of fluoride following oral exposure has been characterized in human (Ekstrand et al. 1977a, 1978, 1979, 1994a, 1994b; Guy et al. 1976; Rigalli et al. 1996) and animal (Ekstrand and Whitford 1984; Richards et al. 1982; Spak et al. 1986; Whitford and Johnson 2003; Whitford et al. 1979a, 1990) studies. The limited available information on the distribution of inhaled fluoride (Baud et al. 1978; Boivin et al. 1988; Chan-Yeung et al. 1983b; Czerwinski et al. 1988; Kaltreider et al. 1972), hydrogen fluoride (Machle and Scott 1935; Morris and Smith 1983; Stokinger 1949), and fluorine (Stokinger 1949) suggested that the long-term distribution is similar to fluoride following oral exposure. No information is available on the distribution of fluoride following dermal exposure; it is likely that the distribution would be similar to the oral route.

Occupational exposure studies provide some information on the excretion of hydrogen fluoride and fluoride dusts (Collings et al. 1951; Ehrnebo and Ekstrand 1986; Rye 1961) and animal inhalation studies provide excretion data for hydrogen fluoride (Stokinger 1949) and fluorine (Stokinger 1949). The excretion of fluoride following ingestion has been extensively investigated in humans (Carlson et al. 1960a; Ekstrand 1977; Ekstrand et al. 1978, 1980a, 1982; Järnberg et al. 1980, 1981, 1983; Jeandel et al. 1992; Oliveby et al. 1989, 1990; Machle and Largent 1943; Schiffl and Binswanger 1982; Spak et al. 1985; Villa et al. 2000; Waterhouse et al. 1980; Whitford et al. 1976). No excretion data are available for the dermal route of exposure. Because the excretion of fluoride, hydrogen fluoride, and fluorine following inhalation or dermal exposure would be similar to that following ingestion of fluoride, no additional excretion studies are needed at this time.

Comparative Toxicokinetics. A study by Whitford et al. (1991) provides evidence for differences in the toxicokinetic properties of fluoride in dogs, cats, rabbits, rats, and hamsters. Plasma, renal, and extrarenal clearance in the dog was most similar to humans. Although there are adequate data to assess the toxicokinetics of fluoride in humans and the current MRLs are based on human data, additional studies are needed to evaluate the relevance of other animal species to humans to allow for the assessment of other potentially relevant end points of toxicity, such as reproductive toxicity and carcinogenicity.

Methods for Reducing Toxic Effects. Fluoride, hydrogen fluoride, and fluorine are rapidly absorbed following inhalation, oral, or dermal exposure. For fluoride, gastric lavage administration of calcium, magnesium, or aluminum compounds can decrease absorption by forming less soluble complexes with the fluoride (Ellenhorn and Barceloux 1988; Goldfrank et al. 1990; Haddad and Winchester 1990; Morgan 1989). For hydrogen fluoride and fluorine, the recommended methods for decreasing absorption involve removal from the area, irrigation of skin and eyes (Bronstein and Curranc 1988; Dibbell et al. 1970), and application of magnesium, calcium, or quaternary ammonium compounds to limit further dermal absorption (Browne 1974; Goldfrank et al. 1990; Haddad and Winchester 1990; Stutz and Janusz 1988). There is some evidence that a diet high in calcium will reduce the fluoride body burden (Susheela and Bhatnagar 2002; Whitford 1994); additional studies are needed to determine if this is an effective method for reducing bone fluoride levels.

Children's Susceptibility. The available human studies that examined the toxicity of fluoride in children primarily focused on effects on teeth, particularly dental fluorosis. It should be noted that there is also an extensive database on the beneficial effects of fluoride in preventing dental caries, which will

not be discussed in this section dealing with fluoride toxicity. Excess fluoride exposure has been shown to cause dental fluorosis in young children; the severity is dependent on the amount of fluoride ingested, the duration of exposure, and the stage of enamel development at the time of exposure (DHHS 1991; Eklund et al. 1987; Heifetz et al. 1988; Jackson et al. 1995; Selwitz et al. 1995; Teotia and Teotia 1994; Warren and Levy 1999). Although the severity of fluorosis is known to increase with dose, the exact dose-response relationship is not known because very few studies measured individual fluoride intake; additional studies are needed to better assess this relationship. 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; Zhao et al. 1996) but, as noted previously, the Gupta et al. (1995), Li et al. (1995a), Lu et al. (2000), and Zhao et al. (1996) 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. Additional animal studies are needed to assess neurodevelopmental potential of fluoride.

A number of studies have examined potential differences in the toxicokinetic properties of fluoride between adults and children. These studies suggest that absorption (Ekstrand et al. 1978, 1983, 1994a, 1994b) and excretion (Whitford 1999) of ingested fluoride do not appear to be strongly influenced by age. However, the uptake of fluoride into bone is strongly influenced by age; with a higher percentage of ingested fluoride being sequestered in bone in very young children compared to adults (Ekstrand and Whitford 1984; Ekstrand et al. 1979, 1994a, 1994b; Lawrenz et al. 1940; Miller and Phillips 1956; Suttie and Phillips 1959; Whitford 1990; Zipkin and McClure 1952; Zipkin et al. 1956).

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

Table 3-9. Ongoing Studies on the Health Effects of Fluoride, Hydrogen Fluoride, or Fluorine

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

Source: FEDRIP 2002

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

The common synonyms and other information for fluorine, hydrogen fluoride, sodium fluoride, fluorosilicic acid, and sodium fluorosilicate 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 "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. The term "fluorine gas" will sometimes be used 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.

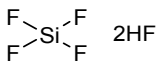
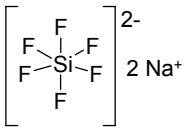
4.2 PHYSICAL AND CHEMICAL PROPERTIES

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, sodium fluoride, fluorosilicic acid, and sodium fluorosilicate are presented in Table 4-2. It should be noted that fluorosilicic acid only exists in aqueous solution, and not in the anhydrous state. Its properties will depend on its concentration and temperature (Aigueperse et al. 1988).

Table 4-1. Chemical Identity of Fluorine, Hydrogen Fluoride, Sodium Fluoride, Fluosilicic Acid, and Sodium Silicofluoride[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

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

Characteristic	Fluorosilicic acid	Sodium fluorosilicate
Synonym(s)[c]	Dihydrogen hexafluorosilicate; hexafluorosilicic acid; fluosilicic acid; hexafluosilicic acid; hydrofluorosilicic acid; hydrogen hexafluorosilicate; hydrosilicofluoric acid; silicofluoric acid; silicon hexafluoride dihydride	Disodium hexafluorosilicate; disodium silicofluoride; silicon sodium fluoride; sodium silicofluoride; sodium fluosilicate; sodium hexafluorosilicate; sodium hexafluosilicate; sodium silicon fluoride
Registered trade name(s)[c]	FKS	Prodan; Salufer
Chemical formula	H_2SiF_6	Na_2SiF_6
Chemical structure		
Identification numbers:		
CAS registry	16961-83-4	16893-85-9
NIOSH RTECS	NIOSH/VV8410000	NIOSH/VV8225000
EPA hazardous waste	No data	No data
OHM/TADS	No data	No data
DOT/UN/NA/IMO shipping	UN 2674; sodium silicofluoride	UN 1778; fluosilicic acid
HSDB	770	2018
EINECS	241-034-8	240-934-8
NCI	No data	No data

[a]All information obtained from HSDB 2003 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, and 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.
[c]IARC 1982

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Organization 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, Sodium Fluoride, Fluosilicic Acid, and Sodium Silicofluoride[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, °C	-219.61	-83.36	993
Boiling point, °C	-188.13	19.51b	1,704
Density, g/cm^3	1.5127 at -188.13 °C	0.991 at 19.54 °C	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 °C
Organic solvents	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 °C	1 mmHg at 1,077 °C
Henry's Law constant at 20 °C	No data	0.104 at m-L/mole[e]	No data
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

Table 4-2. Physical and Chemical Properties of Fluorine, Hydrogen Fluoride, Sodium Fluoride, Fluosilicic Acid, and Sodium Silicofluoride[a]

Property	Fluorosilicic Acid	Sodium Fluorosilicate
Molecular weight	144.1	188.1
Color	Colorless, fuming liquid	white
Physical state	liquid	granular powder
Molecular formula	H_2SiF_6	Na_2SiF_6
Melting point, °C	60-70% solution solidifies at about 19 °C, forming a crystalline dihydrate	decomposes at red heat[b]
Boiling point, °C	decomposes	decomposes at red heat[b]
Density, g/cm^3	1.4634 (60.97% solution) at 25 °C: 17.5/17.5 1.2742 (30% solution)[f]	2.679[f]
Odor	Sour, pungent odor[b]	No data
Odor threshold:		
Water	No data	No data
Air	No data	No data
Solubility:		
Water	No data	0.76 g/100 g water at 25 °C[g]
Organic solvents	No data	No data
Partition coefficients:		
Log K_{ow}	No data	No data
Log K_{oc}	No data	No data
Vapor pressure	No data	No data
Henry's Law constant at 20 °C	No data	No data
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	No data	No data
Conversion factors	Not applicable	Not applicable
Explosive limits	No data	No data

[a]All information obtained from HSDB 2003 except where noted
[b]Budavari 2001
[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)
[f]IARC 1982
[g]Aigueperse et al. 1988

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 2001, the main fluorspar-producing countries, in order of importance, were China, Mexico, South Africa, Russia, Spain, and France (USGS 2002b). The apparent consumption of fluorspar (excluding fluorspar equivalents of fluorosilicic acid, hydrofluoric acid, and cryolite) in the United States was 601,000 metric tons in 2000 and was estimated to be 636,000 metric tons in 2001 (USGS 2002a). 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.

In 2001, 65,200 tons of byproduct fluorosilicic acid (equivalent to 104,000 tons of fluorspar) were produced by 10 plants owned by 6 companies. Fluorosilicic acid was used primarily in water fluoridation, either directly or after processing into sodium silicofluoride. Fluorosilicic acid is also used to make aluminum fluoride for the aluminum industry. About 41,200, 4,700, and 13,200 tons of byproduct fluorosilicic acid were sold for water fluoridation, AlF_3 production for the aluminum industry, and for other uses, such as sodium silicofluoride production, respectively. Domestic production data for fluorosilicic acid for 2001 were developed by the U.S. Geological Survey from voluntary surveys of U.S. operations. Of the 11 fluorosilicic acid operations surveyed, 10 respondents reported production and 1 respondent reported zero production (USGS 2002b).

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 208,000 metric tons in 2001 (SRI 2002). The demand for

hydrofluoric acid, which was 350,000 metric tons in 2001, is expected to increase to 364,000 metric tons in 2005 (CMR 2002).

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. Fluorosilicic acid is a byproduct of the action of sulfuric acid on phosphate rock containing fluorides and silica or silicates. Hydrogen fluoride acts on silica to produce silicon tetrafluoride, which reacts with water to form fluorosilicic acid (Lewis 1997).

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).

Current U.S. manufacturers of fluorine, hydrogen fluoride, sodium fluoride, fluorosilicic acid, and sodium silicofluoride 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 2000, there were, respectively, 1,031 and 15 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 (TRI01 2003). 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 2000, the United States imported 484,000 metric tons of acid grade (>97%) fluorspar and 39,000 metric tons of metallurgical-grade (<97%) fluorspar (USGS 2002a). This importation was supplemented by the fluorspar equivalent of 208,000 metric tons from hydrofluoric acid plus cryolite. The estimated imports of fluorspar for 2001 were 530,000 metric tons of acid-grade, 33,000 of metallurgical-grade, and 181,000 tons from hydrofluoric acid plus cryolite. Between 1997 and 2000, 63% of fluorspar imports came from China, 26% from South Africa, and 11% from Mexico. Exports of

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

Company	Location
Hydrogen Fluoride[b,c]	
Dupont	La Porte, Texas
Honeywell[d]	Geismar, Louisiana
Fluorine	
Honeywell[d]	Metropolis, Illinois
Sodium fluoride	
Mallinckrodt Baker, Inc.	Phillipsburg, New Jersey
Ozark Fluorine Specialties, Inc.	Tulsa, Oklahoma
Solvay Fluorides, Inc.	Alorton, Illinois
Sodium silicofluoride	
IMC Phosphates Company, IMC-Agrico Phosphates	Faustina, Louisiana
Kaiser Aluminum and Chemical Corporation	Mulberry, Florida
Solvay Fluorides, Inc.	Alorton, Illinois
Fluosilicic acid	
Cargill Fertilizer, Inc.	Riverview, Florida
Farmland Hydro, L.P.	Bartow, Florida
IMC Phosphates Company, IMC-Agrico Phosphates	Faustina, Louisiana; Nichols, Florida; South Pierce, Florida; Uncle Sam, Louisiana
PCS Phosphate Co. Inc.	Aurora, North Carolina
Royster-Clark Inc.	Americus, Georgia; Chesapeake, Virginia; Florence, Alabama; Hartsville, South Carolina
Solvay Fluorides, Inc.	Alorton, Illinois
U.S. Agri-Chemicals Corporation	Fort Meade, Florida

[a]Derived from SRI 2002
[b]Plant capacity was available only for hydrogen fluoride, and was reported as 80,000 and 120,000 metric tons for DuPont and Honeywell, respectively.
[c]Merchant producers. Alcoa produces hydrogen fluoride as a nonisolatable product.
[d]Formally General Electric

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	2	0	99,999	1, 5, 13
AL	28	0	9,999,999	1, 5, 6, 11, 12, 13
AR	13	0	9,999,999	1, 5, 6, 7, 8, 11, 12, 13
AZ	23	0	999,999	1, 4, 5, 6, 7, 9, 10, 11, 12, 13
CA	34	0	49,999,999	1, 3, 4, 5, 6, 7, 9, 10, 11, 12, 14
CO	16	0	999,999	1, 5, 7, 9, 11, 12
CT	5	100	99,999	1, 5, 10, 11, 12
DE	3	0	999,999	1, 5, 6
FL	24	0	999,999	1, 2, 3, 5, 6, 7, 9, 10, 11, 12, 13, 14
GA	26	0	999,999	1, 5, 7, 11, 12, 13
IA	15	0	99,999	1, 5, 7, 12
ID	5	100	99,999	1, 5, 10, 11, 12, 13, 14
IL	41	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13
IN	36	0	999,999	1, 5, 7, 10, 11, 12, 13, 14
KS	14	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 13
KY	29	0	9,999,999	1, 2, 3, 5, 6, 9, 10, 11, 12
LA	19	0	9,999,999	1, 3, 4, 5, 6, 10, 12
MA	11	0	99,999	1, 5, 10, 11, 12
MD	12	0	9,999	1, 5, 11, 13
ME	3	0	9,999	1, 11, 13
MI	25	0	99,999	1, 2, 3, 5, 6, 7, 10, 11, 12, 13
MN	14	0	99,999	1, 5, 6, 10, 11, 12, 13
MO	27	0	99,999	1, 5, 7, 11, 12
MS	9	0	999,999	1, 5, 8, 11, 13
MT	6	0	999,999	1, 5, 10
NC	37	0	999,999	1, 5, 11, 12, 13
ND	8	0	999,999	1, 5, 10, 12, 13
NE	8	0	999,999	1, 3, 5, 9, 13
NH	4	0	99,999	1, 5, 12
NJ	15	0	9,999,999	1, 5, 6, 10, 12
NM	7	0	999,999	1, 5, 10, 11, 13
NV	2	0	999,999	1, 5
NY	29	0	99,999	1, 5, 6, 10, 11, 12
OH	62	0	999,999	1, 5, 6, 7, 8, 9, 10, 11, 12, 13
OK	17	0	999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13
OR	20	0	999,999	1, 3, 4, 5, 7, 9, 10, 11, 12
PA	67	0	9,999,999	1, 2, 3, 5, 6, 7, 9, 10, 11, 12, 13
PR	1	100,000	999,999	6
RI	3	100	99,999	6, 10, 11
SC	30	0	999,999	1, 3, 5, 6, 10, 11, 12, 14

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]
SD	1	0	99	1, 13
TN	19	0	999,999	1, 2, 5, 6, 10, 11, 13
TX	82	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14
UT	14	0	999,999	1, 5, 6, 10, 11, 12, 13
VA	23	0	99,999	1, 5, 10, 11, 12
VT	2	1,000	99,999	11
WA	18	0	999,999	1, 5, 10, 11, 12
WI	24	0	99,999	1, 5, 7, 10, 11, 12, 13
WV	20	0	999,999	1, 5, 10, 11, 12
WY	9	0	99,999	1, 2, 3, 5, 10, 13

Source: TRI01 2003

[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
14. Process Impurity

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, 13
IL	1	10,000	99,999	1, 3, 6, 7
KS	1	0	99	1, 5, 12
LA	1	1,000	9,999	1, 3, 6, 12
OK	1	1,000	9,999	8
PA	2	1,000	999,999	1, 3, 4, 6, 9, 10
PR	1	1,000	9,999	10
TX	1	1,000	9,999	12

Source: TRI01 2003

[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
14. Process Impurity

fluorspar for 2000 were 40,000 metric tons and are estimated to be 21,000 in 2001 (USGS 2002a). Exports consist of imported material that was reexported or material obtained from the National Defense Stockpile. In 2001, no disposal of metalurgical-grade fluorspar from the stockpile was reported. In 2001, most of the exports were to Canada and Taiwan (USGS 2002a, 2002b).

U.S. imports for consumption are available for three other fluorides: hydrofluoric acid, cryolite, and aluminum fluoride. For 2001, these were 112,000, 6,750, and 17,400 metric tons, respectively. For hydrofluoric acid, 74% of imports came from Mexico and 23% from Canada (USGS 2002b).

5.3 USE

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 2002). 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.

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

The chemicals most commonly used by American waterworks for water fluoridation are fluorosilicic acid, sodium silicofluoride, and sodium fluoride (Urbansky 2002). Generally, 1.5–2.2 mg of sodium fluoride is added per liter of water (0.7–1.0 mg/L as fluoride) (Mueller 1994). Data from the Centers for Disease Control's (CDC) 1992 Fluoridation Census indicate that 25% of utilities reported using sodium fluoride; however, this corresponds to 9.2% of the U.S. population drinking fluoride-supplemented tap water (Urbansky 2002). 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). Fluorosilicic acid, as a 1–2% solution, is used widely for sterilizing equipment in brewing and bottling. Other concentrations of fluorosilicic acid solutions are used in electrolytic refining of lead, in electroplating, for hardening cement, for crumbling lime or brick work, for removal of lime from hides during the tanning process, for removals of molds, and as a preservative for timber. Sodium fluorosilicate is also used in enamels for china and porcelain, in the manufacturing of opal glass, as an insecticide, as a rodentcide, and for mothproofing of wool. It is also an intermediate in the production of synthetic cryolite (Budavari 2001).

5.4 DISPOSAL

According to the TRI, in 2001, an estimated 2.5 million pounds of hydrogen fluoride were transferred off-site, including to publicly owned-treatment works (POTWs), by 991 reporting facilities presumably for disposal (TRI01 2003). In 2001, 240,196 pounds of fluorine were transferred off-site by 9 reporting facilities. According to the TRI, in 2001, 77% of hydrogen fluoride that was recycled or treated was performed on-site (TRI01 2003). Of the hydrogen fluoride recycled in 2001, 23.8 million pounds were recycled on-site and 251,203 pounds were recycled off-site. Of the hydrogen fluoride that was treated, 234 million pounds were treated on-site and 2 million pounds were treated off-site (TRI01 2003). No information was found concerning how hydrogen fluoride is generally treated for 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 2001, 18,973 pounds of fluorine were treated on-site and 240,196 pounds were treated off-site (TRI01 2003).

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.

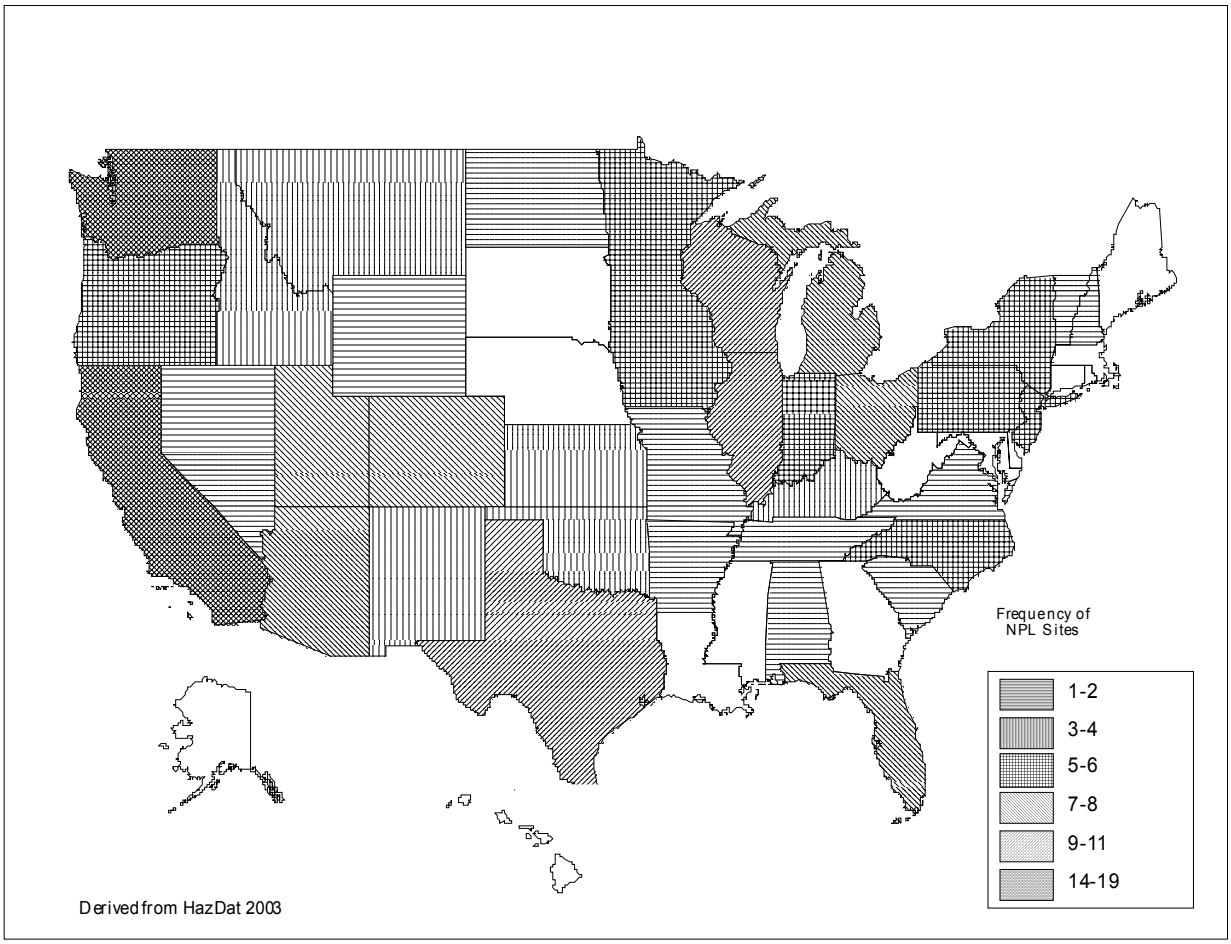
6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Fluorides, hydrogen fluoride, and fluorine have been identified in at least 188 of the 1,636 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2003). However, the number of sites evaluated for fluorides, hydrogen fluoride, and fluorine is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, all are located within the United States.

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. Volcanoes 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. According to the Toxic Chemical Release Inventory (TRI), in 2001, the largest contributing industrial sectors were electrical utilities (TRI01 2003). Total air emissions of hydrogen fluoride by electrical utilities in 1998, 1999, 2000, and 2001 were reported as 64.1, 58.3, 58.3, and 55.8 million tons, respectively. 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. Hydrogen fluoride is one of the 189 chemicals listed as a hazardous air pollutant (HAP) in Title III, Section 112 of the Clean Air Act Amendments of 1990. Maximum achievable control technology (MACT) emission standards are being developed by the EPA for each HAP. The goal of

Figure 6-1. Frequency of NPL Sites with Fluoride, Hydrogen Fluoride, and Fluorine Contamination



HAP emissions control is to reduce human health risks (Kelly et al. 1994). 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 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 may be exposed to high levels of fluoride in water. This is especially true if drinking water is derived from wells.

Fluoride intake in infants depends on whether or not the child is nursed. Fluoride intake by an infant who is exclusively breast fed is generally <2 µg/kg-day(Fomon and Ekstrand 1999). 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). Fluoride exposure was calculated to be 102, 105, and 167 µg/kg-day for infants consuming concentrated liquid milk-based formula, concentrated liquid isolated soy protein-based formula, and powdered milk-based formula, respectively, which were diluted with water that is 1 ppm in fluoride. Infants may be exposed to higher fluoride concentrations now than in the past. In the 1960s, nearly 80% of infants were fed cow's milk by 6 months of age. In 1991, 80% of 6-month-old infants were fed formula (Fomon and Ekstrand 1999).

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 TRI, in 2001, total releases of hydrogen fluoride to the environment (including air, water, soil, and underground injection) from 991 reporting facilities that produced, processed, or used hydrogen fluoride were 72.1 million pounds (TRI01 2003). Table 6-1 lists amounts released from these

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	Under-ground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on and off-site release
AK	2	73,027	No data	0	0	73,027	0	73,027
AL	28	3,304,387	0	0	12,000	3,316,387	18,596	3,334,983
AR	13	942,385	0	0	0	942,385	8	942,393
AZ	23	694,190	No data	0	3,405	697,595	1,062	698,657
CA	35	9,211	5	0	0	9,216	2,886	12,102
CO	17	795,831	No data	0	0	795,831	0	795,831
CT	5	107,388	0	0	0	107,388	10,732	118,120
DE	3	201,815	No data	0	0	201,815	0	201,815
FL	24	2,358,937	5	0	7,965	2,366,907	0	2,366,907
GA	28	3,286,300	0	0	0	3,286,300	2,944	3,289,244
IA	16	1,300,253	No data	0	0	1,300,253	0	1,300,253
ID	5	208,065	0	0	0	208,065	255	208,320
IL	41	2,255,380	1	0	5	2,255,386	1,510	2,256,896
IN	36	3,888,416	250	0	0	3,888,666	0	3,888,666
KS	16	775,771	0	0	0	775,771	930	776,701
KY	29	2,090,877	0	0	0	2,090,877	1,301	2,092,178
LA	19	613,860	250	0	11	614,121	0	614,121
MA	11	197,829	No data	0	0	197,829	237	198,066
MD	14	1,376,506	No data	0	0	1,376,506	15	1,376,521
ME	3	1,286	0	0	0	1,286	0	1,286
MI	27	2,139,731	0	0	0	2,139,731	39,376	2,179,107
MN	15	217,532	0	0	0	217,532	0	217,532
MO	29	2,464,416	0	0	158,300	2,622,716	0	2,622,716
MS	9	461,108	197	0	2,287	463,592	0	463,592
MT	7	167,298	0	0	0	167,298	0	167,298
NC	38	5,160,908	5	0	0	5,160,913	0	5,160,913
ND	8	490,133	0	0	0	490,133	260	490,393
NE	8	1,279,219	No data	0	0	1,279,219	0	1,279,219
NH	4	208,550	No data	0	0	208,550	391	208,941
NJ	15	249,406	0	0	0	249,406	2	249,408
NM	7	209,568	No data	0	0	209,568	420	209,988
NV	2	439,874	No data	0	0	439,874	0	439,874
NY	31	1,137,383	0	0	0	1,137,383	750	1,138,133
OH	64	6,147,565	1,601	4,400,000	0	10,549,166	34,884	10,584,050
OK	18	892,504	100	0	0	892,604	250	892,854
OR	21	67,943	0	0	18,398	86,341	0	86,341
PA	70	5,056,848	35	0	5	5,056,888	17,156	5,074,044

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	Under-ground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on and off-site release
PR	1	500	No data	0	0	500	0	500
RI	3	3,683	No data	0	0	3,683	0	3,683
SC	30	2,153,397	0	0	0	2,153,397	0	2,153,397
SD	2	89,000	No data	0	0	89,000	0	89,000
TN	19	2,069,004	0	0	0	2,069,004	0	2,069,004
TX	83	3,828,730	10	0	21	3,828,761	1,100	3,829,861
UT	14	467,778	0	0	24,930	492,708	0	492,708
VA	23	1,745,413	0	0	0	1,745,413	0	1,745,413
VT	2	4,141	0	0	0	4,141	0	4,141
WA	19	323,942	0	0	0	323,942	1,405	325,347
WI	24	1,231,556	0	0	0	1,231,556	0	1,231,556
WV	21	3,722,619	19,090	0	0	3,741,709	0	3,741,709
WY	9	337,011	No data	0	52,248	389,259	0	389,259
Total	991	67,248,474	21,549	4,400,000	279,575	71,949,598	136,470	72,086,068

Source: TRI01 2003

[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).

facilities grouped by state. In addition, 136,470 pounds of hydrogen fluoride were transferred off-site by these facilities (TRI01 2003). 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, which contributed 78% of the total environmental releases.

According to the TRI, in 2001, total releases of fluorine to the environment (including air, water, soil, and underground injection) from 9 reporting facilities that produced, processed, or used fluorine were 165,938 pounds (TRI01 2003). Table 6-2 lists amounts of fluorine released from these facilities grouped by state. The two largest contributing industrial sectors were electrical utilities and primary metals, which respectively contributed 65 and 19% of the total environmental releases. 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.

Hydrogen fluoride is one of the 189 chemicals listed as a HAP in Title III, Section 112 of the Clean Air Act Amendments of 1990. MACT emission standards are being developed by the EPA for each HAP. The goal of HAP emissions control is to reduce human health risks (Kelly et al. 1994). The Final Air Toxic MACT Rule for fluoride emissions from primary aluminum reduction plants, published in 1997, was projected to reduce fluoride emissions by 3,700 tons per year. The Final Air Toxic MACT Rule for fluoride emissions from phosphoric acid manufacturing and phosphate fertilizer production, published in 1999, was projected to reduce fluoride emissions by 260 tons per year (EPA 2000).

Fluorides have been identified in a variety of environmental media (air, surface water, leachate, groundwater, soil, and sediment) collected at 188 of 1,636 current or former NPL hazardous waste sites (HazDat 2003).

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

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	Under-ground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on and off-site release
AL	1	0	31,328	0	0	31,328	0	31,328
IL	1	4,979	No data	0	0	4,979	0	4,979
KS	1	429	No data	0	107,282	107,711	0	107,711
LA	1	2,280	No data	0	0	2,280	0	2,280
OK	1	263	No data	0	0	263	0	263
PA	2	1,001	No data	0	0	1,001	0	1,001
PR	1	0	18,376	0	0	18,376	0	18,376
TX	1	0	No data	0	0	0	0	0
Total	9	8,952	49,704	0	107,282	165,938	0	165,938

Source: TRI01 2003

[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).

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.

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. The 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 emissions 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 $2.5x10^{10}$ 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 Kierdorf 2000). In the 1990s, levels were almost an order of magnitude lower than the peak levels, which are 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 2001, releases of 67.2 million pounds of hydrogen fluoride to air from 991 reporting facilities accounted for 93% of the total environmental releases of hydrogen fluoride (TRI01 2003). 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 83% of releases to air.

According to the TRI, in 2001, releases of 8,952 pounds of fluorine to air from 9 reporting facilities accounted for 5% of the total environmental releases of fluorine (TRI01 2003). 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.

According to the TRI, total air emissions for hydrogen fluoride ranged from 15.9 million pounds in 1998 to 8.9 million pounds in 1994, during the period from 1988 to 2001. Total air emissions of fluorine have decreased from 18,319 pounds in 1995 to 8,523 pounds in 2001 (TRI01 2003). This trend information only includes emission data from the original industry subtotal, those industries with Standard Industrial Classification (SIC) Codes 20–39. Starting in 1998, metal mining, coal mining, electric utilities, Resource Conservation and Recovery Act (RCRA)/solvent recovery industries, and chemical wholesalers were also required to report. Of these industries, electrical utilities contribute significantly to emissions of hydrogen fluoride to air. Total air emissions of hydrogen fluoride by electrical utilities in 1998, 1999, 2000, and 2001 were reported as 64.1, 58.3, 58.3, and 55.8 million tons, respectively.

Fluorides were detected in the air at 8 of the 188 current or former NPL hazardous waste sites, where they were detected in some environmental media (HazDat 2003).

6.2.2 Water

Natural sources of fluoride released to waters are 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 2001, releases of 21,549 pounds of hydrogen fluoride to water from 991 reporting facilities accounted for 0.030% of the total environmental releases of these substances (TRI01 2003). Table 6-1 lists amounts of hydrogen fluoride released to water from these facilities grouped by state. According to the TRI, in 2001, releases of 49,704 pounds of fluorine to water from 9 reporting facilities accounted for 30% of the total environmental releases of this substance (TRI01 2003). 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 were detected in groundwater and surface water at 135 and 53 sites, respectively, of the 188 NPL hazardous waste sites where they were detected in some environmental media (HazDat 2003).

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 decreased from 292 to 10 µg fluoride/g (Polomski et al. 1982).

According to the TRI, in 2001, releases of 279,575 pounds and 4.4 million pounds of hydrogen fluoride respectively to land and underground injection from 991 reporting facilities accounted for respectively 0.38 and 6.1% of total environmental releases of these substances (TRI01 2003). 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 2001, 107,282 pounds of fluorine were released to land from 9 reporting facilities accounted for 65% of the total environmental releases of this substance (TRI01 2003). However, it is not clear how a gaseous substance can be released to land, and this figure is likely an 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 were detected in soil and sediment collected at 32 and 22 sites, respectively, of the 178 NPL hazardous waste sites, where they were detected in some environmental media (HazDat 2003).

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 fluorides 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 contents 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 than of 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 concentrated 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 hexafluoride, a gaseous dielectric for electrical and electronic equipment, reacts with water at elevated temperatures (>850 °C) 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 undissociated hydrogen fluoride increase. Levels of undissociated 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).

In a recent review article, different models of the equilibria of the hexafluorosilicate anion in water solution were compared. It was concluded that concentrations of any fluorosilicate species are extremely small at drinking water pH (Urbansky 2002). The analysis presented reaffirms the conclusions made earlier by Feldman et al. (1957), that in drinking water with a pH of ≥5, fluoridated with sodium silicofluoride to a concentration of ≤16 ppm of fluoride ion or less, silicofluoride is completely hydrolyzed to silicic acid, fluoride ion, and hydrogen fluoride. While the kinetics of dissociation and hydrolysis of the hexafluorosilicate anion are not well understood from a mechanistic or fundamental perspective, the rate data suggest that equilibrium should be achieved by the time drinking water reaches the consumer (Urbansky 2002).

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^+, and 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, meteorological conditions, and topography (Davis 1972). Ambient concentrations of hydrogen fluoride measured in the United States (ca. 1985) ranged from 1.0 to 7.5 μg/m^3 (Kelly et al. 1993). 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 non-urban stations showed fluoride concentrations below 0.05 μg/m^3, the threshold of detectability. Only 18 measurements (0.2%) exceeded 1.00 μg/m^3; the maximum concentration was 1.89 μg/m^3 at urban locations and 0.16 μg/m^3 at non-urban locations (Yunghans and McMullen 1970).

The ambient air concentration of gaseous fluoride varies from 0.01 to 1.65 μg/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 μg/m^3 (0.15 ppb) and 0.22 μg/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 μg/m^3 (0.38 ppb) to 1.91 μg/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. 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 μg/m^3 (5.53 μg/m^3, 12-hour maximum), and the average gaseous fluoride level was 0.36 μg/m^3 (6.41 μg/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).

Fluoride content of waters for Yellowstone National Park ranged from 0.5 mg/L in Yellowstone River to 24.0 mg/L in the Midway Geyser Basin. Fluoride concentrations in some selected thermal waters in Idaho ranged from 9 to 30 mg/L. Data from more than 300 geothermal waters in the Western United States indicate that at least 68% of these waters contain fluoride, with concentrations ranging from 2.1 to 30 mg/L. Fluoride concentrations from a regular well and a geothermal well from a ranch in Idaho were 0.8 and 14.2 mg/L, respectively. Use of geothermal well water for irrigation induces high fluoride levels in alfalfa and pasture grasses consumed by cattle (Miller et al. 1999).

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. The results of this study suggest that geology has an important influence on the distribution of fluoride in Texas groundwater. 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) that was reported at the time as 1,800 µg/L for public water supplies (Steichen et al. 1988). The highest fluoride level found in this study was 2,300 µg/L.

Rain Water. 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 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 were 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 purchased 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). A study compared fluoride content in foods and beverages from a negligibly fluoridated community (Connersville, Indiana) and an optimally fluoridated community (Richmond, Indiana). The fluoride concentrations in Connersville and Richmond are 0.16±0.01 and 0.90±0.05 μg F/g. It was found that fluoride content in non-cooked and non-reconstituted foods and beverages ranged from 0.12 to 0.55 μg F/g and that there was no significant difference between the two communities. The difference in fluoride content of foods prepared and/or cooked with water from the two study sites were statistically different, except in the case of cooked vegetables (Jackson et al. 2002).

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 ranges (means) 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 Gatorade, 0.02–1.04 ppm (0.85 ppm) (Pang et al. 1992). Fluoride concentrations were measured in 332 carbonated soft drinks, manufactured by 10 companies, which are available in Iowa grocery stores. Fluoride concentrations were found to range from 0.02 to 1.28 ppm, with a mean of 0.72 ppm. For 71% of the drinks analyzed, fluoride concentrations exceeded 0.60 ppm. Concentrations were found to vary substantially by production site, even within the same company and for the same product (Heilman et al. 1999).

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 is tea plants. The highest fluoride concentration 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.

Fluoride concentrations in vegetation form Yellowstone National Park varies over a wide range from 3 to 430 ppm. Studies where plants were watered by spray treatments containing 4 ppm fluoride showed that plants accumulated up to 36 ppm fluoride (dry weight), but a significant amount of this could be removed by washing the leaves in distilled water. In another experiment using 6 ppm fluoride solution, leaf analysis contained up to 55 ppm fluoride in the unwashed leaves and 35 ppm in washed leaves. Fluoride

content in vegetation around a phosphate plant was found to range from 4 to 718 ppm. Fluoride was present in the air in the form of particulate fluorides and hydrogen fluoride gas (Miller et al. 1999).

Fluoride levels in various marine crustaceans were found to range from not detected to 2,500 (whole-body), not detected to 5,977 (exoskeleton), and not detected to 257 (muscle) μg/g, dry weight. Fluoride levels in saltwater fish were found to range from 45 to 1,207 (skeletal bone) and from 1.3 to 26 (muscle) mg/kg, wet weight (Camargo 2003).

The fluoride concentration in most dental products available in the United States ranges from 230 ppm (0.05% NaF mouth rinse) to 12,300 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 monofluorophosphate.

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). Fluoride concentrations in waste water from a coal-fired power plant in Utah ranged from 2.4 to 3.8 ppm (Miller et al. 1999).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The major sources of fluoride intake by the general population are water, beverages, food, and fluoride-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 (OSHA 1985), fluoride intake via inhalation can be 16.8 mg/day, assuming an 8-hour shift and that a person inhales 20 m^3 air/day. 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.

The chemicals most commonly used by American waterworks are fluorosilicic acid, sodium silicofluoride, and sodium fluoride. Data from the CDC's 1992 Fluoridation Census indicate that 25% of utilities reported using sodium fluoride; however, this corresponds to 9.2% of the U.S. population drinking fluoride-supplemented tap water (Urbansky 2002). Concerns over the purity of water fluoridation agents have been raised as well as possible links between fluoridation agents and lead levels in the bloodstream (Masters et al. 2000). Analyses of available grades of fluorosilicic acid, sodium fluoride, and sodium fluorosilicate show the presence of arsenic and lead, but at levels far below that which would necessitate recommended maximum impurity content (RMIC) values based on the maximum dosage of 1.2 mg of fluoride ion per liter (NRC 1982).

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 who 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 intakes 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,

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

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 intakes 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 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 (0.00893±0.00513 and 0.00760 mg/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 fluorophosphate 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 environmental 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 follow-up study Kono et al. (1993) found a linear correlation between urine fluoride levels and hair fluoride levels.

A study evaluated the use of urinary fluoride as an exposure index for a prospective study of asthma in an aluminum smelter. In the first part of the study, 32 subjects wore personal air sampling pumps. The 12-hour time weighted average results show that overall mean levels were 15.7, 4.07, and 0.74 mg/m^3 for particulate mass, total fluoride, and hydrogen fluoride, respectively. Urinary fluoride concentrations were considered reasonably low, 1.3 and 3.0 mg/g creatinine in pre- and post-shift collections. Carbon smelters had the highest exposure levels as compared to workers working as potmen and trappers (Seixas et al. 2000). An average total fluoride exposure of 0.91 mg/m^3, of which 34% was gaseous fluoride, was measured for 41 workers in an aluminum plant in Sweden. Mean fluoride plasma concentrations were determined to be 23 and 48 ng/mL pre- and post-shift, respectively. Use of a safety mask during the shift led to a reduction in exposure of inhaled fluoride. Workers wearing a safety-mask throughout the whole shift reduced inhalation of fluoride to 30–40% of those workers not wearing masks (Ehrnebo and Ekstrand 1986).

Certain populations, such as patients with kidney disease, may be especially sensitive to fluoride exposure. In 1993, 20 patients became ill due to acute fluoride intoxication after receiving hemodialysis

treatment for end-stage renal failure. This outbreak was found to be caused by errors in the maintenance of the deionization system used to treat the water used for dialysis. In this case, the deionization units continued to be used after the ion exchange resins were exhausted, resulting in the release of the resin-bound fluoride into the treated water (Arnow et al. 1994).

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 and dental products. 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, respectively (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 ppm) 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. 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 (Opinya et al. 1991a).

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 or 0.01 mg/L) and provides <0.01 mg fluoride/day (NRC 1993). Fluoride intake by an infant who is exclusively breast fed and consuming 170 mL/kg-day is generally <2 µg/kg-day (Fomon and Ekstrand 1999). 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).

The results of a survey of fluoride levels in 68 samples of cows' milk and 115 samples of infant formulas and oral electrolytes are 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. Fluoride exposure was calculated to be 102, 105, and 167 µg/kg-day for infants consuming 170 mL/kg-day of concentrated liquid milk-based formula, concentrated liquid isolated soy protein-based formula, and powdered milk-based formula, respectively, which were diluted with water that is 1 ppm in fluoride. Infants may be exposed to higher fluoride concentrations now than in the past.

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.

In the 1960s, nearly 80% of infants were fed cow's milk by 6 months of age. In 1991, 80% of 6-month-old infants were fed formula (Fomon and Ekstrand 1999). 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). Fluoride may be an important mineral for babies born prematurely, since prematurity is associated with an increased incidence of dental caries; however, recommendations for fluoride intake are only available for full-term infants (Zlotkin et al. 1995).

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 was 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 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 dental 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. Mean fluoride concentrations of 1.85, 5.28, and 7.52 mg/kg were found in fingernails of Brazilian children, 6–7 years old, living in communities where fluoride concentrations were 0.1, 1.6, and 2.3 ppm, respectively. Analysis of these data indicated a direct relationship between fluoride concentrations in drinking water and fingernails. The 95% confidence intervals for the 0.1 and 1.6–2.3 ppm areas showed no overlap; a small overlap was noted for the 1.6 and 2.3 ppm areas (Whitford et al. 1999a).

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.

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 ventilation rates

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

Site Population	Sample	Concentration	Type	Units	Reference
Human plasma from blood banks in five U.S. cites with different fluoride levels in drinking water					Guy et al. 1976
Albany, NY (n=30) <0.1 ppm fluoride	Blood plasma	0.38 (0.14-1.1)	Mean (Range)	µmol/L	
Rochester, NY (n=30) 1 ppm fluoride		0.89 (0.35-4.2)			
Corpus Christi, TX (n=12) 0.9 ppm fluoride		1.0 (0.60-1.7)			
Hillsboro, TX (n=4) 2.1 ppm fluoride		1.9 (0.60-2.6)			
Andrews, TX (n=30) 5.6 ppm fluoride		4.3 (1.4-8.7)			
Poland (1980)					Miszke et al. 1984
Employee of electrolysis shop of aluminum plant	Urine, random	1.87		mg/dm^3	
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)			
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)			

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

Site Population	Sample	Concentration	Type	Units	Reference
Danish adults					Poulsen et al. 1994
Representative population (n=168)	Serum	470 (270)	Mean (SD)	nmol/L	
Brazilian children (6-7 years old) exposed to different water fluoride concentrations					Whitford et al. 1999a
Fluoride concentration in drinking water:					
0.1 ppm (n=19)	fingernail	1.85 (0.75-3.53)	Mean (range)	mg/kg	
1.6 ppm (n=12)		5.28 (2.28-7.53)			
2.3 ppm (n=15)		7.52 (4.00-13.18)			
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)			
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

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 fluorine, hydrogen fluoride, and 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 fluorine, hydrogen fluoride, and 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 2002; 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 2001, is currently available. 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.

A recent review (Urbansky 2002) looked at the fate of fluorosilicate drinking water additives. Various fluorosilicates and aquo/hydroxo/oxo/fluorosilicates may exist in fluoridated water systems and these species may occur, regardless of the fluoridating agent used, since water may contain natural silica. The author states that it would be desirable to be able to identify and measure or calculate concentrations of those species that do exist and rule out those that do not exist (Urbansky 2002).

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 (i.e., by children) 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. Recent serial measurements of fluorides in air are needed. 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 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 2003; 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, nails, 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; Fomon and Ekstrand 1999; NRC 1993). 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, respectively. The mean intakes of 2 year olds, but not 6 month olds, were 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. Infants may be exposed to higher fluoride concentrations now than in the past. While nearly 80% of infants were fed cow's milk by 6 months of age in the 1960s, in 1991, 80% of 6-month-old infants were fed formula, which contains higher fluoride concentrations than either human or cow's milk (Fomon and Ekstrand 1999). 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 may be an important mineral for babies born prematurely, since prematurity is associated with an increased incidence of dental caries; however, recommendations for fluoride intake are only available for full-term infants (Zlotkin et al 1995).

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 2002) 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 188 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) was 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, hydrogen fluoride, and fluorine, its metabolites, and other biomarkers of exposure and effect to fluorides, hydrogen fluoride, and fluorine. 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. The most accurate method of sample preparation is microdiffusion techniques, such as the acid-hexamethyldisiloxane (HMDS) diffusion method by Taves (1968). These methods allows for the liberation of fluoride from organic or inorganic matrices (WHO 2002). During sample preparation, the analyst must be careful to avoid sample contamination, incomplete

release from matrices, and losses due to volatilization (NRC Canada 1971). Vogel et al. (1990) reported methodologies for sample manipulation and fluoride analysis on very small sample volumes. Techniques included micropipette procedures for transferring samples, preparation of micro fluoride-selective electrodes, and methods for adapting standard electrodes for micro- and semi-micro volumes (0.005–5 μL). These techniques have been used for fluoride analysis of various biological samples, such as salvia, plaque, and tooth enamel (Vogel et al. 1990, 1992a, 1992b). 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 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. The pH of the solution analyzed is adjusted to approximately 5 to eliminate interference. ISE is the methodology recommended by 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 the sample preparation required. Sample for ISE analysis must be prepared to solubilize the fluoride in the sample. For some samples, ashing or NaOH fusion is required. A total-ionic strength adjustment buffer (TISAB) is used to adjust samples and standards to the same ionic strength and pH; 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-hexylene-dinitrilotetraacetic 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). Fingernail fluoride levels can be measured using the ISE technique after nail clippings were prepared by HMDS-facilitated diffusion overnight. This sample preparation was found to quantitatively remove fluoride from the nail material (Whitford et al. 1999a). Whitford et al. (1999a) also reported that soaking the fingernail samples in deionized water for 6 hours or in a solution of 1.0 ppm fluoride for 2 hours did not change the concentration of fluoride found in the nail.

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

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%	Petersson 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 °C (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
Bone	Ash sample; dissolve in perchloric acid; add 1,2-cyclohexylenedinitrotetraacetic 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
Fingernail	HMDS-facilitated diffusion overnight	ISE	No data	No data	Whitford et al. 1999a

GC = gas chromatography; HClO4 = perchloric acid; HMDS = hexamethyldisiloxane; 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

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 °C in borosilicate vials. This closed-system approach decreases contamination, eliminates dry ashing, and yields high recoveries. Dabeka and McKenzie (1981) employed microdiffusion with 40% perchloric acid to food samples in Petri dishes at 60 °C for 24–48 hours. Difficulties arose in controlling contamination and fluoride loss in the Petri dishes, and low recoveries were reported. Preparation of total fluoride in dry plant material (i.e., hay, barley, straw, corn, grass) was described by Eyde (1982); samples were fused in nickel crucibles with sodium hydroxide at 350–475 °C. The ash was diluted and filtered for analysis. This method is more tedious than the others, and fluoride loss is expected from the high 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 °C is mediated by a current of air or pure oxygen to evolve hydrogen fluoride. An advantage of this approach is that fluoride is collected from inorganic and organic fluorides in one operation. Ashing, which may produce loss of organic fluorine, is eliminated.

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/minute 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 1998c
	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 1998c
	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 1998c

Table 7-2. Analytical Methods for Determining Fluoride in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
	Extract with TMCS; analyze organic phase (microwave induced plasma emission detector)	GC	4 µg/L	93–100%	Chiba et al. 1982
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 °C 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 Samplesa

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 poly-propylene element.	ISE	100 µg/L	No data	Young and Monat 1982
	Dual cellulose filter to separate particulate and gaseous fluoride; heat filters at 75 °C; 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

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-di-hydroxy-3,6-naphthalenedisulfonate (SPADNS) reagent is used, and the color loss is measured at 570 nm (EPA 1998c). In EPA Method 340.3, the red cerium complex with alizarin complex one turns blue on the addition of fluoride (EPA 1998c).

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 of 3.19, 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 are 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 an 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-9 (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 for 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, hydrogen fluoride, and fluorine 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, hydrogen fluoride, and fluorine.

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, and 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; Whitford et al. 1999a), saliva (Petersson 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 1998c; Eyde 1982; Kakabadse et al. 1971; Lopez and Navia 1988; NIOSH 1994; NRC Canada 1971; WHO 1984).

7.3.2 Ongoing Studies

One ongoing study regarding techniques for measuring and determining fluoride in biological and environmental samples was located. Noah Seixas of the University of Washington proposes to adapt real-time instruments for monitoring HF and SO_2 and a nonspecific particulate, integrating currently available, electrochemical sensor, and light scattering technology and, using these instruments, to monitor exposure in four aluminum smelting operations (FEDRIP 2002).

8. REGULATIONS AND ADVISORIES

No international regulations pertaining to fluorides were found. The national and state regulations and guidelines regarding fluorides, hydrogen fluoride, and fluorine in air, water, and other media are summarized in Table 8-1.

A chronic-duration oral MRL of 0.05 mg fluoride/kg/day has been derived for fluoride. This MRL is based on a NOAEL of 0.15 mg fluoride/kg/day and a LOAEL of 0.25 mg fluoride/kg/day for skeletal effects (increased fracture rate) (Li et al. 2001). The MRL was derived by dividing the NOAEL by an uncertainty factor of 3 to account for human variability.

An acute-duration inhalation MRL of 0.02 ppm fluoride has been derived for hydrogen fluoride. This MRL is based on a minimal LOAEL of 0.5 ppm for upper respiratory tract inflammation in humans exposed to hydrogen fluoride for 1 hour (Lund et al. 1997, 1999). The MRL was derived by dividing the unadjusted LOAEL by an uncertainty factor of 30 (3 for a use of a minimal LOAEL and 10 to account for human variability).

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 irritation in humans exposed to fluorine for 15 minutes (Keplinger and Suissa 1968). The MRL was derived by dividing the 24-hour adjusted NOAEL of 0.1 ppm by an uncertainty factor of 10 to account for human variability.

EPA (IRIS 2003) 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, Sodium Fluoride, Hydrogen Fluoride, and Fluorine

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification		IARC 1987
	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	
	Highly hazardous chemicals		OSHA 2001d
	Threshold quantity		29CFR1910.119
	Fluorine	1,000 pounds	Appendix A
	Highly hazardous chemicals		OSHA 2001e
	Threshold quantity		29CFR1926.64
	Hydrogen fluoride	1,000 pounds	Appendix A

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

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
OSHA	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)		NIOSH 2001a
	Fluorine	0.2 mg/m^3	NIOSH 2001b
	Hydrogen fluoride	2.5 mg/m^3	NIOSH 2001c
	Sodium fluoride	2.5 mg/m^3	
	IDLH		NIOSH 2001a
	Fluorine	25 ppm	NIOSH 2001b
	Hydrogen fluoride	30 ppm	NIOSH 2001c
	Sodium fluoride	250 ppm	
USC	HAP		USC 2001 42USC7412
b. Water			
EPA	BPT effluent limitation—fluoride		EPA 2001c
	Maximum for 1 day	6.1 kg/kkg	40CFR415.82
	Average of daily values for 30 consecutive days	2.9 kg/kkg	
	Effluent limitation—fluoride		EPA 2001e
	Maximum for 1 day	75 mg/L	40CFR422.42
	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
	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		EPA 2001n 40CFR180.145
	Apricots, beets, blackberries, blueberries, boysenberries, broccoli, brussels sprouts, cabbage, cauliflower, citrus fruits, collards, cranberries	7 ppm	

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

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Pesticides—fluorine compounds; residue tolerances		EPA 2001n 40CFR180.145
	Cucumbers, dewberries, eggplant, grapes, kale, kohlrabi, lettuce, loganberries, melons, nectarines, peaches, peppers, plums, pumpkins, radish, raspberries, rutabaga, squash, strawberries, tomatoes, turnip, youngberries	7 ppm	
	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	Total fluoride from all sources not to exceed 1% by weight of the finished adhesive	FDA 2000e 21CFR175.105(c)(5)
	Hydrogen fluoride		
	Sodium fluoride		
	Bottled water—no fluoride added	Temperature[b] / mg/L 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	FDA 2000g 21CFR165.110
	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)

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

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
FDA	Surface component, food contact—sodium fluoride for use as preservative only		FDA 2000h 21CFR177.2800 (d)(5)
d. Other			
ACGIH	Carcinogenicity classification		ACGIH 2000
	Fluoride	A4[c]	
	BEI		
	Fluorides in urine		
	Prior to shift	3 mg/g creatinine	
	End of shift	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
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 2003
	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	Not more than 25% of	EPA 2001m
	Sodium fluoride	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	

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

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Superfund—extremely hazardous		EPA 2001p
	Reportable quantity		40CFR355
	Fluorine	10 pounds	Appendix A
	Hydrogen fluoride	100 pounds	
	Threshold planning quantity		
	Fluorine	500 pounds	
	Hydrogen fluoride	100 pounds	
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	

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

Agency	Description	Information		Reference
STATE *(cont.)*				
Washington	Toxic air pollutant—ASIL			BNA 2001
	Fluoride	8.3 μg/m^3		
	Fluorine	5.3 μg/m^3		
	Hydrogen fluoride	8.7 μg/m^3		
	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 2003
	Reporting limit—fluoride	2.0 mg/L		BNA 2001
California	Drinking water standards—fluoride	2.0 mg/L		HSDB 2003
Connecticut	MCL—fluoride	4.0 mg/L		BNA 2001
Delaware	Drinking water standards—fluoride	1.8 mg/L		HSDB 2003
Georgia	MCL—fluoride	4.0 mg/L		BNA 2001
Hawaii	Drinking water standards—fluoride	1.4–2.4 mg/L		HSDB 2003
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 2003
	Maximum exposure guideline	2.4 mg/L		BNA 2001
	Action level	1.2 mg/L		
Mississippi	Groundwater standards—fluoride	4.0 ppm		BNA 2001
Nebraska	MCL—fluoride	4.0 mg/L		BNA 2001

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

Agency	Description	Information	Reference
STATE *(cont.)*			
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 2003
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 2003
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
Wisconsin	MCLG—fluoride	4.0 mg/L	BNA 2001
	MCL—fluoride	4.0 mg/L	
	Groundwater standards—fluoride		BNA 2001
	Enforcement standard	4.0 mg/L	
	Preventive action limit	0.8 mg/L	
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

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

Agency	Description	Information	Reference
STATE *(cont.)*			
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 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 that 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 of people that 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 that 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 that 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 group.

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, whereas 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 that 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.

q1*—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.

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 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

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) (TD50)—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 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 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: Fluoride
CAS Number: NA
Date: December 1, 2003
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to Figure: 53
Species: Humans

Minimal Risk Level: 0.05 [X] mg/kg/day [ ] mg/m^3

Reference: Li Y, Liang C, Slemenda CW, et al. 2001. Effect of long-term exposure to fluoride in drinking water on risks of bone fractures. J Bone Miner Res 16:932-939.

Experimental design (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Six communities in rural China with different levels of naturally occurring fluoride in the water were examined. The subjects were 50 years and older; the mean ages ranged from 62.6 to 64.0 years. The majority of the subjects had been living in the same community since birth. There was a higher percentage of males in the highest fluoride group (52.4%) than in the other groups (41.8–47.0%). The water fluoride concentrations were 0.25–0.34, 0.58–0.73, 1.00–1.06, 1.45–2.19, 2.62–3.56, and 4.32–7.97 ppm. Three-day dietary surveys were collected for 10% of randomly selected subjects; estimated nutrition levels were adequate for all six populations. None of the subjects used fluoride-containing toothpaste or mouthwashes and there was a minimal use of packaged beverages and canned foods; fluoride levels in brewed tea samples were largely determined by the levels of fluoride in the water. The authors calculated total daily fluoride intakes of 0.7, 2, 3, 7, 8, and 14 mg/day. The subjects self-reported bone fractures. If the fracture received medical attention, then original x-rays were obtained; for other fractures, x-rays were taken to verify self-reported fractures. The reliability of the reported fracture was 99.1%.

Effects noted in study and corresponding concentrations: Age, gender, alcohol consumption, and level of physical activity were significant factors for the risk of overall bone fractures since age 20 years; cigarette smoking and BMI did not significantly alter bone fracture prevalence. The trend for overall bone fracture prevalence (adjusted for age and gender) had a U-shaped pattern. As compared to the 1.00–1.06 ppm group, significantly higher prevalences of bone fracture were found in the lowest (0.25–0.34 ppm fluoride) and highest (4.32–7.97 ppm) groups. The prevalences were 7.41, 6.40, 5.11, 6.04, 6.09, and 7.40%, respectively. When only hip fractures since age 20 were examined, significantly higher prevalences (adjusted for age and BMI) were found in the highest fluoride group, as compared to the 1.00–1.06 ppm group. The prevalences of hip fractures were 0.37, 0.43, 0.37, 0.89, 0.76, and 1.20%, respectively. A similar pattern was observed when overall fractures since age 50 were examined; the prevalences were 4.33, 3.20, 3.28, 3.30, 3.62, and 4.80 ($p=0.02$), respectively. Only a small number of subjects reported spine fractures (49); none of the fluoride groups significantly differed from the 1.00–1.06 ppm group.

Concentration and end point used for MRL derivation:

The MRL is based on a NOAEL of 0.15 mg fluoride/kg/day for increased fracture rate.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL in a sensitive subpopulation
[ ] 10 for extrapolation from animals to humans
[X] 3 for human variability; a value less than 10 was used because the most sensitive population, elderly men and women, were examined.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Yes. Doses were calculated using the reported daily fluoride intakes of 0.7, 2, 3, 7, 8, and 14 mg/day and a reference body weight of 55 kg.

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 number of studies have examined the possible association between exposure to fluoridated water and the risk of increased bone fractures, in particular, hip fractures. In general, the studies involved comparing the incidence of hip fractures among residents aged 55 years and older living in a community with fluoridated water (around 1 ppm) with the incidence in a comparable community with low levels of fluoride in the water. Inconsistent results have been found, with studies finding decreases (Lehmann et al. 1998; Phipps et al. 2000; Simonen and Laittinen 1985), increases (Cooper et al. 1990, 1991; Danielson et al. 1992; Jacobsen et al. 1990, 1992; Kurttio et al. 1999), or no effect (Arnala et al. 1986; Cauley et al. 1995; Goggin et al. 1965; Jacobsen et al. 1993; Karagas et al. 1996; Kröger et al 1994; Suarez-Almazor et al. 1993) on hip fracture risk. Studies by Li et al. (2001) and Sowers et al. (1986) have examined communities with higher levels of naturally occurring fluoride in the water. Both studies found increases in the incidence of hip fractures in residents exposed to 4 ppm fluoride and higher (Li et al. 2001; Sowers et al. 1986, 1991); the hip fracture incidence in the highly exposed community was compared to the rates in communities with approximately 1 ppm fluoride in the water. Significant increases in the occurrence of nonvertebral fractures were also observed in postmenopausal women ingesting sodium fluoride (34 mg fluoride/kg/day) for the treatment of osteoporosis (Riggs et al. 1990, 1994). This result was not found in another study of postmenopausal women with spinal osteoporosis treated with 34 mg fluoride/kg/day as sodium fluoride (Kleerekoper et al. 1991). 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 (Haguenauer et al. 2000).

Agency Contact (Chemical Manager): Carolyn A. Tylenda, D.M.D., Ph.D., Dennis Jones, D.V.M..

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Hydrogen Fluoride
CAS Number: 7664-39-3
Date: December 1, 2003
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to Figure: 6
Species: Humans

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

Reference: Lund K, Ekstrand J, Poe J, et al. 1997. Exposure to hydrogen fluoride: an experimental study in humans of concentrations of fluoride in plasma, symptoms, and lung function. Occup Environ Med 54:32-37.

Lund K, Refsnes M, Sandstrøm T, et al. 1999. Increased CD3 positive cells in bronchoalveolar lavage fluid after hydrogen fluoride inhalation. Scand J Work Environ Health 25:326-334.

Experimental design (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Groups of 7-9 healthy, nonsmoking males (21–44 years of age) were exposed to 0.2-0.6, 0.7–2.4, or 2.5–5.2 mg/m³ hydrogen fluoride for 1 hour. For the last 15 minutes of the exposure, the subjects performed an ergometric test at a fixed work load of 75W. Bronchoalveolar lavage (BAL) was performed 3 weeks prior to exposure and 24 hours after exposure. Lung function tests were performed immediately before exposure, every 15 minutes during exposure, at exposure termination, 30 minutes after exposure, and 1, 2, 3, and 4 hours after exposure. Symptom surveys were completed before exposure initiation, after 30 minutes of exposure, at exposure termination, and 4 and 24 hours after exposure. Eye, upper airway (nose and throat), and lower airway symptoms were scored based on a 5 point scale with 5 being the most severe.

The midpoint of the range of concentrations was used to calculate ppm levels: 0.4 mg hydrogen fluoride/m³ x 24.45/20 x 19/20 = 0.5 ppm fluoride; 1.7 mg/m³ = 1.9 ppm, 3.9 mg/m³ = 4.5 ppm

Effects noted in study and corresponding concentrations: No significant exposure-related alterations in lung function (FEV1 or FVC) were observed and no significant correlations between plasma fluoride concentrations and FVC or FEV1 were found. Increases (as compared to scores prior to exposure) in upper airway symptom scores were observed in the low ($p=0.06$) and high ($p=0.02$) concentration groups and for all concentrations combined ($p<0.001$); similarly, total symptom scores were significantly ($p<0.04$) increased in the low and high concentration groups and all groups combined. The severity of the upper airway score was low (scores of 1–3) in the low exposure group. All subjects reported a change in the upper airway symptom score in the high concentration group; four subjects scored the symptoms as low and three scored them as high. A significant increase in eye symptom score was also observed in all groups combined, but not for individual exposure level groups. The effect of hydrogen fluoride exposure was assessed by comparing the before and after exposure BAL fluid. Significant increases in the percentage of CD3-positive cells were found in the bronchial portion of the mid- and high-dose group and in the bronchoalveolar portion of the high-dose group. A significant increase in the percentage of lymphocytes in the bronchial and bronchoalveolar portions in the mid-concentration group was observed. A significant correlation between the individual changes in the percentage of CD3-positive cells and the

changes in the percentage of lymphocytes from the bronchoalveolar portion was also observed. Significant increases in myeloperoxidase and interkeukin-6 levels were found in the high dose group.

Concentration and end point used for MRL derivation: The MRL is based on a minimal LOAEL of 0.5 ppm fluoride as hydrogen fluoride for upper respiratory tract irritation.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[ ] 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:

Was a conversion used from intermittent to continuous exposure? No. Data on nasal irritation from the Largent (1960) report, the Lund et al. (2002) study, and the intermediate-duration study by Largent (1960) provide suggestive evidence that the severity of nasal irritation does not increase with increasing exposure duration. These three studies identified similar LOAEL values for different exposure durations: 3.22 ppm 6 hours/day for 10 days (Largent 1960), 3.8 ppm 1 hour/day for 1 day (Lund et al. 2002), and 2.98 ppm 6 hours/day, 6 days/week for 15–50 days. Thus, time scaling was not used to derive the acute MRL.

Other additional studies or pertinent information that lend support to this MRL: The respiratory tract appears to be the primary target of hydrogen fluoride toxicity. Upper respiratory tract irritation and inflammation and lower respiratory tract inflammation have been observed in several human studies. Nasal irritation was reported by one subject exposed to 3.22 ppm fluoride as hydrogen fluoride 6 hours/day for 10 days (Largent 1960). Very mild to moderate upper respiratory symptoms were reported by healthy men exposed to 0.5 ppm fluoride as hydrogen fluoride for 1 hour (Lund et al. 1997). At higher concentrations, 4.2–4.5 ppm fluoride as hydrogen fluoride for 1 hour, more severe symptoms of upper respiratory irritation were noted (Lund et al. 1997, 2002). In subjects exposed to 4.2 ppm for 1 hour, analysis of nasal lavage fluid provided suggestive evidence that hydrogen fluoride induces an inflammatory response in the nasal cavity (Lund et al. 2002). Similarly, bronchoalveolar lavage fluid analysis revealed suggestive evidence of bronchial inflammation in another study of subjects exposed to 1.9 ppm fluoride as hydrogen fluoride for 1 hour (Lund et al. 1999); no alterations were observed at 0.5 ppm. Respiratory effects have also been reported in rats acutely exposed to hydrogen fluoride. Mild nasal irritation was observed during 60-minute exposure to 120 ppm fluoride (Rosenholtz et al. 1963), and respiratory distress was observed at 2,310, 1,339, 1,308, and 465 ppm fluoride for 5, 15, 30, or 60 minutes, respectively (Rosenholtz et al. 1963). 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 (Dalbey et al. 1998a, 1998b). These effects were not observed when the tracheal cannula was not used.

The Lund et al. (1997, 1999) study was selected as the basis of the acute-duration inhalation MRL for hydrogen fluoride. As reported in the 1997 publication, a trend ($p=0.06$) toward increased upper respiratory tract symptom score, as compared to pre-exposure symptom scores, was observed at the lowest concentration tested (0.5 ppm). A significant increase in the total symptom score was also

observed at this concentration. No significant alterations in symptom scores were observed at the mid concentration (1.9 ppm), and increases in upper respiratory and total symptom scores were observed at the high concentration (4.5 ppm). Suggestive evidence of bronchial inflammation was also observed at ≥1.9 ppm fluoride (Lund et al. 1999), although no alterations in lower respiratory tract symptoms (Lund et al. 1997) or lung function (Lund et al. 1997) were observed at any of the tested concentrations.

Agency Contact (Chemical Manager): Carolyn A. Tylenda, D.M.D., Ph.D., Dennis Jones, D.V.M.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Fluorine
CAS Number: 7782-41-4
Date: December 1, 2003
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to Figure: 6
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 5 minutes, 50 ppm for 3 minutes, 67 ppm for 1 minute, 78 ppm for 1 minute, and 100 ppm for 0.5 or 1 minute. The fluorine was administered via a mask that covered the eyes and nose; the subjects could remove the mask from their face and could breathe fresh air via their mouth. 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 or eye irritation was noted by subjects exposed to 10 ppm for 3, 5, or 15 minutes; it was also noted that the 15-minute exposure did not result in respiratory tract irritation. Eye irritation was observed at ≥23 ppm; nose irritation at ≥50 ppm, and skin irritation at ≥78 ppm. 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 and LOAEL of 23 ppm fluorine for irritation in humans.

[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 15-minute exposure duration was adjusted for a continuous 24-hour exposure using the following equation:

10 ppm x 0.25 hours/24 hours = 0.1 ppm

The study authors noted that exposure to 10 ppm for 3–5 minutes every 15 minutes over a 2- or 3-day period resulted slight irritation to the eyes and skin, but no other subjective effects (no additional details on this study were provided). These data are suggestive that the toxicity of fluorine may be dependent on concentration and duration of exposure. Thus, it is appropriate to adjust for continuous exposure.

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.

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APPENDIX A

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 that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and 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.

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, ATSDR has derived 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.

MRLs 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 that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

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 no-observed-adverse-effect level (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 levels of significant exposure (LSE) Tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures 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, 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 NOAELs, 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 Sample LSE Table 3-1 (page B-6)

(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. Typically 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 two "18r" data points in sample 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/day, 5 days/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, one systemic effect (respiratory) was investigated.

(8) NOAEL. A 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 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 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 that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

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, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38r is one of three studies for which CELs were derived. The diamond symbol refers to a CEL 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

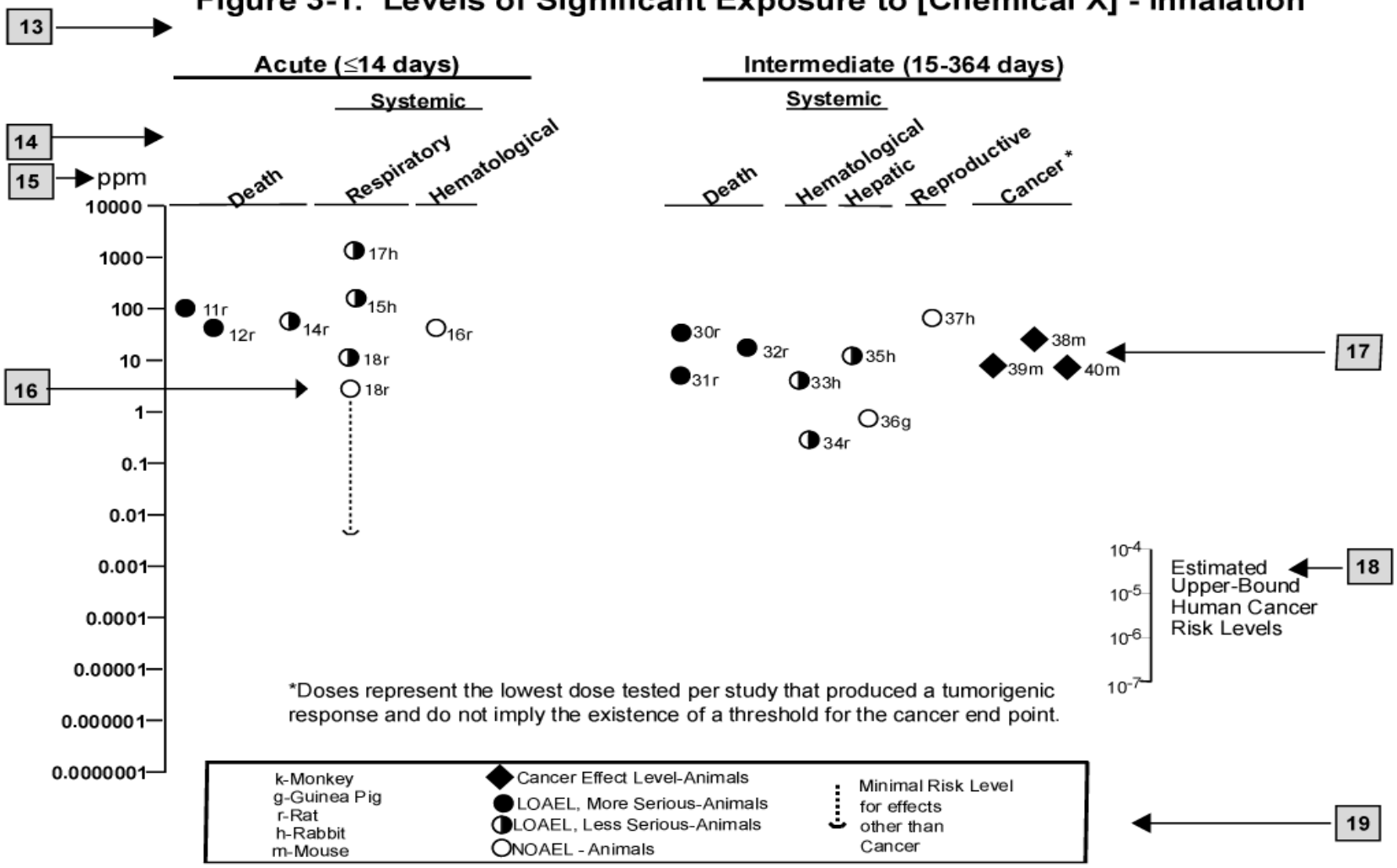
1 → TABLE 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer					11 ↓		
	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

12 → a The number corresponds to entries in Figure 3-1.
b Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ 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
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
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
BMD	benchmark dose
BMR	benchmark response
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
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
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
FR	*Federal Register*
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal

MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
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
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
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
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
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
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized 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 carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	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. FLUORIDE AND DENTAL CARIES

Dental caries or tooth decay is a progressively destructive disease of the tooth caused by cariogenic bacteria. These bacteria, which reside in dental plaque, colonize on tooth surfaces and produce polysaccharides that enhance adherence of the plaque to the tooth enamel. Once plaque is formed, the bacteria on the teeth produce an enzyme that promotes erosion of the enamel by converting sugars and other fermentable carbohydrates into acids. The acids dissolve the minerals (calcium and phosphorus) in the tooth enamel in a process known as demineralization (DHHS 2001b).

Several studies conducted by Dean and associates in the 1930s and 1940s demonstrated a relationship between the levels of naturally-occurring fluoride in drinking water and the prevalence of dental caries (Dean 1938; Dean et al. 1939, 1941, 1942). Children living in communities with high levels of fluoride in the drinking water had lower occurrences of dental caries. This relationship between fluoride and dental caries prompted the city of Grand Rapids, Michigan to implement a water fluoridation program in 1945. Studies conducted in some of the earliest cities to adopt a fluoridation program reported dramatic decreases in the occurrence of dental caries (Ast et al. 1951; Dean et al. 1950; Hill et al. 1951; Hutton et al. 1951). The prevalence of dental caries in children living in communities with fluoridated water was 50–70% lower than in children living in areas without fluoridated water. Surveys conducted after the late 1980s found smaller differences; the occurrence of dental caries was 9–25% lower in communities with fluoridated water as compared to communities without fluoridated water (Brunelle and Carlos 1990; DeLiefde 1998; Eklund et al. 1987; Englander and DePaola 1979; Jackson et al. 1995; Selwitz et al. 1995). In one study, no significant differences in the occurrence of dental caries was found in school-aged children 5–17 years old (Yiamouyiannis 1990); however, when just 5 year olds were examined, the incidence of dental caries was 42% lower in children with lifetime exposure to fluoridated water and 24% lower in children exposed to fluoridated water for only a portion of their lifetime. Several studies have also examined the impact of termination of a water fluoridation program on the incidence of dental caries. Conflicting results have been reported. Some studies found increases in dental caries occurrence (Attwood and Blinkhorn 1991; Stephen et al. 1987; Thomas et al. 1995), some found no change in the occurrence of dental caries (Burt et al. 2000; Kalsbeek et al. 1993; Künzel and Fischer 1997; Seppä et al. 2000; Stephen et al. 1987), and other studies found decreases in dental caries occurrence (Künzel and Fischer 2000; Künzel et al. 2000; Maupomé et al. 2001). A meta-analysis of 26 studies examined the relationship between water fluoridation and prevalence of dental caries or the change in decayed, missing, and filled teeth (DMFT) (McDonagh et al. 2000). In 19 of the 30 analyses conducted, a significant increase in the prevalence of children without dental caries was found in the fluoridated areas compared

to non-fluoridated areas. Additionally, 15 of the 16 analyses found a significant increase in the mean change in DMFT in fluoridated water areas (levels of DMFT declined in response to fluoridation).

The decline or stabilization of the occurrence of dental caries in the absence of water fluoridation has been attributed to a number of factors (Horowitz 1996), including diffusion of effects of fluoridated drinking water, dilution effects from other sources of fluoride on the measurement of effectiveness of community water fluoridation, and improved dental care. The diffusion effect occurs when residents of communities without fluoridated water consume products manufactured or bottled in areas with fluoridated water (thus fluoride enters the foodstuff) or attend schools in areas with fluoridated water. An often cited example of the diffusion effect is the 1986–1987 NIDR survey of dental health status of U.S. school children (Brunelle and Carlos 1990). In the Pacific region, which has a low percentage of communities with fluoridated water (19%), children living in area with nonfluoridated water have 61% higher dental caries score as compared to children living in areas with fluoridated water. In contrast, in the Midwest region with a high percentage of communities with fluoridated water (74%), there is no difference in dental caries scores between fluoridated and nonfluoridated areas. The dilution effect is due to the development and use of other fluoride agents, including fluoride supplements, fluoride solutions, gels, and varnishes used by dental professionals, fluoridated toothpaste, and fluoride mouthwash. The use of the fluoride products that provide protection from dental decay diminishes the difference in the levels of dental decay between fluoridated and nonfluoridated communities (Ripa 1993).

The primary mechanism by which fluoride prevents the occurrence of dental caries is through its influence on the demineralization and remineralization process (Featherstone 1999; Koulourides 1990; Ten Cate 1999). The acid produced from the metabolism of sugars and fermentable carbohydrates by cariogenic bacteria in plaque begins to dissolve or demineralize the enamel crystal surface of the tooth resulting in the loss of calcium, phosphate, and carbonate from the tooth enamel. The increased acid production results in a decrease in plaque pH and the release of fluoride from the dental plaque. This fluoride, along with calcium and phosphate, is incorporated into the apatite molecule to form fluor(hydroxyl)apatite. In the presence of fluoride, cycles of partial demineralization and then remineralization will create apatite, which has less carbonate, more fluoride, and is less soluble. Fluor(hydroxyl)apatite, which has high levels of fluoride and low levels of carbonate, is more acid resistant (Chow 1990; Ericsson 1977; Featherstone 1999; Kidd et al. 1980; Ten Cate 1999; Thylstrup 1990; Thylstrup et al. 1979). When the beneficial effects of fluoride on caries prevention was first discovered, it was believed that the incorporation of the fluoride into developing enamel resulted in improved enamel and dental caries prevention (Dean et al. 1935; McClure and Likins 1951). However,

more recent data suggest that fluoride works primarily after teeth have erupted (Clarkson et al. 1996). In a fluoride-rich environment, demineralization and remineralization cycling, which occurs throughout the lifetime of the tooth, will result in teeth that are more resistant to cariogenic bacterial damage. Another mechanism in which fluoride prevents dental caries is via a direct effect on cariogenic bacterial metabolism. There are *in vitro* data that demonstrate that fluoride can inhibit bacterial metabolism of carbohydrates, which results in a decreased production of acids (Bowden 1990; Bowden et al. 1982; Marquis 1990; Rosen et al. 1978). However, it is likely that this would occur at fluoride levels that far exceed those present in the mouth (Geddes and Bowen 1990).

Based on this relationship between fluoride and dental caries prevention, the Institute of Medicine (IOM 1997) and the World Health Organization (WHO 2002) consider fluoride to be an essential dietary element. The Institute of Medicine has derived adequate intake levels (AIs) ranging from 0.01 to 4 mg/day (IOM 1997). The AIs for each age group are presented below:

Age Range	Adequate Intake Level (mg/day)
0–6 months	0.01
6–12 months	0.5
1–3 years	0.7
4–8 years	1
9–13 years (males and females)	2
14–18 years (males and females)	3
>18 years (males)	4
>18 years (females)	3

Expert panels convened by the U.S. Department of Health and Human Services (DHHS 1991, 2000, 2001b) and the World Health Organization (WHO 1994) support optimal fluoridation of drinking water. A work group assembled by the Centers for Disease Control and Prevention (DHHS 2001b) made the following recommendation:

> "Because frequent exposure to small amounts of fluoride each day will best reduce the risk for dental caries in all age groups, the work group recommends that all persons drink water with an optimal fluoride concentration and brush their teeth twice daily with fluoride toothpaste. For persons at high risk of dental caries, additional fluoride measures might be needed. Measured use of fluoride modalities is particularly appropriate during the time of anterior tooth enamel development (i.e., age <6 years)."