TOXICOLOGICAL PROFILE FOR ALUMINUM

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

September 2008

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

A Toxicological Profile for Aluminum, Draft for Public Comment, was released in September 2006. 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:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine/Applied Toxicology Branch
1600 Clifton Road NE
Mailstop F-32
Atlanta, Georgia 30333

This page is intentionally blank.

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

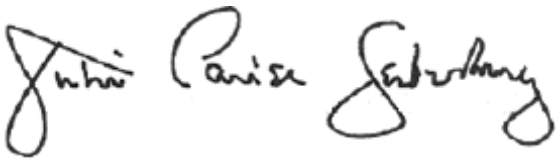
(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

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.

Howard Frumkin M.D., Dr.P.H.
Director
National Center for Environmental Health/
Agency for Toxic Substances and
Disease Registry



Julie Louise Gerberding, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

*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 December 7, 2005 (70 FR 72840). 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); October 21, 1999(64 FR 56792); October 25, 2001 (66 FR 54014) and November 7, 2003 (68 FR 63098). 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: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY) ***Fax:*** (770) 488-4178
E-mail: cdcinfo@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, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHOR(S):

Sam Keith, M.S.
Dennis Jones, D.V.M.
Zemoria Rosemond, B.A.
ATSDR, Division of Toxicology and Environmental Medicine, Atlanta, Georgia

Lisa Ingerman, Ph.D., DABT
Lara Chappell, Ph.D.
Syracuse Research Corporation, North Syracuse, New York

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 Applied Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

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

This page is intentionally blank.

PEER REVIEW

A peer review panel was assembled for aluminum. The panel consisted of the following members:

1. Dr. Jerrold Abraham, Professor of Family Medicine, Upstate Medical University, Syracuse, New York,

2. Dr. Michael Aschner, Director, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee, and

3. Dr. Robert Yokel, Professor, Division of Pharmaceutical Sciences, University of Kentucky, College of Pharmacy, Lexington, Kentucky.

These experts collectively have knowledge of aluminum'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.

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.

This page is intentionally blank.

CONTENTS

APPENDICES

LIST OF FIGURES

This page is intentionally blank.

LIST OF TABLES

This page is intentionally blank.

1. PUBLIC HEALTH STATEMENT

This public health statement tells you about aluminum and the effects of exposure to it.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Aluminum (in some form, e.g., in compounds with other elements such as oxygen, sulfur, or phosphorus) has been found at elevated levels in at least 596 of the 1,699 current or former NPL sites. Although the total number of NPL sites evaluated for this substance is not known, the possibility exists that the number of sites at which aluminum is found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to this substance at high levels may be harmful.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be 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. However, it should be noted that aluminum is a very abundant and widely distributed element and will be found in most rocks, soils, waters, air, and foods. You will always have some exposure to low levels of aluminum from eating food, drinking water, and breathing air.

If you are exposed to aluminum, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS ALUMINUM?

Description	Aluminum is the most abundant metal in the earth's crust and it is widely distributed. Aluminum is a very reactive element and is never found as the free metal in nature. It is found combined with other elements, most commonly with oxygen, silicon, and fluorine. These chemical compounds are commonly found in soil, minerals (e.g., sapphires, rubies, turquoise), rocks (especially igneous rocks), and clays. Aluminum as the metal is obtained from aluminum-containing minerals, primarily bauxite. Aluminum metal is light in weight and silvery-white in appearance.
Uses • **Aluminum metal**	Aluminum is used to make beverage cans, pots and pans, airplanes, siding and roofing, and foil. Powdered aluminum metal is often used in explosives and fireworks.
• **Aluminum compounds**	Aluminum compounds are used in many diverse and important industrial applications such as alums (aluminum sulfate) in water-treatment and alumina in abrasives and furnace linings.
• **Consumer products**	Aluminum is found in consumer products including: • antacids • astringents • buffered aspirin • food additives • antiperspirants • cosmetics

For more information on the physical and chemical properties of aluminum and its production, disposal, and use, see Chapters 4 and 5.

1.2 WHAT HAPPENS TO ALUMINUM WHEN IT ENTERS THE ENVIRONMENT?

Sources	Aluminum occurs naturally in soil, water, and air. High levels in the environment can be caused by the mining and processing of aluminum ores or the production of aluminum metal, alloys, and compounds. Small amounts of aluminum are released into the environment from coal-fired power plants and incinerators.
Break down • **Air** • **Water and soil**	Aluminum cannot be destroyed in the environment. It can only change its form or become attached or separated from particles. Aluminum particles in air settle to the ground or are washed out of the air by rain. However, very small aluminum particles can stay in the air for many days. Most aluminum-containing compounds do not dissolve to a large extent in water unless the water is acidic or very alkaline.

For more information on aluminum in the environment, see Chapter 6.

1.3 HOW MIGHT I BE EXPOSED TO ALUMINUM?

Food—primary source of exposure	Unprocessed foods like fresh fruits, vegetables, and meat contain very little aluminum. Aluminum compounds may be added during processing of foods, such as: • flour • baking powder • coloring agents • anticaking agents An average adult in the United States eats about 7–9 mg of aluminum per day in their food.
Air	Most people take in very little aluminum from breathing. Levels of aluminum in the air generally range from 0.005 to 0.18 micrograms per cubic meter ($\mu g/m^3$), depending on location, weather conditions, and type and level of industrial activity in the area. Most of the aluminum in the air is in the form of small suspended particles of soil (dust). Aluminum levels in urban and industrial areas may be higher and can range from 0.4 to 8.0 $\mu g/m^3$.

Water and soil	The concentration of aluminum in natural waters (e.g., ponds, lakes, streams) is generally below 0.1 milligrams per liter (mg/L). People generally consume little aluminum from drinking water. Water is sometimes treated with aluminum salts while it is processed to become drinking water. But even then, aluminum levels generally do not exceed 0.1 mg/L. Several cities have reported concentrations as high as 0.4–1 mg/L of aluminum in their drinking water.
Consumer Products	People are exposed to aluminum in some cosmetics, antiperspirants, and pharmaceuticals such as antacids and buffered aspirin. • Antacids have 300–600 mg aluminum hydroxide (approximately 104–208 mg of aluminum) per tablet, capsule, or 5 milliliter (mL) liquid dose. Little of this form of aluminum is taken up into the bloodstream. • Buffered aspirin may contain 10–20 mg of aluminum per tablet • Vaccines may contain small amounts of aluminum compounds, no greater than 0.85 mg/dose.

For more information on how you might be exposed to aluminum, see Chapter 6.

1.4 HOW CAN ALUMINUM ENTER AND LEAVE MY BODY?

Enter your body	
• **Inhalation**	A small amount of the aluminum you breathe will enter your body through your lungs.
• **Ingestion**	A very small amount of the aluminum in food or water will enter your body through the digestive tract. An extremely small amount of the aluminum found in antacids will be absorbed.
• **Dermal contact**	A very small amount may enter through your skin when you come into contact with aluminum.
Leave your body	Most aluminum in food, water, and medicines leaves your body quickly in the feces. Much of the small amount of aluminum that does enter the bloodstream will quickly leave your body in the urine.

For more information on how aluminum enters and leaves the body, see Chapter 3.

1.5 HOW CAN ALUMINUM AFFECT MY HEALTH?

This section looks at studies concerning potential health effects in animal and human studies.

Workers **• Inhalation**	Workers who breathe large amounts of aluminum dusts can have lung problems, such as coughing or changes that show up in chest X-rays. The use of breathing masks and controls on the levels of dust in factories have largely eliminated this problem. Some workers who breathe aluminum-containing dusts or aluminum fumes have decreased performance in some tests that measure functions of the nervous system.
Humans **• Oral**	Oral exposure to aluminum is usually not harmful. Some studies show that people exposed to high levels of aluminum may develop Alzheimer's disease, but other studies have not found this to be true. We do not know for certain that aluminum causes Alzheimer's disease. Some people who have kidney disease store a lot of aluminum in their bodies. The kidney disease causes less aluminum to be removed from the body in the urine. Sometimes, these people developed bone or brain diseases that doctors think were caused by the excess aluminum. Although aluminum-containing over the counter oral products are considered safe in healthy individuals at recommended doses, some adverse effects have been observed following long-term use in some individuals.
Laboratory animals **• Inhalation** **• Oral**	Lung effects have been observed in animals exposed to aluminum dust. Scientists do not know if these effects are dur to the aluminum or to the animals breathing in a lot of dust. Studies in animals show that the nervous system is a sensitive target of aluminum toxicity. Obvious signs of damage were not seen in animals after high oral doses of aluminum. However, the animals did not perform as well in tests that measured the strength of their grip or how much they moved around.

Further information on the health effects of aluminum in humans and animals can be found in Chapters 2 and 3.

1.6 HOW CAN ALUMINUM AFFECT CHILDREN?

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

Effects in children	Brain and bone disease caused by high levels of aluminum in the body have been seen in children with kidney disease. Bone disease has also been seen in children taking some medicines containing aluminum. In these children, the bone damage is caused by aluminum in the stomach preventing the absorption of phosphate, a chemical compound required for healthy bones. Aluminum is found in breast milk, but only a small amount of this aluminum will enter the infant's body through breastfeeding. Typical aluminum concentrations in human breast milk range from 0.0092 to 0.049 mg/L. Aluminum is also found in soy-based infant formula (0.46–0.93 mg/L) and milk-based infant formula (0.058–0.15 mg/L).
Birth defects	We do not know if aluminum will cause birth defects in people. Birth defects have not been seen in animals. Very young animals appeared weaker and less active in their cages and some movements appeared less coordinated when their mothers were exposed to large amounts of aluminum during pregnancy and while nursing. In addition, aluminum also affected the animal's memory. These effects are similar to those that have been seen in adults. It does not appear that children are more sensitive than adult animals.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO ALUMINUM?

Food	You cannot avoid exposure to aluminum because it is so common and widespread in the environment. Exposure to the levels of aluminum that are naturally present in food and water and the forms of aluminum that are present in dirt and aluminum pots and pans are not considered to be harmful. Eating large amounts of processed food containing aluminum additives or frequently cooking acidic foods in aluminum pots may expose a person to higher levels of aluminum than a person who generally consumes unprocessed foods and uses pots made of other materials (e.g., stainless steel or glass). However, aluminum levels found in processed foods and foods cooked in aluminum pots are generally considered to be safe.

Consumer products	Limiting your intake of large quantities of aluminum-containing antacids and buffered aspirin and using these medications only as directed is the best way to limit exposure to aluminum from these sources. As a precaution, such products should have child-proof caps or should be kept out of reach of children so that children will not accidentally injest them.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO ALUMINUM?

Detecting exposure	All people have small amounts of aluminum in their bodies. It can be measured in the blood, bones, feces, or urine.
Measuring exposure	Urine and blood aluminum measurements can tell you whether you have been exposed to larger-than-normal amounts of aluminum, especially for recent amounts. Measuring bone aluminum can also indicate exposure to high levels of aluminum, but this requires a bone biopsy.

Information about tests for detecting aluminum in the body is given in Chapters 3 and 7.

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

Regulations and recommendations can be expressed as “not-to-exceed” levels, that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value that is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are also updated periodically 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 aluminum include the following:

Drinking water	The EPA has recommended a Secondary Maximum Contaminant Level (SMCL) of 0.05–0.2 mg/L for aluminum in drinking water. The SMCL is not based on levels that will affect humans or animals. It is based on taste, smell, or color.
Consumer products	The FDA has determined that aluminum used as food additives and medicinals such as antacids are generally safe. FDA set a limit for bottled water of 0.2 mg/L.
Workplace air	OSHA set a legal limit of 15 mg/m^3 (total dust) and 5 mg/m^3 (respirable fraction) aluminum in dusts averaged over an 8-hour work day.

For more information on regulations and advisories, 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 contact ATSDR at the address and phone number below.

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

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and technical assistance number at 1-800-CDC-INFO (1-800-232-4636), by e-mail at cdcinfo@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

1. PUBLIC HEALTH STATEMENT

This page is intentionally blank.

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO ALUMINUM IN THE UNITED STATES

Aluminum is ubiquitous; the third most common element of the earth's crust. It is naturally released to the environment from the weathering of rocks and volcanic activity. Human activities such as mining also result in the release of aluminum to the environment. Aluminum levels in environmental media vary widely depending upon the location and sampling site. In general, background levels of aluminum in the atmosphere are low, typically ranging from about 0.005 to 0.18 μg/m^3. Much higher levels are routinely observed in urban and industrial locations. Aluminum levels in surface water is usually very low (<0.1 mg/L); however, in acidic waters or water high in humic or fulvic acid content, the concentration of soluble aluminum increases due to the increased solubility of aluminum oxide and aluminum salts. Its concentration in soils varies widely, ranging from about 7 to over 100 g/kg.

In the environment, aluminum exists in only one oxidation state (+3), and does not undergo oxidation-reduction reactions. It can react with other matter in the environment to form various complexes. The fate and transport of aluminum is largely controlled by environmental factors such as pH, salinity, and the presence of various species with which it may form complexes. In general, the solubility and mobility of aluminum in soil is greatest when the soil is rich in organic matter capable of forming aluminum-organic complexes and when the pH is low, such as in areas prone to acid rain or in acidic mine tailings.

The general population is primarily exposed to aluminum through the consumption of food items, although minor exposures may occur through ingestion of aluminum in drinking water and inhalation of ambient air. Aluminum found in over-the-counter medicinals, such as antacids and buffered aspirin, is used as a food additive, and is found in a number of topically applied consumer products such as antiperspirants, and first aid antibiotic and antiseptics, diaper rash and prickly heat, insect sting and bite, sunscreen and suntan, and dry skin products. The concentration of aluminum in foods and beverages varies widely, depending upon the food product, the type of processing used, and the geographical areas in which food crops are grown (see Section 6.4). Based on the FDA's 1993 Total Diet Study dietary exposure model and the 1987–1988 U.S. Department of Agriculture (USDA) Nationwide Food Consumption Survey, the authors estimated daily aluminum intakes of 0.10 mg Al/kg/day for 6–11-month-old infants; 0.30–0.35 mg Al/kg/day for 2–6-year-old children; 0.11 mg Al/kg/day for 10-year-old children; 0.15–0.18 mg Al/kg/day for 14–16-year-old males and females; and 0.10–0.12 mg Al/kg/day for adult (25–30- and 70+-year-old) males and females. Users of aluminum-

containing medications who are healthy (i.e., have normal renal function) can ingest much larger amounts of aluminum than in the diet, possibly as high as 12–71 mg Al/kg/day from antacid/anti-ulcer products and 2–10 mg Al/kg/day from buffered analgesics when taken at recommended dosages.

Gastrointestinal absorption of aluminum is low, generally in the range of 0.1–0.4% in humans, although absorption of particularly bioavailable forms such as aluminum citrate may be on the order of 0.5–5%. Although large bolus doses of as much as half a gram of aluminum as aluminum hydroxide throughout the day can be ingested during antacid therapy, absorption of aluminum hydroxide is usually $\leq$0.01% of the intake amount. Bioavailability of aluminum varies depending mainly on the chemical form of the ingested compound (i.e., type of anion) and the concurrent exposure to dietary chelators such as citric acid, ascorbic acid, or lactic acid. The total body burden of aluminum in healthy human subjects is approximately 30–50 mg. Normal levels of aluminum in serum are approximately 1–3 μg/L. Of the total body burden of aluminum, about one-half is in the skeleton, and about one-fourth is in the lungs.

2.2 SUMMARY OF HEALTH EFFECTS

There are numerous studies that have examined aluminum's potential to induce toxic effects in humans exposed via inhalation, oral, or dermal exposure. Most of these findings are supported by a large number of studies in laboratory animals. Occupational exposure studies and animal studies suggest that the lungs and nervous system may be the most sensitive targets of toxicity following inhalation exposure. Respiratory effects, in particular impaired lung function and fibrosis, have been observed in workers exposed to aluminum dust or fumes; however, this has not been consistently observed across studies and it is possible that co-exposure to other compounds contributed to observed effects. Respiratory effects (granulomatous lesions) have also been observed in rats, hamsters, and guinea pigs. There is concern that these effects are due to dust overload rather than a direct effect of aluminum in lung tissue. Occupational studies in workers exposed to aluminum dust in the form of McIntyre powder, aluminum dust and fumes in potrooms, and aluminum fumes during welding provide suggestive evidence that there may be a relationship between chronic aluminum exposure and subclinical neurological effects such as impairment on neurobehavioral tests for psychomotor and cognitive performance and an increased incidence of subjective neurological symptoms. With the exception of some isolated cases, inhalation exposure has not been associated with overt symptoms of neurotoxicity. A common limitation of these occupational exposure studies is that aluminum exposure has not been well characterized. The available animal inhalation studies are inadequate for assessing the potential for aluminum-induced neurotoxicity because

the only neurological end points examined were brain weight and histology of the brain; no function tests were performed.

There is limited information on aluminum toxicity following dermal exposure. Application of aluminum compounds to the skin, such as aluminum chloride in ethanol or alum, may cause rashes in some people. Skin damage has been observed in mice, rabbits, and pigs exposed to aluminum chloride or aluminum nitrate, but not following exposure to aluminum sulfate, aluminum hydroxide, aluminum acetate, or aluminum chlorhydrate.

There is a fair amount of human data on the toxicity of aluminum following oral exposure. However, the preponderance of human studies are in patients with reduced renal function who accumulated aluminum as a result of long-term intravenous hemodialysis therapy with aluminum-contaminated dialysis fluid and, in many cases, concurrent administration of high oral doses of aluminum to regulate phosphate levels (i.e., reduce uptake of phosphate by binding it in the gut) and have limited usefulness in predicting toxicity in the general population because the very large aluminum exposure levels and impaired renal function results in aluminum accumulation. Dialysis encephalopathy syndrome (also referred to as dialysis dementia) can result from this accumulation of aluminum in the brain. Dialysis encephalopathy is a degenerative neurological syndrome, characterized by the gradual loss of motor, speech, and cognitive functions. Another neurological effect that has been proposed to be associated with aluminum exposure is Alzheimer's disease. Although a possible association was proposed over 40 years ago, this association is still highly controversial and there is little consensus regarding current evidence. A number of studies have found weak associations between living in areas with elevated aluminum levels in drinking water and an increased risk (or prevalence) of Alzheimer's disease; other studies have not found significant associations. In contrast, no significant associations have been found between tea consumption or antacid use and the risk of Alzheimer's disease; although the levels of aluminum in tea and antacids are very high compared to drinking water, aluminum from these sources is poorly absorbed. The available data do not suggest that aluminum is a causative agent of Alzheimer's disease; however, it is possible that it may play a role in the disease development.

Aluminum is found in several ingested over-the-counter products such as antacids and buffered aspirin; clinical studies on health effects of aluminum medicinals in people with normal renal function have been identified. These aluminum-containing products are assumed to be safe in healthy individuals at recommended doses based on historical use. The assumed safety of aluminum is also partly due to the generally regarded as safe (GRAS) status of aluminum-containing food additives. However, there is

some indication that adverse effects can result from long-term use of aluminum-containing medications in some healthy individuals. There are a number of case reports of skeletal changes (e.g., osteomalacia) in adults and children with normal kidney function due to long-term antacid use for the treatment of gastrointestinal disorders. These skeletal effects are secondary to hypophosphatemia and phosphate depletion caused by aluminum impairing phosphorus absorption by binding with dietary phosphorus.

There is a rather extensive database on the oral toxicity of aluminum in animals. These studies clearly identify the nervous system as the most sensitive target of aluminum toxicity and most of the animal studies have focused on neurotoxicity and neurodevelopmental toxicity. Other adverse effects that have been observed in animals orally exposed to aluminum include impaired erythropoiesis in rats exposed to 230 mg Al/kg/day and higher, erythrocyte damage (as evidenced by decreases in hemoglobin, hematocrit, and erythrocyte osmotic fragility, and altered erythrocyte morphology) in rats exposed to 230 mg Al/kg/day and higher, increased susceptibility to infection in mouse dams exposed to 155 mg Al/kg/day, delays in pup maturation following exposure of rats to 53 mg Al/kg/day, and decreases in pup body weight gain in rats and mice exposed to 103 mg Al/kg/day and higher.

Neurodegenerative changes in the brain, manifested as intraneuronal hyperphosphorylated neuro-filamentous aggregates, is a characteristic response to aluminum in certain species and nonnatural exposure situations generally involving direct application to brain tissue, particularly intracerebral and intracisternal administration and *in vitro* incubation in rabbits, cats, ferrets, and nonhuman primates. Oral studies in rats and mice have not found significant histopathological changes in the brain under typical exposure conditions; however, altered myelination was found in the spinal cord of mouse pups exposed to 330 mg Al/kg/day on gestation day 1 through postnatal day 35. Overt signs of neurotoxicity are rarely reported at the doses tested in the available animal studies ($\leq$330 mg Al/kg/day for bioavailable aluminum compounds); rather, exposure to these doses is associated with subtle neurological effects detected with neurobehavioral performance tests. Significant alterations in motor function, sensory function, and cognitive function have been detected following exposure to adult or weanling rats and mice or following gestation and/or lactation exposure of rats and mice to aluminum lactate, aluminum nitrate, and aluminum chloride. The most consistently affected performance tests were forelimb and/or hindlimb grip strength, spontaneous motor activity, thermal sensitivity, and startle responsiveness. Significant impairments in cognitive function have been observed in some studies, although this has not been found in other studies even at higher doses. Adverse neurological effects have been observed in rats and mice at doses of 100–200 mg Al/kg/day and neurodevelopmental effects have been observed in rats and mice at doses of 103–330 mg Al/kg/day.

A number of human studies have examined the occurrence of cancer among aluminum industry workers and found a higher-than-expected cancer mortality rate, but this is probably due to the other potent carcinogens to which they are exposed, such as polycyclic aromatic hydrocarbons (PAHs) and tobacco smoke. Available cancer studies in animals have not found biologically relevant increases in malignant tumors. The International Agency for Research on Cancer (IARC) concluded that aluminum production was carcinogenic to humans and that pitch volatiles have fairly consistently been suggested in epidemiological studies as being possible causative agents. The Department of Health and Human Services and EPA have not evaluated the human carcinogenic potential of aluminum.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for aluminum. 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.

Inhalation MRLs

No acute-, intermediate-, or chronic-duration inhalation MRLs were derived for aluminum. Results from human and animal studies suggest that the respiratory tract, particularly the lung, is a sensitive target of airborne aluminum toxicity; human studies also suggest that the nervous system may also be a target of

inhaled aluminum. Interpretation of the human data is complicated by the lack of exposure assessment and the potential for concomitant exposure to other toxic compounds. Numerous studies have found impaired lung function in a variety of aluminum workers (Abbate et al. 2003; Al-Masalkhi and Walton 1994; Bast-Pettersen et al. 1994; Bost and Newman 1993; Burge et al. 2000; Chan-Yeung et al. 1983; Herbert et al. 1982; Hull and Abraham 2002; Jederlinic et al. 1990; Korogiannos et al. 1998; Miller et al. 1984b; Radon et al. 1999; Simonsson et al. 1985; Vandenplas et al. 1998). Other effects that have been observed include occupational asthma (Abramson et al. 1989; Burge et al. 2000; Kilburn 1998; Vandenplas et al. 1998) and pulmonary fibrosis (Al-Masalkhi and Walton 1994; De Vuyst et al. 1986; Edling 1961; Gaffuri et al. 1985; Gilks and Churg 1987; Jederlinic et al. 1990; Jephcott 1948; McLaughlin et al. 1962; Mitchell et al. 1961; Musk et al. 1980; Riddell 1948; Shaver 1948; Shaver and Riddell 1947; Ueda et al. 1958; Vallyathan et al. 1982).

Acute-, intermediate-, and chronic-duration animal studies have also reported respiratory effects. These respiratory effects include increases in alveolar macrophages, granulomatous lesions in the lungs and peribronchial lymph nodes, and increases in lung weight (Drew et al. 1974; Klosterkotter 1960; Pigott et al. 1981; Steinhagen et al. 1978; Stone et al. 1979). The lung effects observed in humans and animals are suggestive of dust overload. Dust overload occurs when the volume of dust in the lungs markedly impairs pulmonary clearance mechanisms. Lung overload is not dependent on the inherent toxicity of the compound, and dust overloading has been shown to modify both the dosimetry and toxicological effects of the compound (Morrow 1988). When excessive amounts of widely considered benign dusts are persistently retained in the lungs, the resultant lung effects are similar to those observed following exposure to dusts that are highly toxic to the lungs. Because it is unclear whether the observed respiratory effects are related to aluminum toxicity or to dust overload, inhalation MRLs based on respiratory effects were not derived.

Subtle neurological effects have also been observed in workers chronically exposed to aluminum dust or fumes. These effects include impaired performance on neurobehavioral tests (Akila et al. 1999; Bast-Pettersen et al. 2000; Buchta et al. 2003, 2005; Hänninen et al. 1994; Hosovski et al. 1990; Polizzi et al. 2001; Rifat et al. 1990; Riihimäki et al. 2000; Sjögren et al. 1990) and increased reporting of subjective neurological symptoms (Bast-Pettersen et al. 1994, 2000; Hänninen et al. 1994; Hosovski et al. 1990; Iregren et al. 2001; Rifat et al. 1990; Riihimäki et al. 2000; Sim et al. 1997; Sjögren et al. 1990, 1996; White et al. 1992). Neurological exams in the available animal studies (Steinhagen et al. 1978; Stone et al. 1979) have been limited to measurement of brain weight and/or histopathology of the brain; no function tests were performed. The identification of neurotoxicity as a sensitive end point in workers

exposed to aluminum dust and fumes is well supported by a large number of animal studies reporting a variety of neurobehavioral alterations following oral exposure. However, the poor characterization of aluminum exposure in the occupational exposure studies precludes using these studies to develop an inhalation MRL for aluminum.

Oral MRLs

Data on health effects of ingested aluminum in humans are unsuitable for MRL consideration because studies have centered on specific patient populations (i.e., dialysis, neurodegenerative disease) and are not the types typically used in risk evaluation. Studies in patients with reduced renal function who accumulated aluminum as a result of long-term intravenous hemodialysis therapy with aluminum-contaminated dialysate and the use of aluminum-containing phosphate binding agents provide evidence that aluminum is an important etiologic factor in dialysis-related health disorders, particularly the neurological syndrome dialysis encephalopathy. The effects are manifested under unnatural exposure conditions in which the gastrointestinal barrier is bypassed (exposure to aluminum in dialysate fluid) and aluminum excretion is impaired by the poor renal function. There are case reports of skeletal changes (e.g., osteomalacia) consequent to long-term ingestion of antacids in healthy adults and children with normal kidney function (Carmichael et al. 1984; Chines and Pacifici 1990; Pivnick et al. 1995; Woodson 1998), but these effects are attributable to an interaction between aluminum and phosphate in the gut (aluminum binds with phosphate in the gut resulting in decreased phosphate absorption and hypophosphatemia). Although the use of aluminum medicinals in people is widespread, there are a limited number of experimental studies that examined the potential toxicity of the aluminum in these medicinals in individuals with normal renal function.

Derivation of an MRL(s) for aluminum based on animal studies is complicated by limitations in the database, particularly the lack of information on aluminum content in the base diet. As discussed in the introduction to Section 3.2.2, commercial laboratory animal feeds contain high levels of aluminum that can significantly contribute to total experimental exposure. Due to the likelihood of significant base dietary exposure to aluminum, studies with insufficient information on aluminum content in the base diet must be assumed to underestimate the actual aluminum intake. The magnitude of the underestimate can be considerable; for example, approximate feed concentrations of 250 and 350 ppm aluminum reported in some rat and mouse studies, respectively (Colomina et al. 1998; Domingo et al. 1993; Oteiza et al. 1993), are roughly equivalent to daily doses of 25 mg Al/kg/day (rats) and 68 mg Al/kg/day (mice), which represents a significant portion of the lethal dose for these species. Consequently, although studies with

inadequate data on base dietary levels of aluminum provide useful information on health effects of aluminum, no-observed-adverse-effect levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs) from these studies cannot be assumed to be accurate, are not suitable for comparing with effect levels from studies that used diets with known amounts of aluminum, and are inappropriate for MRL consideration.

The available data were considered inadequate for derivation of an acute-duration oral MRL for aluminum. Two studies were identified that provided sufficient information on the levels of aluminum in the basal diet. McCormack et al. (1979) and Domingo et al. (1989) did not find any significant alterations in pup viability/lethality, pup body weight, or the incidence of malformation in rats exposed to 110 mg Al/kg/day as aluminum chloride in the diet on gestation days 6–19 (McCormack et al. 1979) or 141 mg Al/kg/day as aluminum nitrate administered via gavage on gestation days 6–15 (Domingo et al. 1989). Neither study evaluated the potential neurotoxicity of aluminum following acute-duration exposure; intermediate-duration studies provide strong evidence that the nervous system (in adults and developing organisms) is the most sensitive target of aluminum toxicity.

- An MRL of 1 mg Al/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to aluminum.

A fair number of animal studies have examined the oral toxicity of aluminum following intermediate-duration exposure. A subset of these studies that provide information on the aluminum content of the basal diet and involved exposure to aluminum via the diet or drinking water will be the focus of this discussion. With the possible exception of reproductive function, these studies have examined most potential end points of aluminum toxicity. Systemic toxicity studies have not consistently reported adverse effects in rats exposed to up to 284 mg Al/kg/day (Domingo et al. 1987b; Gomez et al. 1986; Konishi et al. 1996), mice exposed to doses as high as 195 mg Al/kg/day (Oteiza et al. 1989), or dogs exposed to doses as high as 88 mg Al/kg/day (Katz et al. 1984; Pettersen et al. 1990). An increased susceptibility to bacterial infections was observed in mouse dams exposed to 155 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through lactation day 21 (Yoshida et al. 1989). However, a similar aluminum dose did not result in a change in susceptibility in virgin female mice exposed to 107 mg Al/kg/day as aluminum lactate in the diet for 6 weeks (Yoshida et al. 1989). Immunological alterations (decreased spleen concentrations of interleukin-2, interferon g, and tumor necrosis factor and a decrease in CD^{4+} cells) were observed in mice exposed to 200 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through postnatal day 180 (Golub et al. 1993). There is limited information on the potential for aluminum to induce reproductive effects. Although a number of studies have reported no

alterations in the occurrence of resorption, litter size, sex ratio, or pup body weight, no studies have examined fertility or potential effects on sperm morphology or motility. A significant alteration in gestation length was observed in mice exposed to 155 or 330 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through lactation 21 (Donald et al. 1989); in the aluminum exposed mice, 4 of the 17 litters were born earlier or later (days 17, 19, or 20 versus day 18 in controls) than control litters. However, this has not been reported in other studies in mice or rats (Colomina et al. 2005; Golub and Germann 2001; Golub et al. 1992a, 1995).

The preponderance of available intermediate-duration studies has focused on the potential for aluminum to induce neurological and neurodevelopmental effects. Although neurotoxicity of aluminum has not been established in people with normal renal function, the data for dialysis encephalopathy (as well as some occupational studies) establish that the human nervous system is susceptible to aluminum and neurotoxicity is a well-documented effect of aluminum in orally-exposed in mice and rats. A wide variety of behavioral tests were conducted in rats and mice, in which the most consistently affected behaviors involve motor function. Alterations in forelimb and hindlimb grip strength have been observed in adult mice exposed to 195 mg Al/kg/day as aluminum lactate in the diet for 90 days (Golub et al. 1992b), mice (6 weeks of age at study beginning) exposed to 195 mg Al/kg/day as aluminum lactate in the diet for 5–7 weeks (Oteiza et al. 1993), the offspring of mice exposed on gestation day 1 through lactation day 21 to 155 mg Al/kg/day (Donald et al. 1989; Golub et al. 1995) or 250 mg Al/kg/day (Golub et al. 1995) as aluminum lactate, and the offspring of rats exposed to 103 mg Al/kg/day as aluminum nitrate in drinking water (with added citric acid) for 15 days prior to mating and on gestation day 1 through lactation day 21 (Colomina et al. 2005). Decreases in spontaneous motor activity were observed in mice exposed to 130 mg Al/kg/day for 6 weeks (Golub et al. 1989) or 195 mg Al/kg/day for 90 days (Golub et al. 1992b). Motor impairments have also been detected in mice in the wire suspension test in which offspring exposed to 130 mg Al/kg/day had a shorter latency to fall from the wire and in the rotorod test in which offspring exposed to 260 mg Al/kg/day had a higher number of rotations (which occur when the animals lost its footing, clung to the rod, and rotated with it for a full turn) (Golub and Germann 2001). Neurobehavioral alterations that have occurred at similar dose levels include decreased responsiveness to auditory or air-puff startle (Golub et al. 1992b, 1995), decreased thermal sensitivity (Golub et al. 1992a), increased negative geotaxis latency (Golub et al. 1992a), and increased foot splay (Donald et al. 1989). Additionally, one study found significant impairment in performance of the water maze test in offspring of mice exposed to 130 mg Al/kg/day on gestation day 1 through lactation day 21 (Golub and Germann 2001). Colomina et al. (2005) did not find alterations in this test in rats exposed to 53 mg Al/kg/day; however, this study did not run probe tests, which showed significant

alterations in the Golub and Germann (2001) study. Other studies have utilized passive avoidance tests or operant training tests to evaluate potential impairment of cognitive function. However, the interpretation of the results of these tests is complicated by an increase in food motivation in aluminum exposed mice (Golub and Germann 1998).

There is also strong evidence that gestational and/or lactational exposure can cause other developmental effects. Gestation and/or lactation exposure can result in significant decreases in pup body weight gain in rats and mice (Colomina et al. 2005; Golub and Germann 2001; Golub et al. 1992a). The decreases in pup body weight are often associated with decreases in maternal body weight during the lactation phase of the study; however, decreases in body weight have also been observed in a cross-fostering study when gestation-exposed pups were nursed by control mice (Golub et al. 1992a). Other studies involving gestation and lactation exposure to aluminum did not find changes in pup growth in mice (Donald et al. 1989; Golub and Germann 1998; Golub et al. 1995). In rats, a delay in physical maturation, particularly delays in vagina opening, testes descent, and incisor eruption, has been reported at 53 mg Al/kg/day (Colomina et al. 2005). In the Colomina et al. (2005) study, a delay in vagina opening was observed in rat offspring exposed to 53 mg Al/kg/day. The number of days to vagina opening was 31.1, 40.9, and 45.9 days in the control, 53, and 103 mg Al/kg/day groups, respectively. Delays in maturations were also observed for testes descent (23.9, 22.8, and 27.1 days in the control, 53, and 103 mg Al/kg/day groups, significant at 103 mg Al/kg/day) and incisor eruption in males (5.5, 6.1, and 5.3 days, significant at 53 mg Al/kg/day, but not at 103 mg Al/kg/day). Significant delays in vagina opening and testes descent were also observed at 103 mg Al/kg/day in the offspring of rats similarly exposed but with the addition of restraint stress on gestation days 6–20. The mean number of days to maturation in the control, 53, and 103 mg Al/kg/day groups were 32.5, 40.4, and 44.9 days for vagina opening and 24.9, 23.2, and 27.7 days for testes descent. However, another study by Colomina et al. (1999) did not find significant delays in vagina opening or testes descent, but did find significant delays in pinna attachment and eye opening following administration of 75 mg/kg/day (15 mg Al/kg/day) aluminum chloride via intraperitoneal injection to mice on gestation days 6–15. Another study did not find delays in pinna attachment, eye opening, or incisor eruption in the offspring of rats administered via gavage 73 mg Al/kg/day as aluminum chloride (aluminum content of the diet was not reported) on gestation days 8–20 (Misawa and Shigeta 1992). Collectively, these studies provide equivocal evidence that aluminum induces delays in maturation.

The Golub et al. (1989), Golub and Germann (2001), and Colomina et al. (2005) studies identified the lowest LOAELs for the critical effects (neurotoxicity, neurodevelopmental toxicity, and delays in

maturation) and were considered as possible principal studies. Golub et al. (1989) identified the lowest LOAEL for neurotoxicity. In this study in which mice were exposed to aluminum lactate in the diet for 6 weeks, significant decreases in total activity and vertical activity (rearing) were observed at 130 mg Al/kg/day; no significant alterations were observed at 62 mg Al/kg/day. One limitation of this study is that motor activity was the only neurobehavioral test evaluated; other studies have shown that grip strength is one of the more sensitive end points. Golub and Germann (2001) examined a number of sensitive end points of neurodevelopmental toxicity in the offspring of mice exposed to aluminum lactate in the diet on gestation day 1 through lactation day 21, after which the pups were fed a diet containing the same levels of aluminum as the dams on postnatal days 21–35. The study identified a NOAEL of 26 mg Al/kg/day and a LOAEL of 130 mg Al/kg/day for alterations in tests of motor function (a shorter latency to fall off a wire) and cognitive function (impaired performance in the water maze test). This study used a suboptimal diet, which complicates the interpretation of the study results. The dietary levels of phosphorus, calcium, magnesium, iron, and zinc were lower than the National Research Council's recommendation in an attempt to mimic the intakes of these nutrients by young women. The investigators noted that even though the intakes of several nutrients were below the recommendations, the diet was not deficient. The impact of the suboptimal diet on the developmental toxicity of aluminum is not known. The observed effects are similar to those reported in other studies, as are the adverse effect levels. In the Colomina et al. (2005) study, a significant decrease in forelimb grip strength was observed in the offspring of rats exposed to 103 mg Al/kg/day as aluminum nitrate in the drinking water (with citric acid added to increase aluminum absorption) for 15 days prior to mating and during gestation and lactation; grip strength was not adversely affected at 53 mg Al/kg/day. This study also found significant delays in vagina opening at 53 mg Al/kg/day. As previously noted, there are limited data to confirm or refute the identification of delays in maturation as a critical effect of aluminum. The delays in maturation may be secondary to decreases in maternal weight or food intake or decreases in pup body weight and/or food intake; however, these data are only reported for some time periods. The Golub et al. (1989) study was not selected as the principal study because the NOAEL of 62 mg Al/kg/day identified in this study is higher than the dose associated with delayed maturation in the Colomina et al. (2005) study. The Golub and Germann (2001) and Colomina et al. (2005) studies were selected as co-principal studies. A short description of these studies follows.

In the Golub and Germann (2001) study, groups of pregnant Swiss Webster mice were exposed to 0, 100, 500, or 1,000 mg Al/kg diet on gestational days 0–21 and during lactation until day 21. On postnatal day (PND) 21, one male and one female pup from each litter were placed on the same diet as the dam. The offspring were exposed until PND 35. The composition of the diet was modified from the National

Research Council's recommendations; the investigators noted that the nutrients were reduced to correspond to the usual intake of these nutrients by young women. The average daily intakes of phosphorus, calcium, magnesium, iron, and zinc in women aged 18–24 years are 83, 56, 71, 69, and 67% of the recommended dietary allowance (RDA); these percents were used to modify the recommended dietary intake for the mice used in this study. Doses of 26, 130, and 260 mg Al/kg/day are calculated by averaging reported estimated doses of 10, 50, and 100 mg Al/kg/day for adults (i.e., at beginning of pregnancy) and 42, 210, and 420 mg Al/kg/day maximal intake during lactation. The doses at lactation were calculated using doses estimated in previous studies with similar exposure protocols performed by the same group of investigators (Golub et al. 1995). At 3 months of age, the females were tested for neurotoxicity using the Morris water maze. At 5 months of age, males were tested for motor activity and function using rotarod, grip strength, wire suspension, mesh pole descent, and beam traversal tests. No alterations in pregnancy weight gain or pup birth weights were observed. At PND 21, significant decreases in pup body weights were observed at 130 and 260 mg Al/kg/day. No information on maternal weight gain during lactation was reported; however, the investigators noted that the decrease in pup weight was not associated with reduced maternal food intake. At PND 35, the decrease in body weight was statistically significant at 260 mg Al/kg/day. On PND 90, female mice in the 260 mg Al/kg/day group weighed 15% less than controls. Decreases in heart and kidney weights were observed at 260 mg Al/kg/day in the females. Also, increases in absolute brain weight were observed in females at 26 mg Al/kg/day and relative brain weights were observed at 26 or 260 mg Al/kg/day, but not at 130 mg Al/kg/day. In the males, significant decreases in body weight were observed at 130 (10%) and 260 (18%) mg Al/kg/day at 5 months; an increase in food intake was also observed at these doses. In the Morris maze (tested at 3 months in females), fewer animals in the 260 mg Al/kg/day group had escape latencies of <60 seconds during sessions 1–3 (learning phase) and a relocation of the visible cues resulted in increased latencies at 130 and 260 mg Al/kg/day. Body weight did not correlate with latency to find the platform or with the distribution of quadrant times. The investigators concluded that controls used salient and/or nonsalient cues, 26 and 130 mg Al/kg/day animals used both cues, but had difficulty using only one cue, and 260 mg Al/kg/day animals only used the salient cues. In the males tested at 5 months, a significant decrease in hindlimb grip strength was observed at 260 mg Al/kg/day, an increase in the number of rotations on the rotorod as observed at 260 mg Al/kg/day, and a shorter latency to fall in the wire suspension test was observed at 130 and 260 mg Al/kg/day. The investigators noted that there were significant correlations between body weight and grip strength and number of rotations. When hindlimb grip strength was statistically adjusted for body weight, the aluminum-exposed mice were no longer significantly different from controls; the number of rotations was still significantly different from control after adjustment for body weight.

In the Colomina et al. (2005) study, groups of female Sprague Dawley rats were exposed to 0, 50, or 100 mg Al/kg/day aluminum nitrate nonahydrate in drinking water; citric acid (710, 355, and 710 mg/kg/day in the control, 50, and 100 ppm groups, respectively) was added to the drinking water to increase aluminum absorption. The adult rats were exposed to aluminum for 15 days prior to mating and during gestation and lactation periods; after weaning, the pups were exposed to the same aluminum concentration as the mothers from PND 21 through 68. The basal diet (Panlab rodent chow) contained 41.85 µg Al/g diet. Aluminum doses were calculated by adding the basal dietary aluminum doses (calculated using reference values for mature Sprague-Dawley rats) to reported aluminum doses from water; the total aluminum doses were 3, 53, and 103 mg Al/kg/day. In addition to aluminum exposure, some animals in each group underwent restraint stress for 2 hours/day on gestation days 6–20; the restraint consisted of placing the rats in cylindrical holders. The following neurobehavioral tests were performed on the offspring: righting reflex (PNDs 4, 5, 6), negative geotaxis (PNDs 7, 8, 9), forelimb grip strength (PNDs 10–13), open field activity (PND 30), passive avoidance (PND 35), and water maze (only tested at 53 mg/kg/day on PND 60). The rats were killed on PND 68. No significant alterations in body weight, food consumption, or water consumption were observed during gestation in the dams exposed to aluminum. The investigators noted that decreases in water and food consumption were observed during the lactation period in the rats exposed to 103 mg Al/kg/day, but the data were not shown and maternal body weight during lactation was not mentioned. No significant alterations in the number of litters, number of fetuses per litter, viability index, or lactation index were observed. Additionally, no differences in days at pinna detachment or eye opening were observed. Age at incisor eruption was significantly higher in males exposed to 53 mg/kg/day, but not in males exposed to 103 mg/kg/day or in females. A significant delay in age at testes descent was observed at 103 mg/kg/day and vagina opening was delayed at 53 and 103 mg/kg/day. A decrease in forelimb grip strength was observed at 103 mg/kg/day; no alterations in other neuromotor tests were observed. Additionally, no alterations in open field behavior or passive avoidance test were observed. In the water maze test, latency to find the hidden platform was decreased in the 53 mg/kg/day group on test day 2, but not on days 1 or 3; no significant alteration in time in the target quadrant was found.

The Golub and Germann (2001) and Colomina et al. (2005) studies identify four end points that could be used as the point of departure for derivation of the intermediate-duration oral MRL:

(1) latency to fall off wire in wire suspension test; adverse effect level of 130 mg Al/kg/day, no effect level of 26 mg Al/kg/day (Golub and Germann 2001);

(2) latency to locate the platform following cue relocation in the water maze test; adverse effect level of 130 mg Al/kg/day, no effect level of 26 mg Al/kg/day (Golub and Germann 2001);

(3) decreased forelimb grip strength; adverse effect level of 103 mg Al/kg/day, no effect level of 53 mg Al/kg/day (Colomina et al. 2005); and

(4) delay in vagina opening; adverse effect level of 53 mg Al/kg/day, no effect level not identified (Colomina et al. 2005).

Benchmark dose (BMD) modeling was considered for each of these end points. As discussed in Appendix A, BMD modeling was not used to identify the point of departure due to incomplete reporting of the data or because the models did not provide adequate fit.

Using a NOAEL/LOAEL approach, the NOAEL of 26 mg Al/kg/day identified in the Golub and Germann (2001) study was selected as the point of departure for the MRL. An MRL based on this NOAEL should be protective for neurological effects, neurodevelopmental effects, and for delays in maturation. Dividing the NOAEL by an uncertainty factor of 100 (10 to account for the extrapolation from mice to humans and 10 for human variability) and a modifying factor of 0.3 to account for possible differences in the bioavailability of the aluminum lactate used in the Golub and Germann (2001) study and the bioavailability of aluminum from drinking water and a typical U.S. diet results in an MRL of 1 mg Al/kg/day. No studies were identified that estimated the bioavailability of aluminum lactate following long-term dietary exposure; however, a bioavailability of 0.63% was estimated in rabbits receiving a single dose of aluminum lactate (Yokel and McNamara 1988). Yokel and McNamara (2001) and Powell and Thompson (1993) suggest that the bioavailability of aluminum from the typical U.S. diet was 0.1%; the bioavailability of aluminum from drinking water ranges from 0.07 to 0.39% (Hohl et al. 1994; Priest et al. 1998; Stauber et al. 1999; Steinhausen et al. 2004). These data suggest that aluminum lactate has a higher bioavailability than aluminum compounds typically found in drinking water or the diet.

- An MRL of 1 mg Al/kg/day has been derived for chronic-duration oral exposure (365 days or longer) to aluminum.

A small number of animal studies examined the chronic toxicity of aluminum. Schroeder and Mitchener (1975a, 1975b) examined the systemic toxicity of aluminum following lifetime exposure of rats and mice to very low doses of aluminum sulfate in the drinking water. Although the levels of aluminum in the diet were not reported, they are assumed to be low because the animals were fed a low-metal diet in metal-free environmental conditions. Studies conducted by Roig et al. (2006) and Golub et al. (2000) primarily

focused on the neurotoxicity of aluminum following lifetime exposure (gestation day 1 through 24 months of age). In the Golub et al. (2000) study, significant decreases in forelimb and hindlimb grip strength, and a decrease in thermal sensitivity were observed in mice exposed to 100 mg Al/kg/day; negative geotaxis was significantly altered at 18 months, but not at 24 months. No effect on horizontal activity was observed. A 10% increase in body weight and a 20% decrease in body weight were observed in the males and females, respectively. In a companion study by this group, no significant cognitive impairments were found in the Morris water maze test; in fact, aluminum-exposed mice performed better than controls in the learning tasks. Roig et al. (2006) also found no significant alterations in performance on the Morris water maze in rats exposed to 100 mg Al/kg/day as aluminum nitrate in the drinking water (with added citric acid). Although significant differences were found between the two aluminum groups (50 and 100 mg Al/kg/day); this was primarily due to the improved performance (as compared to controls, no significant differences) in the 50 mg Al/kg/day group. Roig et al. (2006) also found no significant alterations in open field activity.

Based on the results of these chronic-duration studies, the decreases in forelimb and hindlimb grip strength and the decrease in thermal sensitivity identified in the Golub et al. (2000) study were selected as the critical effect for derivation of a chronic-duration oral MRL for aluminum. The selection of these end points, and neurotoxicity in general, is well supported by the findings of a number of intermediate-duration studies that indicate that this is one of the most sensitive targets of aluminum toxicity (Colomina et al. 2005; Donald et al. 1989; Golub and Germann 2001; Golub et al. 1992a, 1995).

In the Golub et al. (2000) study, groups of 8 male and 10 female Swiss Webster mice were exposed to 7 or 1,000 μg Al/g diet as aluminum lactate in a purified diet. The investigators estimated adult doses of <1 and 100 mg/kg/day. The mice were exposed to aluminum from conception (via feeding the dams) through 24 months of age. Body weight, food intake, and clinical signs were determined during the last 6 months of the study. A neurobehavioral test battery (foot splay, temperature sensitivity, negative geotaxis, and grip strength), 1 hour spontaneous activity measurement, and auditory startle tests were conducted at 18 and 24 months. In a companion study, groups of 6–9 male and female Swiss Webster mice or 7 male and female C57BL/6J mice (number per sex were not reported) were exposed to 7 or 1,000 μg Al/g diet as aluminum lactate in a purified diet (<1 and 100 mg/kg/day) from conception (via feeding the dams) through 24 months of age. Body weight, food intake, and clinical signs were determined during the last 6 months of the study. A neurobehavioral test battery (foot splay, temperature sensitivity, negative geotaxis, and grip strength) and Morris maze testing were performed at 22–23 months of age. In the principal study, no significant alterations in mortality were observed. A

significant decrease in body weight was observed in the female mice (approximately 20%). In the males, there was a significant increase in body weight (approximately 10%). No significant alterations in food intake were observed in either sex. However, food intake/g body weight was significantly higher in the aluminum-exposed mice. No significant alterations in the occurrence of clinical signs or indications of neurodegenerative syndromes were found. Significant increases in relative spinal cord, heart, and kidney weights were found. Significant alterations in negative geotaxis and tail withdrawal time in the temperature sensitivity test (males only) were observed at 18 months. At 24 months, significant alterations in forelimb and hindlimb grip strength and temperature sensitivity were found in male and female mice. Forelimb and hindlimb grip strengths were decreased and thermal sensitivity was decreased, as evidenced by an increase in tail withdrawal times. Auditory startle response tests could not be completed in the older mice. Similarly, vertical spontaneous movement could not be measured; no effect on horizontal movement was found. In the companion study, no alterations in neurobehavioral battery test performance were observed; the investigators note that this may be due to the small number of animals per group. In general, aluminum-exposed mice performed better on the water maze test than controls.

A chronic-duration oral MRL was derived using the LOAEL of 100 mg Al/kg/day for decreased forelimb and hindlimb grip strength and decreased thermal sensitivity identified in the Golub et al. (2000) study. A BMD approach for deriving an MRL was not utilized because the Golub et al. (2000) study only tested one aluminum group. The MRL of 1 mg Al/kg/day was calculated by dividing the LOAEL of 100 mg Al/kg/day by an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability) and a modifying factor of 0.3 to account for possible differences in the bioavailability of the aluminum lactate used in the Golub and Germann (2001) study and the bioavailability of aluminum from drinking water and a typical U.S. diet. No studies were identified that estimated the bioavailability of aluminum lactate following long-term dietary exposure; however, a bioavailability of 0.63% was estimated in rabbits receiving a single dose of aluminum lactate (Yokel and McNamara 1988). Yokel and McNamara (2001) and Powell and Thompson (1993) suggest that the bioavailability of aluminum from the typical U.S. diet was 0.1%; the bioavailability of aluminum from drinking water ranges from 0.07 to 0.39% (Hohl et al. 1994; Priest et al. 1998; Stauber et al. 1999; Steinhausen et al. 2004). These data suggest that aluminum lactate has a higher bioavailability than aluminum compounds typically found in drinking water or the diet.

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 aluminum. 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.

Once mineral-bound aluminum is recovered from ores, it forms metal compounds, complexes, or chelates. Examples of the different forms of aluminum include aluminum oxide, aluminum chlorhydrate, aluminum hydroxide, aluminum chloride, aluminum lactate, aluminum phosphate, and aluminum nitrate. The metal itself is also used. With the exception of aluminum phosphide, the anionic component does not appear to influence toxicity, although it does appear to influence bioavailability. Aluminum phosphide, which is used as a pesticide, is more dangerous than the other forms; however, this is because of the evolution of phosphine gas (a potent respiratory tract and systemic toxin) rather than to the exposure to aluminum.

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

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.

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

3.2.1.1 Death

No studies were located regarding death following acute- or intermediate-duration inhalation exposure to various forms of aluminum in humans.

Several deaths have been reported after occupational exposure to a finely powdered metallic aluminum used in paints, explosives, and fireworks (Mitchell et al. 1961); it should be noted that changes in production technology have resulted in decreased occupational exposures to finely powdered aluminum. In one case, a 19-year-old male who worked in an atmosphere heavily contaminated with this powder developed dyspnea after 2.5 years. This symptom grew worse, and the man had to stop working 3 months later and died after a further 8 months. Before death, respiratory excursion was poor and chest X-rays showed signs of pulmonary nodular interstitial fibrosis. Of a total of 27 workers examined in this factory,

2 died and 4 others had radiological changes on chest X-rays. Total dust in the workplace air was 615–685 mg Al/m^3, and respirable dust was 51 mg Al/m^3. Chemical analysis showed the dust to be 81% metallic aluminum and 17% various oxides and hydroxides of aluminum. There have also been a number of case reports of deaths of workers exposed to aluminum flake powder (McLaughlin et al. 1962), welding fumes (Hull and Abraham 2002), or smelter fumes (Gilks and Churg 1987); it is likely that the cause of death in these men was respiratory tract damage.

No studies were located that evaluated death from an intermediate-duration inhalation exposure in animals to aluminum or its compounds. Of the experiments performed in animals, none has shown death from inhalation exposure to aluminum or its compounds. For example, no deaths were reported following an acute 4-hour exposure to up to 1,000 mg Al/m^3 as aluminum oxide in groups of 12–18 male Fischer 344 rats (Thomson et al. 1986) or following chronic exposure to 2.18–2.45 mg Al/m^3 as refractory alumina fiber for 86 weeks in groups of 50 male and female Wistar rats (Pigott et al. 1981).

3.2.1.2 Systemic Effects

No studies were located regarding gastrointestinal, dermal, or body weight effects in humans or metabolic effects in animals after acute-duration inhalation exposure to various forms of aluminum.

The highest NOAEL values and all LOAEL values for inhalation exposure from each reliable study for systemic effects in each species and duration category for aluminum are shown in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. No studies were located regarding respiratory effects following acute-duration inhalation exposure to various forms of aluminum in humans.

A number of studies have examined the potential for airborne aluminum to induce respiratory effects in chronically exposed workers. Exposure to aluminum fumes and dust occurs in potrooms where hot aluminum metal is recovered from ore, in foundries where aluminum alloys are melted and poured into molds, in welding operations, and the production and use of finely powdered aluminum. Because these workers were also exposed to a number of other toxic chemicals including sulfur dioxide, polycyclic aromatic hydrocarbons (PAHs), carbon monoxide, hydrogen fluoride, and chlorine, it is difficult to ascribe the respiratory effects to aluminum. Wheezing, dyspnea, and/or impaired lung function have been

Table 3-1 Levels of Significant Exposure to Aluminum and Compounds - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Systemic								
1	Rat (Fischer- 344)	5 x 4 hr	Resp	10 M	200 M (multifocal microgranulomas in lungs)		Thomson et al. 1986 Aluminum flakes	
					50 M (increased lactate dehydrogenase, glucose-6-phosphate dehydrogenase, and alkaline phosphatase activity in lavage fluid)			
2	Hamster (Golden Syrian)	3 d 4 or 6 hr/d (NS)	Resp		33 M (alveolar wall thickening and increased number of macrophages; bronchopneumonia)		Drew et al. 1974 Aluminum chlorhydrate	
			Bd Wt		33 M (unspecified decreased body weight)			
3	Hamster (Golden Syrian)	3 d 4 or 6 hr/d (NS)	Resp	3 M	7 M (13% increased lung weight)		Drew et al. 1974 Aluminum chlorhydrate	
4	Hamster (Golden Syrian)	3 d 4 hr/d (NS)	Resp		10 M (approximately 24% increased lung weight)		Drew et al. 1974 Aluminum chlorhydrate	

Table 3-1 Levels of Significant Exposure to Aluminum and Compounds - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
5	Hamster (Golden Syrian)	3 d 4 hr/d	Resp		31 (alveolar wall thickening and increased number of macrophages and heterophils)		Drew et al. 1974 Aluminum chlorhydrate	
6	Rabbit (New Zealand)	5 d 4 hr/d (NS)	Resp		43 (alveolar wall thickening, increased number of macrophage; 65% increase in lung weight)		Drew et al. 1974 Aluminum chlorhydrate	
INTERMEDIATE EXPOSURE								
Systemic								
7	Rat (Fischer- 344)	6 mo 5 d/wk 6 hr/d (NS)	Resp	0.061	0.61 (increase in alveolar macrophages; granulomatous lesions in lungs)		Steinhagen et al. 1978 Aluminum chlorhydrate	
			Cardio	6.1				
			Gastro	6.1				
			Hemato	6.1				
			Musc/skel	6.1				
			Hepatic	6.1				
			Renal	6.1				
			Endocr	6.1				
			Dermal	6.1				
			Ocular	6.1				
			Bd Wt	6.1				

Table 3-1 Levels of Significant Exposure to Aluminum and Compounds - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
8	Rat (Fischer- 344)	6 mo 5 d/wk 6 hr/d	Resp	0.065 M	0.65 M (12% increased relative lung weight)		Stone et al. 1979 Aluminum chlorhydrate	
			Hemato	5.4				
			Bd Wt	5.4				
9	Gn Pig (Hartley)	6 mo 5 d/wk 6 hr/d (NS)	Resp	0.061	0.61 (increase in alveolar macrophages; granulomatous lesions in lungs)		Steinhagen et al. 1978 Aluminum chlorhydrate	
			Cardio	6.1				
			Gastro	6.1				
			Hemato	6.1				
			Musc/skel	6.1				
			Hepatic	6.1				
			Renal	6.1				
			Endocr	6.1				
			Dermal	6.1				
			Ocular	6.1				
			Bd Wt	6.1				

Table 3-1 Levels of Significant Exposure to Aluminum and Compounds - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
10	Gn Pig (Hartley)	6 mo 5 d/wk 6 hr/d	Resp	0.65	5.4 (19-23% increased relative lung weight)		Stone et al. 1979 Aluminum chlorhydrate	
			Hemato	5.4				
			Bd Wt	5.4				
11	Hamster (Golden Syrian)	5 or 6 wk 5 d/wk 6 hr/d	Resp		10 M (alveolar thickening and increased number of foci of macrophages and heterophils)		Drew et al. 1974 Aluminum chlorhydrate	
CHRONIC EXPOSURE								
Systemic								
12	Rat (Wistar)	86 wk 5 d/wk 6 hr/d (NS)	Resp	2.45			Pigott et al. 1981 Aluminum oxide	
13	Rat (Fischer- 344)	12-24 mo 5 d/wk 6 hr/d	Resp	0.65	5.4 (108-274% increased relative lung weight at 2 years)		Stone et al. 1979 Aluminum chlorhydrate	
			Hemato	5.4				
			Bd Wt	0.65	5.4 (16-26% decrease in body weight at 2 years)			
14	Gn Pig (Hartley)	12-21 mo 5 d/wk 6 hr/d	Resp		0.065 M (21% increased relative lung weight at 2 years)		Stone et al. 1979 Aluminum chlorhydrate	
			Hemato	5.4				

Table 3-1 Levels of Significant Exposure to Aluminum and Compounds - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
			Bd Wt	5.4				

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

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; Gn pig = guinea pig; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); x = time(s)

Figure 3-1 Levels of Significant Exposure to Aluminum and Compounds - Inhalation

Acute (≤14 days)

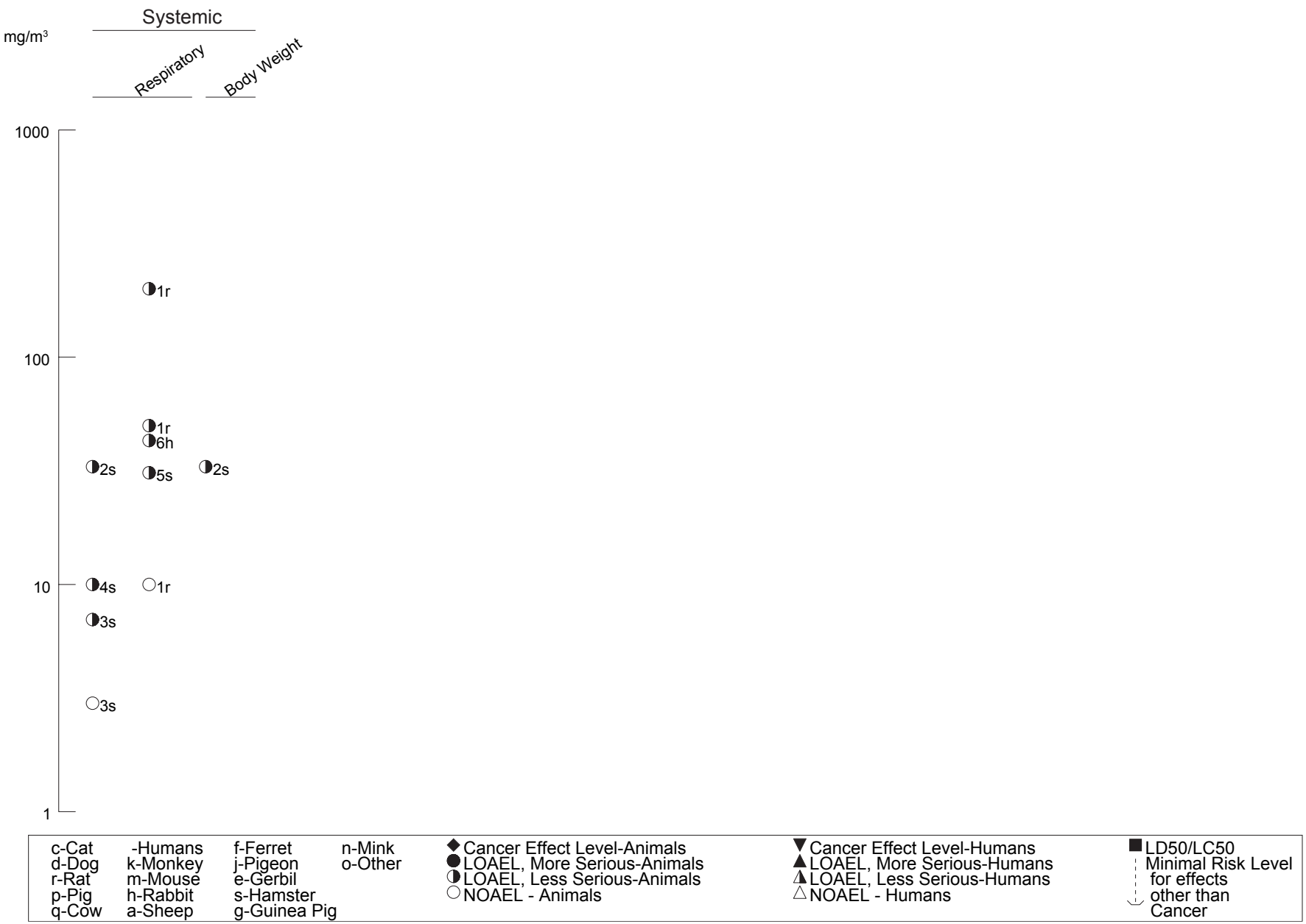


Figure 3-1 Levels of Significant Exposure to Aluminum and Compounds - Inhalation *(Continued)*

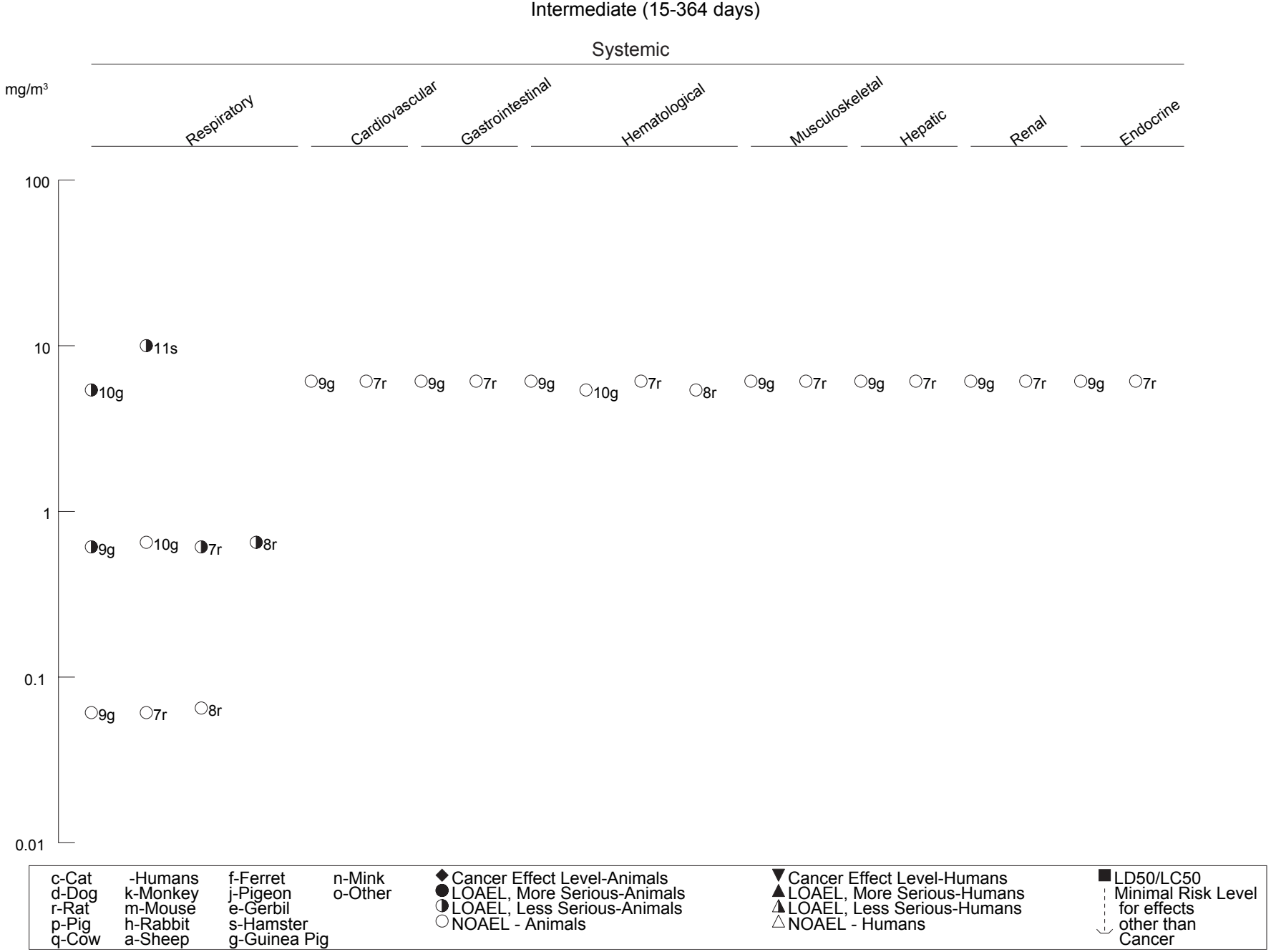


Figure 3-1 Levels of Significant Exposure to Aluminum and Compounds - Inhalation *(Continued)*

Intermediate (15-364 days)

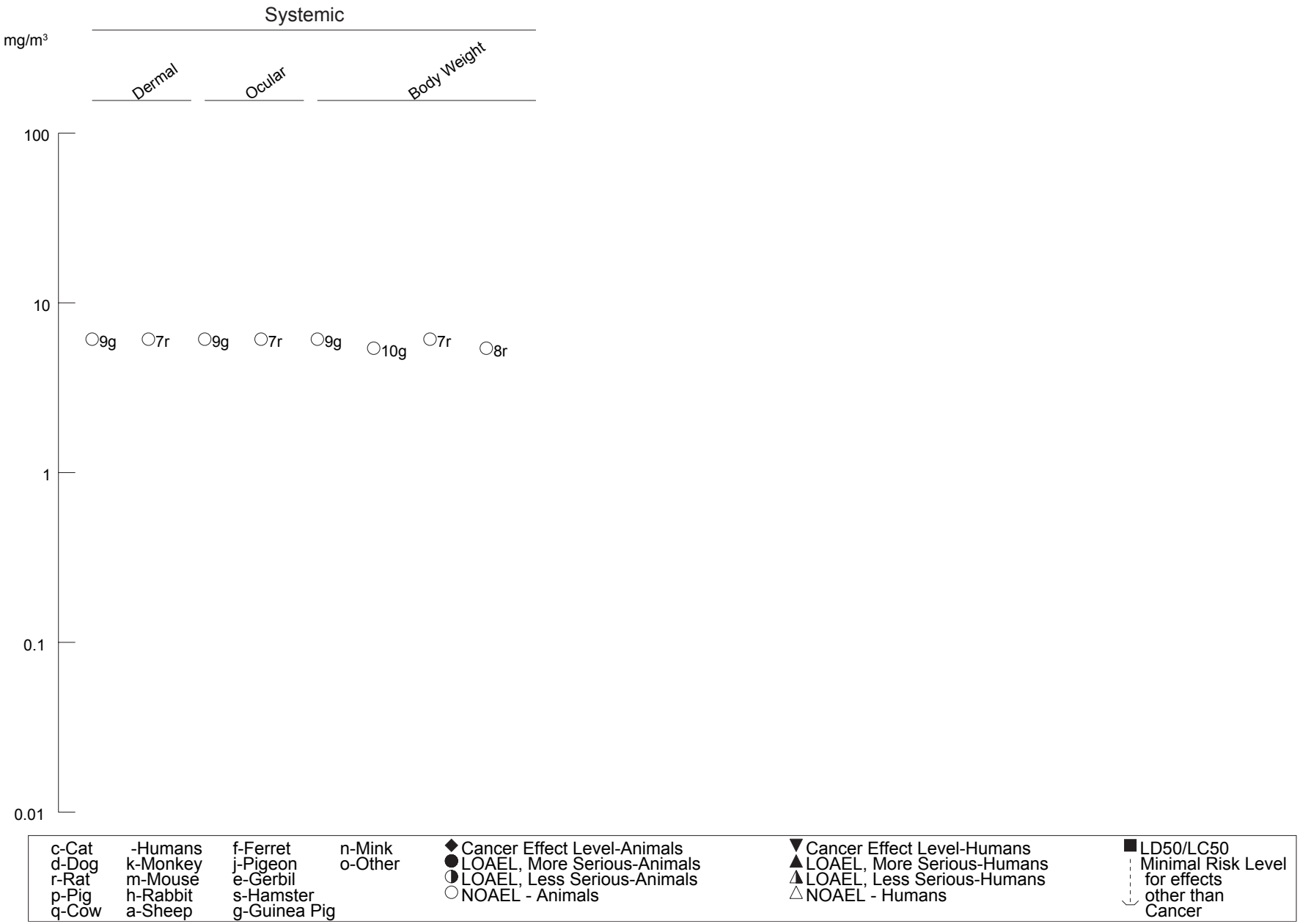
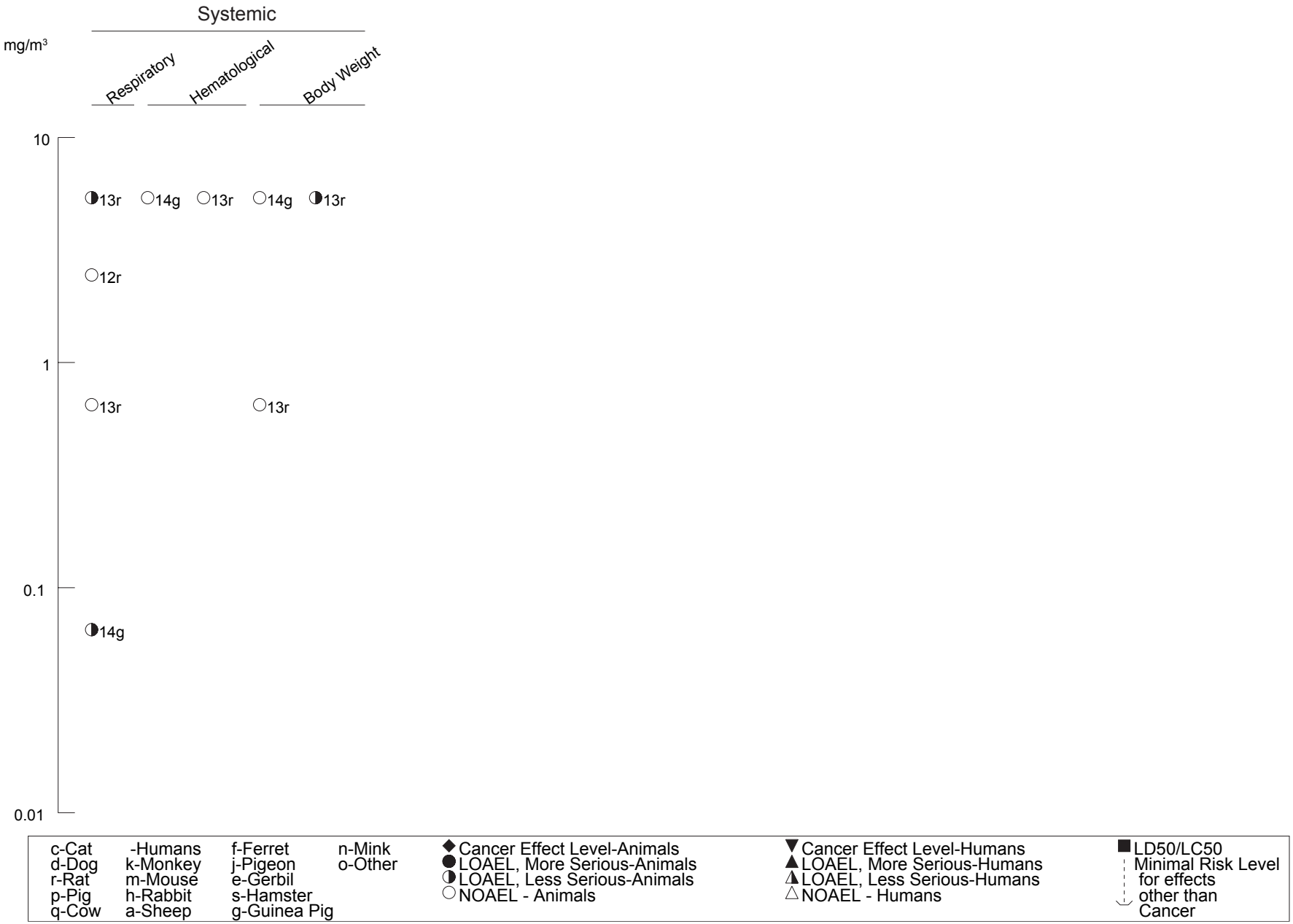


Figure 3-1 Levels of Significant Exposure to Aluminum and Compounds - Inhalation *(Continued)*

Chronic (≤365 days)



observed in potroom workers (Bast-Pettersen et al. 1994; Chan-Yeung et al. 1983; Radon et al. 1999; Simonsson et al. 1985), foundry workers (Al-Masalkhi and Walton 1994; Burge et al. 2000; Halatek et al. 2006), workers exposed to fine aluminum dust (including grinders) (Jederlinic et al. 1990; Korogiannos et al. 1998; Miller et al. 1984b), a worker spray painting with an aluminum paint (Bost and Newman 1993), and welders (Abbate et al. 2003; Herbert et al. 1982; Hull and Abraham 2002; Vandenplas et al. 1998), although other studies have not found a significant effect (Musk et al. 2000). Occupational asthma has been reported in aluminum potroom workers (as reviewed by Abramson et al. 1989 and Kilburn 1998); there is some debate whether the asthma is related to exposure to respiratory irritants, such as hydrogen fluoride and chlorine, or due to aluminum exposure. Case reports provide suggestive evidence that chronic exposure to aluminum may cause occupational asthma. An asthmatic reaction was observed following a bronchial provocation test an aluminum foundry worker (Burge et al. 2000) and an aluminum welder (Vandenplas et al. 1998).

Pulmonary fibrosis is the most commonly reported respiratory effect observed in workers exposed to fine aluminum dust (pyropowder), alumina (aluminum oxide), or bauxite. However, conflicting reports are available on the fibrogenic potential of aluminum. In some of the cases, the fibrosis was attributed to concomitant exposure to other chemicals. For example, pulmonary fibrosis has been observed in a number of bauxite workers or potroom workers (De Vuyst et al. 1986; Gaffuri et al. 1985; Gilks and Churg 1987; Jederlinic et al. 1990; Jephcott 1948; Musk et al. 1980; Riddell 1948; Shaver 1948; Shaver and Riddell 1947); in these workers, it is very likely that there was simultaneous exposure to silica and that the latter was the causative agent rather than the aluminum. Some of the earliest cases of pulmonary fibrosis were reported in German munition workers exposed to pyropowder (Goralewski 1947). Case reports of fibrosis in workers exposed to finely ground aluminum have been also been reported by Edling (1961), McLaughlin et al. (1962), Mitchell et al. (1961), and Ueda et al. (1958). However, other studies have not found any radiological evidence of pulmonary fibrosis in workers exposed to alumina (Meiklejohn and Posner 1957; Posner and Kennedy 1967) or fine aluminum powder (Crombie et al. 1944). It is believed that the conflicting study results are due to differences in the lubricant used to retard surface oxidation during milling (Dinman 1987). Stearic acid is the most commonly used lubricant in the aluminum industry; the stearic acid combines with the aluminum to form aluminum stearate. Exposure to the aluminum stearate does not appear to be fibrogenic to workers (Crombie et al. 1944; Meiklejohn and Posner 1957; Posner and Kennedy 1967). In contrast, the previous and now discontinued use of a nonpolar aliphatic oil lubricant, such as mineral oil, has been associated with fibrosis (Edling 1961; McLaughlin et al. 1962; Mitchell et al. 1961; Ueda et al. 1958). Pulmonary fibrosis has also been observed in an aluminum arc welder (Vallyathan et al. 1982), an aluminum production worker exposed to

aluminum oxide fumes (Al-Masalkhi and Walton 1994), and in workers in an unspecified aluminum industry (Akira 1995). There is also some evidence suggesting aluminum-induced pneumoconiosis (Hull and Abraham 2002; Korogiannos et al. 1998; Kraus et al. 2000), pulmonary alveolar proteinosis (Miller et al. 1984b), interstitial pneumonia (Herbert et al. 1982), and granulomas (Cai et al. 2007; Chen et al. 1978; De Vuyst et al. 1987); however, these reports are based on a small number of cases, which limits their interpretation.

Respiratory effects typically associated with inhalation of particulates and lung overload have been observed in animals. The pulmonary toxicity of alchlor (a propylene glycol complex of aluminum chlorhydrate), a common component of antiperspirants, was examined in hamsters in a series of studies conducted by Drew et al. (1974). A 3-day exposure to 31 or 33 mg Al/m^3 resulted in moderate-to-marked thickening of the alveolar walls due to neutrophil and macrophage infiltration and small granulomatous foci at the bronchioloalveolar junction (a likely site of particulate deposition). A decrease in the severity of the pulmonary effects was observed in animals killed 3, 6, 10, or 27 days after exposure termination. Similar pulmonary effects were observed in rabbits exposed to 42 mg Al/m^3 for 5 days (Drew et al. 1974). Significant increases in absolute lung weights have been observed in hamsters exposed for 3 days to ≥7 mg Al/m^3 (no effects were observed at 3 mg Al/m^3) and in rabbits exposed to 43 mg Al/m^3 for 5 days (no effects were observed in rabbits exposed to 48 or 39 mg Al/m^3 for 1 or 4 days, respectively). In rats exposed to aluminum flakes for 5 days, there were alterations in the cytological (increase in the number of polymorphonuclear neutrophils [PMNs]) and enzymatic (increased activity of alkaline phosphatase and lactate dehydrogenase) content of the lavage fluid at ≥50 mg Al/m^3 and multifocal microgranulomas in the lungs and hilar lymph nodes at ≥100 mg Al/m^3 (Thomson et al. 1986). The enzymatic changes in the lavage fluid probably resulted from the presence of PMNs, increased phagocytosis of alveolar macrophages, and Type II cell hyperplasia.

Similar pulmonary effects were observed in animals following intermediate-duration exposure. An increase in the number of alveolar macrophages and heterophils were observed in hamsters exposed to 10 mg Al/m^3 as alchlor for 6 hours/day, 5 days/week for 2, 4, or 6 weeks (Drew et al. 1974). The severity was directly related to exposure duration. Granulomatous nodules and thickening of the alveolar walls due to infiltration of heterophils and macrophages were observed 2 weeks after termination of a 6-week exposure. An increase in the number of alveolar macrophages and granulomatous lesions in the lungs and peribronchial lymph nodes were also observed in rats and guinea pigs exposed to 0.61 or 6.1 mg Al/m^3 aluminum chlorhydrate for 6 hours/day, 5 days/week for 6 months (Steinhagen et al. 1978); the severity of the alterations was concentration-related. In addition, statistically significant increases in

absolute and relative lung weight were observed in the rats exposed to 6.1 mg Al/m^3; the authors noted that pulmonary edema was not observed in these rats. No statistically significant histological alterations or changes in lung weight were observed at 0.061 mg Al/m^3. Suggestive evidence of alveolar macrophage damage was observed in rats following a 5-month exposure (6 hours/day, 5 days/week) to either aluminum chloride (0.37 mg Al/m^3) or aluminum fluoride (0.41 mg Al/m^3); increases in lysozyme levels, protein levels (aluminum chloride only), and alkaline phosphatase (aluminum chloride only) were observed in the lavage fluid (Finelli et al. 1981). Alveolar proteinosis was observed in rats, guinea pigs, and hamsters exposed to ≥15, 20, or 30 mg/m^3 of several types of aluminum flake powders; the particle sizes ranged from 2.5 to 4.8 μm (Gross et al. 1973). The investigators noted that aluminum powders did not induce pulmonary fibrosis in the guinea pigs or hamsters; in rats, foci of lipid pneumonitis were observed. A similar exposure to aluminum oxide did not result in alveolar proteinosis, pulmonary fibrosis, or pneumonitis; effects were limited to foci consisting of alveoli filled with macrophages; the particle size of the aluminum oxide dust was much smaller (0.8 μm) than the aluminum flake powders. Interpretation of this study is limited by the lack of incidence data and the high mortality observed in treated and control animals.

There are limited data on the pulmonary toxicity of aluminum in animals following chronic exposure. Increases in relative lung weights (21–274%) have been observed in rats and guinea pigs exposed to 5.1 mg Al/m^3 aluminum chlorhydrate for 6 hours/day, 5 days/week for approximately 2 years (Stone et al. 1979). Lung weights were not affected at 0.61 mg Al/m^3. It should be noted that this study did not conduct histological examinations of the lungs. Pigott et al. (1981) did not find evidence of lung fibrosis in rats exposed to 2.18 or 2.45 mg/m^3 manufactured or aged Saffil alumina fibers; Saffil alumina fiber is a refractory material containing aluminum oxide and about 4% silica. The animals were exposed for 86 weeks followed by a 42-week observation period.

Cardiovascular Effects. No studies were located regarding cardiovascular effects of various forms of aluminum following acute- or intermediate-duration inhalation exposure in humans. Dilation and hypertrophy of the right side of the heart were reported in male factory workers chronically exposed by inhalation to aluminum flake powder and who eventually died (McLaughlin et al. 1962; Mitchell et al. 1961). The cardiac effects may have been secondary to pulmonary fibrosis and poor pulmonary function. Epidemiological studies of aluminum industry workers failed to identify an increase in deaths related to cardiovascular disease (Milham 1979; Mur et al. 1987; Rockette and Arena 1983; Theriault et al. 1984a). Cohort sizes ranged from 340 to 21,829 men. Results of cardiovascular tests (electrocardiogram, blood

pressure measurement) were similar between 22 aluminum workers exposed for 10 years or more and an unexposed control group of 16 men (Bast-Pettersen et al. 1994).

No histological alterations were observed in the hearts of Fischer 344 rats or Hartley guinea pigs exposed by inhalation (6 hours/day, 5 days/week) to 6.1 mg Al/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects of various forms of aluminum following acute-, intermediate-, or chronic-duration inhalation exposure in humans or acute- or chronic-duration inhalation exposure in animals. No histological changes were observed in the gastrointestinal tissues of Fischer 344 rats or Hartley guinea pigs exposed by inhalation (6 hours/day, 5 days/week) to 6.1 mg Al/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978).

Hematological Effects. No studies were located regarding hematological effects of various forms of aluminum following acute-duration inhalation exposure in humans. No adverse hematological effects were noted in a group of seven workers following 6 months of exposure to aluminum fumes or dust (Mussi et al. 1984). Exposure levels from personal sampling ranged from 1 to 6.2 mg Al/m^3, predominantly as aluminum oxide. Decreased red blood cell hemoglobin and increased erythrocyte sedimentation rates were reported in the case of a male aluminum industry worker chronically exposed by inhalation to aluminum flake powder (McLaughlin et al. 1962). A prolongation of prothrombin time was seen in 30 of 36 aluminum workers chronically exposed by inhalation to alumina dust (Waldron-Edward et al. 1971). The authors suggested that increasing serum aluminum levels may be used to provide beneficial antithrombogenic effects (Waldron-Edward et al. 1971).

No studies were located regarding hematological effects in animals after acute-duration inhalation exposure to aluminum or its compounds. No hematological effects were observed in Fischer 344 rats or Hartley guinea pigs exposed by inhalation (6 hours/day, 5 days/week) to 6.1 mg Al/m^3 as aluminum chlorhydrate for 6–24 months (Steinhagen et al. 1978; Stone et al. 1979).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects following acute- or intermediate-duration inhalation exposure to various forms of aluminum in humans. Two case reports have been identified in which finger clubbing was observed in male factory workers chronically exposed to aluminum powder (De Vuyst et al. 1986; McLaughlin et al. 1962). Joint pain was reported by a female worker exposed by inhalation to dried alunite residue (a hydrated sulphate of aluminum and

potassium) for 18 months (Musk et al. 1980). Schmid et al. (1995) did not find any significant alterations in bone mineral content (assessed via osteodensitometry) in workers exposed to aluminum powder (average concentration 12.1 mg/m^3) for an average duration of 12.6 years.

No studies were located regarding musculoskeletal effects following acute- or chronic-duration inhalation exposure to aluminum or its compounds in animals. No histological changes were observed in the muscle or bone of Fischer 344 rats or Hartley guinea pigs exposed by inhalation (6 hours/day, 5 days/week) to 6.1 mg Al/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978).

Hepatic Effects. No studies were located regarding hepatic effects in humans following acute- or chronic-duration inhalation exposure to various forms of aluminum. Intermediate occupational inhalation exposure to aluminum fumes, dusts, or powders did not affect liver function or hepatic microanatomy in a group of seven workers as determined from biopsy samples (Mussi et al. 1984).

In animals, no histological or organ weight changes were observed in livers of Fischer 344 rats or Hartley guinea pigs exposed by inhalation (6 hours/day, 5 days/week) to 6.1 mg Al/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978). No acute- or chronic-duration inhalation studies examining the liver were identified.

Renal Effects. No studies were located regarding renal effects in humans following acute-duration inhalation exposure to various forms of aluminum.

No adverse effects on renal function or standard urine tests have been noted in humans following intermediate-duration inhalation exposure to aluminum fumes or dust (Mussi et al. 1984) or chronic-duration inhalation exposure to metallic aluminum powder (De Vuyst et al. 1987; McLaughlin et al. 1962).

No histological or organ weight changes were observed in kidneys of Fischer 344 rats or Hartley guinea pigs exposed by inhalation (6 hours/day, 5 days/week) to 6.1 mg Al/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978).

Endocrine Effects. No studies were located regarding endocrine effects in humans following acute- or intermediate-duration inhalation exposure to various forms of aluminum. Post-mortem enlargement of

the thyroid was reported in the case of a male factory worker chronically exposed by inhalation to aluminum flake powder (McLaughlin et al. 1962).

No studies were located regarding endocrine effects in animals following acute- or chronic-duration inhalation exposure to aluminum or its compounds. No adverse histological changes were observed in the adrenal, thyroid, or pituitary glands of Fischer 344 rats or Hartley guinea pigs exposed by inhalation (6 hours/day, 5 days/week) to 6.1 mg Al/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978).

Dermal Effects. No studies were located regarding dermal effects in animals following acute- or chronic-duration inhalation exposure to various forms of aluminum. No histologic changes of the skin were observed in Fischer 344 rats or Hartley guinea pigs exposed by inhalation to 6.1 mg Al/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978).

Ocular Effects. No studies were located regarding ocular effects in humans following acute- or intermediate-duration inhalation exposure to various forms of aluminum. No adverse effects were observed during an eye examination in a man chronically exposed by inhalation to metallic aluminum and aluminum oxide powders (De Vuyst et al. 1987).

No studies were located regarding ocular effects in animals following acute- or chronic-duration inhalation exposure to aluminum or its compounds. No histological changes were observed in the eyes of Fischer 344 rats or Hartley guinea pigs exposed by inhalation to 6.1 mg Al/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978).

Body Weight Effects. No studies were located regarding body weight effects in humans following inhalation exposure to aluminum or its compounds. Unspecified body weight decreases were reported for male Golden Syrian hamsters acutely exposed via whole-body inhalation to 3, 10, or 33 mg Al/m^3 as alchlor, a common component of antiperspirants (Drew et al. 1974). In contrast, no body weight effects were observed in Sprague-Dawley rats exposed by inhalation to 0.37 mg Al/m^3 as aluminum chloride or 0.41 mg Al/m^3 as aluminum fluoride dust for 5 months (Finelli et al. 1981), or in Fischer 344 rats or Hartley guinea pigs exposed by inhalation to 6.1 mg Al/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978) or to 0.61 mg Al/m^3 as aluminum chlorhydrate for up to 24 months (Stone et al. 1979). Significant reduction in body weight (>10%) was observed in Fischer 344 rats after 24 months of exposure to 6.1 mg/m^3 as aluminum chlorhydrate. No effect on body weight was seen in Hartley guinea

pigs similarly exposed (Stone et al. 1979). These NOAEL and LOAEL values are recorded in Table 3-1 and plotted in Figure 3-1.

Metabolic Effects. No studies were located regarding metabolic effects in humans following acute- or chronic-duration inhalation exposure to various forms of aluminum. No adverse effect on phosphate metabolism was identified in humans following intermediate-duration inhalation exposure to aluminum fumes or dust (Mussi et al. 1984).

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological/lymphoreticular effects in humans after acute- or intermediate-duration inhalation exposure to various forms of aluminum. Helper T-lymphocyte alveolitis and blastic transformation of peripheral blood lymphocytes in the presence of soluble aluminum compounds *in vitro* were found in an individual with sarcoid-like epitheliod granulomas and exposed to metallic aluminum and aluminum dust (De Vuyst et al. 1987). Additional testing 1 year after termination of exposure indicated the man no longer had alveolitis. A significantly higher percentage of $CD4^{-}CD8^{+}$ T lymphocytes were observed in aluminum electrolytic workers (He et al. 2003).

Several animal studies have found histological alterations in the lymphoreticular system, in particular granulomas in the hilar lymph nodes; these effects are secondary to the pulmonary effects (Steinhagen et al. 1978; Thomson et al. 1986) and resulted from the removal of aluminum from the lungs by alveolar macrophages.

3.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans following acute- or intermediate-duration inhalation exposure to various forms of aluminum. A number of studies have investigated the neurotoxic potential in workers chronically exposed to aluminum. With the exception of isolated cases (for example, McLaughlin et al. 1962), none of these studies reported overt signs of neurotoxicity in workers exposed to aluminum dust (potroom and foundry workers) (Bast-Pettersen et al. 1994; Dick et al. 1997; Hosovski et al. 1990; Sim et al. 1997; White et al. 1992), in aluminum welders (Hänninen et al. 1994; Sjögren et al. 1996), or in miners exposed to McIntyre powder (finely ground aluminum and aluminum oxide) (Rifat et al. 1990). Higher incidences of subjective neurological symptoms (e.g., incoordination, difficulty buttoning, problems concentrating, headaches, depression, fatigue) were reported in aluminum potroom or foundry workers at aluminum smelters (Halatek et al. 2005; Iregren et

al. 2001; Sim et al. 1997; Sińczuk-Walczak et al. 2003; White et al. 1992), workers exposed to aluminum flake powder (Iregren et al. 2001), and aluminum welders (Bast-Pettersen et al. 2000; Riihimäki et al. 2000; Sjögren et al. 1990). Among the studies examining the potential association between neurological symptoms and aluminum exposure estimates (urinary and/or blood aluminum levels), some found a significant association (Riihimäki et al. 2000; Sińczuk-Walczak et al. 2003) and others did not (Bast-Pettersen et al. 2000; Iregren et al. 2001; Kiesswetter et al. 2007).

Subclinical effects have been reported in various types of aluminum workers. Significant alterations in performance tests assessing reaction time, eye-hand coordination, memory, and/or motor skills were found in aluminum foundry workers (Hosovski et al. 1990; Polizzi et al. 2001), aluminum welders (Akila et al. 1999; Bast-Pettersen et al. 2000; Buchta et al. 2005; Riihimäki et al. 2000; Sjögren et al. 1990), electrolyte workers (He et al. 2003), and miners exposed to McIntyre powder (Rifat et al. 1990). Three studies of aluminum welders did not find significant decrements in neurobehavioral performance as compared to controls; however, significant correlations between aluminum exposure estimates (urinary or plasma aluminum levels or air aluminum levels) and memory and/or reaction-time tests were found (Bast-Pettersen et al. 2000; Buchta et al. 2003; Hänninen et al. 1994). Other studies did not find alterations in neuroperformance tests in aluminum potroom workers (Sim et al. 1997) or aluminum welders (Kiesswetter et al. 2007); two studies in aluminum welders did not find effects on motor performance (Buchta et al. 2003, 2005). A higher incidence of subclinical tremors was found in a study of potroom workers (Bast-Pettersen et al. 1994); another study did not find a significant alteration (Dick et al. 1997). Several studies have examined aluminum's potential to induce quantitative EEG changes; some studies found alterations (Hänninen et al. 1994; Riihimäki et al. 2000; Sińczuk-Walczak et al. 2003) and others did not (Iregren et al. 2001). In general, the available occupational exposure studies poorly characterize aluminum exposure. Some of the studies reported aluminum air concentrations for a single time period (Dick et al. 1997; Sim et al. 1997; Sjögren et al. 1996; White et al. 1992) or a couple of time periods (Buchta et al. 2003; Kiesswetter et al. 2007), but did not have earlier monitoring data when aluminum exposures may have been higher. A meta-analysis using data from most of these studies found a statistically significant decline in performance on the digit symbol neurobehavioral test (Meyer-Baron et al. 2007). Although decreases in performance were observed for other neurobehavioral tests, the differences were not statistically significant. The lack of adequate exposure monitoring data, potential exposure to other neurotoxicants, and the different types of aluminum exposure make it difficult to draw conclusions regarding the neurotoxic potential of inhaled aluminum in workers.

Three studies have examined the possible association between occupational exposure to aluminum and the risk of Alzheimer's disease. Two case-control studies did not find a significant association between occupational exposure to aluminum dust or fumes and the risk of Alzheimer's disease (Graves et al. 1998; Salib and Hillier 1996). Another study of former aluminum dust-exposed workers (retired for at least 10 years) found some impairment in some tests of cognitive function; the investigators raised the possibility that cognitive impairment may be a pre-clinical indicator of Alzheimer's disease (Polizzi et al. 2002).

No studies were located regarding neurological effects in animals following acute-duration inhalation exposure to various forms of aluminum. No brain weight or histological changes were observed in Fischer 344 rats or Hartley guinea pigs exposed by inhalation to up to 6.1 mg Al/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978). No brain weight effects were observed in Sprague-Dawley rats exposed by inhalation to 0.37 mg Al/m^3 as aluminum chloride or 0.41 mg Al/m^3 as aluminum fluoride for 5 months, although tissues were not examined histologically (Finelli et al. 1981). No brain weights were observed in Fischer 344 rats or Hartley guinea pigs exposed by inhalation to 6.1 mg Al/m^3 as aluminum chlorhydrate for up to 24 months (Stone et al. 1979).

3.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following acute-, intermediate-, or chronic-duration inhalation exposure to various forms of aluminum.

No reliable studies were located regarding reproductive effects in animals following acute- or chronic-duration inhalation exposure to various forms of aluminum. No histological changes were observed in reproductive tissues of Fischer 344 rats or Hartley guinea pigs exposed by inhalation to 6.1 mg Al/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978). These NOAEL values are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to various forms of aluminum.

3.2.1.7 Cancer

No studies were located regarding cancer effects in humans following acute- or intermediate-duration inhalation exposure to various forms of aluminum.

A reported high incidence of bladder cancer in a region of Quebec, Canada where aluminum production takes place (Wigle 1977) resulted in the initiation of a case-control study (Theriault et al. 1984a). Workers in five aluminum reduction plants were assessed with respect to incidence of bladder cancer. The number of men working in the plants was 300–1,200 except for one plant with 7,800 workers. The number of bladder cancer cases was collected from regional hospitals over a 10-year period, and the number of current or former employees from the aluminum plants identified. For each case, three controls who had never had bladder cancer were selected. Detailed occupational histories of each man (case and controls) were collected from the companies and included each division, department, and job to which the men had been assigned; smoking history; and estimated assessment of tar and PAH exposure (based on benzene soluble material and benz(a)pyrene concentrations in workplace air) for each occupation. An index of lifetime exposure of each worker to tar and PAHs was created. Over the 10-year study period, 488 cases of bladder cancer were found in men from the designated regions. Of these, 96 were identified as being current or former aluminum company employees, and 11 were eliminated from the study because they had worked <12 months at the companies. The distribution of tumors was as follows: transitional epitheliomas grade I (n=3), grade II (n=43), grade III (n=18), and grade IV (n=21). The mean age at diagnosis was 61.7 years, and the mean age at first employment in aluminum work was 28.2 years. The interval between beginning of employment in the aluminum industry and diagnosis was 23.9 years. A higher proportion of cases than controls were smokers. The risk for bladder cancer was highest in workers in Soderberg reactor rooms (where the reduction process takes place), and risk increased steadily with time worked in this department. The risk also increased steadily with estimated exposure to tar and PAHs. The interaction between cigarette smoking and PAH exposure in the generation of bladder cancer was more than additive.

Several studies on cancer mortality patterns have been conducted in aluminum reduction factory workers (Gibbs and Horowitz 1979; Milham 1979; Mur et al. 1987; Rockette and Arena 1983). The workplace inhalation exposure was to aluminum dust or fumes for chronic durations, but the exposure levels were not determined. In addition to aluminum, most workers were concurrently exposed by inhalation to known carcinogens, such as tobacco smoke or PAHs from coal tars. In a historical prospective study of 2,103 aluminum production workers, standardized mortality ratios (SMRs) of 117 for lung cancer

(35 cases), 180 for pancreatic cancer (9 cases), and 184 for all lymphatic and hematopoietic cancers (17 cases) were observed (Milham 1979). Smoking histories were not available, and only the SMR for lymphatic and hematopoietic cancers were statistically significant. In a study that focused on mortality from lung cancer in a group of 5,406 aluminum production workers (Gibbs and Horowitz 1979), a dose-response relationship was observed between lung cancer mortality and both years of exposure to tar and "tar-years" in specific occupations. A study of mortality patterns in 21,829 aluminum production workers in the United States (Rockette and Arena 1983) indicated that the risk of lung cancer mortality increased among workers with ≥25 years of experience in the carbon bake department, who presumably had higher exposure to potential hydrocarbon carcinogens than other workers. Increased deaths from bladder and hematolymphopoietic cancers were also reported.

Based on current evidence, the International Agency for Research on Cancer (IARC) has stated (IARC 1984) that "the available epidemiological studies provide limited evidence that certain exposures in the aluminum production industry are carcinogenic to humans, giving rise to cancer of the lung and bladder. A possible causative agent is pitch fume." It is important to emphasize that the potential risk of cancer in the aluminum production industry is probably due to the presence of known carcinogens (e.g., PAHs) in the workplace and is not due to aluminum or its compounds.

No reliable studies were located regarding cancer effects in animals following acute- or intermediate-duration inhalation exposure to aluminum or its compounds. An increase in cancer was not observed in male and female Wistar rats exposed via whole-body inhalation to atmospheres containing 2.18–2.45 mg Al/m^3 as alumina fibers (≈96% aluminum oxide) for 86 weeks (Pigott et al. 1981).

3.2.2 Oral Exposure

Major sources of human oral exposure to aluminum include food (due to its use in food additives, food and beverage packaging, and cooking utensils), drinking water (due to its use in municipal water treatment), and aluminum-containing medications (particularly antacid/antiulcer and buffered aspirin formulations) (Lione 1985b). Dietary intake of aluminum, estimated to be in the 0.10–0.12 mg Al/kg/day range in adults (Pennington and Schoen 1995), has not been of historical concern with regard to toxicity due to its presence in food and the generally recognized as safe (GRAS) status of aluminum-containing food additives by the FDA. Users of aluminum-containing medications that are healthy (i.e., have normal kidney function) can ingest much larger amounts of aluminum than in the diet, possibly as high as 12–

71 mg Al/kg/day from antacid/antiulcer products and 2–10 mg Al/kg/day from buffered analgesics when taken at recommended dosages (Lione 1985b).

The oral toxicity of aluminum in animals is well-studied, although many of the studies are limited by a lack of reported information on aluminum content in the base diet. Commercial grain-based feeds for laboratory animals contain high levels of aluminum that typically far exceed the aluminum content of the human diet. Commercial laboratory animal chow can significantly contribute to total experimental exposure, as well as provide excess and variable amounts of essential and nonessential trace minerals and metal binding ligands that can alter aluminum uptake in comparison to diets that are semipurified or purified in which trace metal levels are precisely determined (Golub et al. 1992b). Base diets containing 250–350 ppm Al were used in some rat and mouse studies, but this cannot be assumed to be a normal or representative concentration range because analyses for aluminum were not routinely performed, substantial brand-to-brand and lot-to-lot variations are apparent, and formal surveys of aluminum content of laboratory animal feed are not available. For example, concentrations ranging from 60 to 280 ppm Al for Panlab rodent standard diet (Colomina et al. 1998; Domingo et al. 1987a, 1993) and 120–8,300 ppm for Purina Rodent Laboratory Chow (Fleming and Joshi 1987; Provan and Yokel 1990; Varner et al. 1994, 1998) have been reported. Due to the likelihood of significant base dietary exposure to aluminum, studies with insufficient information on aluminum content in the base diet must be assumed to underestimate the actual aluminum intake. The magnitude of the underestimate can be considerable. For example, based on approximate values of 250 ppm (Colomina et al. 1998; Domingo et al. 1993) and 350 ppm (Oteiza et al. 1993) for Al in feed used in some studies in rats and mice, respectively, and using reference values for food consumption and body weight in rats and mice (EPA 1988) for ingestion during the period from weaning to 90 days, estimated doses of 25 mg Al/kg/day (rats) and 68 mg Al/kg/day (mice) may be provided by diet alone. These figures can represent a significant portion of the intake for which Table 3-2 reports health effects in animal studies. Consequently, although studies with inadequate data on base dietary levels of aluminum provide useful information on health effects of aluminum, NOAELs and LOAELs from these studies cannot be assumed to be accurate, they may not be suitable for comparison with effect levels from studies that used diets with known amounts of aluminum, and are not included in Table 3-2 and Figure 3-2. Studies for which data on base dietary aluminum content are available are mainly limited to those conducted by Golub and coworkers (Donald et al. 1989; Golub and Germann 1998, 2001; Golub et al. 1989, 1992a, 1992b, 1994, 1995, 2000; Oteiza et al. 1993) and Domingo and coworkers (Colomina et al. 1992, 1994, 1998, 2005; Domingo et al. 1987a, 1987b, 1989, 1993; Gomez et al. 1986, 1991; Paternain et al. 1988; Roig et al. 2006).

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Sprague-Dawley)	once (G)				261 (LD50)	Llobet et al. 1987 Aluminum nitrate	
2	Rat (Sprague-Dawley)	once (G)				370 (LD50)	Llobet et al. 1987 Aluminum chloride	
3	Rat (Sprague-Dawley)	once (G)				162 (LD50)	Llobet et al. 1987 Aluminum bromide	
4	Mouse (Swiss-Webster)	once (G)				286 (LD50)	Llobet et al. 1987 Aluminum nitrate	
5	Mouse (Swiss-Webster)	once (G)				222 (LD50)	Llobet et al. 1987 Aluminum chloride	
6	Mouse (Swiss-Webster)	once (G)				164 (LD50)	Llobet et al. 1987 Aluminum bromide	
7	Mouse (Dobra Voda)	once (G)				770 M (LD50)	Ondreicka et al. 1966 Aluminum chloride	
8	Mouse (Dobra Voda)	once (G)				980 M (LD50)	Ondreicka et al. 1966 Aluminum sulfate	

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
9	Rabbit (New Zealand)	once (GW)				540 F (5/5 died)	Yokel and McNamara 1985 Aluminum lactate	
Developmental								
10	Rat (Sprague-Dawley)	Gd 6-19 (F)		110			McCormack et al. 1979 Aluminum chloride	
11	Mouse (Swiss)	Gd 6-15 (GW)		141 F			Domingo et al. 1989 Aluminum hydroxide	
INTERMEDIATE EXPOSURE								
Systemic								
12	Rat (NS)	100 d (W)	Bd Wt		97 M (decreased body weight gain in aged rats)		Colomina et al. 2002 Aluminum nitrate	Citric acid was added to water to increase absorption.
13	Rat (Sprague-Dawley)	100 d (W)	Cardio	284 F			Domingo et al. 1987b Aluminum nitrate	
			Hemato	284 F				
			Hepatic	284 F				
			Renal	284 F				
			Bd Wt	284 F				

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
14	Rat (Sprague-Dawley)	1 mo (W)	Resp	133 F			Gomez et al. 1986 Aluminum nitrate	
			Cardio	133 F				
			Gastro	133 F				
			Hemato	52 F	79 F (hyperemia in the red pulp of the spleen)			
			Hepatic	79 F	133 F (hyperemia in the liver, periportal monocytic infiltrate in liver)			
			Renal	133 F				
			Bd Wt	133 F				
15	Rat (Wistar)	10 wk (F)	Musc/skel	90 M			Konishi et al. 1996 Aluminum lactate	
			Bd Wt	90 M				
16	Rat (Sprague-Dawley)	8 mo (W)	Hemato		230 F (decreased hemoglobin, hematocrit and haptoglobin levels, increased reticulocyte levels; inhibition of CFU-E proliferation)		Vittori et al. 1999 Aluminum citrate	
17	Mouse (Swiss-Webster)	Gd 1- Ld 21 (F)	Bd Wt	330 F			Donald et al. 1989 Aluminum lactate	

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
18	Mouse (Swiss-Webster)	6 wk (F)	Bd Wt	130 F			Golub et al. 1989 Aluminum lactate	
19	Mouse (Swiss-Webster)	Gd 1-21 Ld 1-21 Gd 1- Ld 21 (F)	Bd Wt		250 F (decreased body weight gain in lactating mice)		Golub et al. 1992a Aluminum lactate	
20	Mouse (Swiss-Webster)	90 d (F)	Bd Wt	195 F			Golub et al. 1992b Aluminum lactate	
21	Mouse (Swiss-Webster)	7-10 wk (F)	Bd Wt	170 F			Oteiza et al. 1989 Aluminum lactate	
22	Mouse (Swiss-Webster)	5 or 7 wk (F)	Hemato	195 F			Oteiza et al. 1993 Aluminum chloride	
			Hepatic	195 F				
			Bd Wt	195 F				
23	Dog (Beagle)	6 mo (F)	Cardio	88			Katz et al. 1984 Aluminum phosphate	
			Hemato	88				
			Hepatic	88				
			Renal	88				
			Endocr	88				
			Ocular	88				

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
24	Dog (Beagle)	26 wk (F)	Cardio	75			Pettersen et al. 1990 Aluminum phosphate	
			Hemato	75				
			Renal	75				
			Endocr	75				
Immuno/ Lymphoret								
25	Human	3 x/d 6 wk (F)		25			Gräske et al. 2000 Aluminum hydroxide	
26	Rat (Sprague-Dawley)	100 d (W)		259 F			Domingo et al. 1987b Aluminum nitrate	
27	Rat (Sprague-Dawley)	1 mo (W)		52 F	79 F (hyperemia in the red pulp of the spleen)		Gomez et al. 1986 Aluminum nitrate	
28	Mouse (Swiss-Webster)	Gd 0- pnd 180 (F)			200 (in offspring: 19% increased absolute spleen weights; depressed spleen cell concentrations of interleukin-2, interferon-g and tumor necrosis factor-a; deficiency of CD4+ cells in T-cell populations)		Golub et al. 1993 Aluminum lactate	

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
29	Mouse (Swiss-Webster)	6 wk (F)		107 F			Yoshida et al. 1989 Aluminum lactate	
30	Mouse (Swiss-Webster)	Gd 1- pnd 31 (F)			155 F (increased susceptibility to bacterial infection in dams)		Yoshida et al. 1989 Aluminum lactate	
Neurological								
31	Rat (NS)	100 d (W)		97 M			Colomina et al. 2002 Aluminum nitrate	Citric acid was added to water to increase absorption.
32	Rat (Sprague-Dawley)	6.5 mo (W)		125 M			Domingo et al. 1996 Aluminum nitrate	Citric acid was added to water to improve aluminum absorption.
33	Rat (Wistar)	daily 3 mo (W)		21.5 M	43.1 M (impairment of post-rotatory nystagmus)		Mameli et al. 2006 Aluminum chloride	
34	Mouse (Swiss-Webster)	Gd 1- Ld 21 (F)		330 F			Donald et al. 1989 Aluminum lactate	
35	Mouse (Swiss-Webster)	NR (F)		100 M			Golub and Germann 1998 Aluminum lactate	

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
36	Mouse (Swiss-Webster)	6 wk (F)		62 F	130 F (decreased total activity and vertical activity)		Golub et al. 1989 Aluminum lactate	
37	Mouse (Swiss-Webster)	Gd 1-21 Ld 1-21 Gd 1- Ld 21 (F)		250 F			Golub et al. 1992a Aluminum lactate	
38	Mouse (Swiss-Webster)	90 d (F)			195 F (decreased forelimb and hindlimb grip strengths and startle response, decreased total activity, horizontal activity, and percent interval with high activity counts)		Golub et al. 1992b Aluminum lactate	
39	Mouse (Swiss-Webster)	Gd 1- pnd 170 (F)		100 M	200 M (increased cage mate aggression)		Golub et al. 1995 Aluminum lactate	
40	Mouse (Swiss-Webster)	5 or 7 wk (F)			195 F (reduced forelimb and hindlimb grip strength)		Oteiza et al. 1993 Aluminum chloride	
41	Dog (Beagle)	26 wk (F)		75			Pettersen et al. 1990 Aluminum phosphate	

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Reproductive								
42	Mouse (Swiss-Webster)	Gd 1- Ld 21 (F)			155 F (altered gestational length)		Donald et al. 1989 Aluminum lactate	
43	Mouse (Swiss-Webster)	Gd 1-21 Ld 1-21 Gd 1- Ld 21 (F)		250 F			Golub et al. 1992a Aluminum lactate	
Developmental								
44	Rat (Sprague-Dawley)	15 d premating Gd 1- Ld 21 (W)			103 (decreased forelimb grip strength, decreased pup body weight)		Colomina et al. 2005 Aluminum nitrate	Citric acid was added to water to increase absorption.
					53 (delay in vaginal opening)			
45	Mouse (Swiss-Webster)	Gd 1- Ld 21 (F)			155 (decreased forelimb and increased hindlimb grip strength and increased foot splay in weanlings)		Donald et al. 1989 Aluminum lactate	
46	Mouse (Swiss-Webster)	Gd 1- pnd 35 (F)		330 M			Golub and Germann 1998 Aluminum lactate	

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
47	Mouse (Swiss-Webster)	Gd 0- Ld 21, pnd 21-35 (F)		26[b]	130 (impaired performance on the water maze test in females, shorter latency to fall in wire suspension test in males)		Golub and Germann 2001 Aluminum lactate	Diet levels of phosphorus, calcium, magnesium, iron, and zinc were marginally adequate.
48	Mouse (Swiss-Webster)	Gd 1- pnd 35 (F)			330 (altered myelination in spinal cord)		Golub and Tarara 1999 Aluminum lactate	
49	Mouse (Swiss-Webster)	Gd 1-19 Gd 1- Ld 21 Ld 1-21 (F)			250 (decrease in pup weight, crown-rump length, forelimb grip strength in gestation exposed group, increase in hindlimb grip and tail withdrawal times in gestation and lactation exposed groups, increase in negative geotaxis latency in lactation exposed groups)		Golub et al. 1992a Aluminum lactate	
50	Mouse (Swiss-Webster)	Gd 1- pnd 21 (F)			155 (decreased fore- and hindlimb grip strengths and startle response)		Golub et al. 1995 Aluminum lactate	

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
51	Mouse (Swiss-Webster)	Gd 1- pnd 31 (F)		330			Yoshida et al. 1989 Aluminum lactate	Assessed immunotoxicity.
CHRONIC EXPOSURE								
Systemic								
52	Rat (Sprague-Dawley)	Gd 1- Ld 21 weaning-1 yr of age or 2 yr of age (W)	Bd Wt	103 M			Roig et al. 2006 Aluminum nitrate	Citric acid was added to water to increase absorption.
53	Rat (Long- Evans)	2.5 yr (W)	Resp	0.6			Schroeder and Mitchener 1975a Aluminum sulfate	
			Cardio	0.6				
			Hepatic	0.6				
			Renal	0.6				
			Bd Wt	0.6				
54	Mouse (Swiss-Webster)	2 yr conception to 24 mo (F)	Bd Wt		100 F (20% decrease in body weight gain)		Golub et al. 2000 Aluminum lactate	

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
55	Mouse (Swiss)	lifetime (W)	Resp	1.2			Schroeder and Mitchener 1975b Aluminum sulfate	
			Cardio	1.2				
			Hepatic	1.2				
			Renal	1.2				
			Bd Wt	1.2				
Neurological								
56	Rat (Sprague-Dawley)	Gd 1- Ld 21 weaning-1 yr of age or 2 yr of age (W)		103 M			Roig et al. 2006 Aluminum nitrate	Citric acid was added to water to increase absorption.
57	Mouse (Swiss-Webster)	2 yr conception to 24 mo (F)			100[c]	(decreased forelimb and hindlimb grip strength, decreased thermal sensitivity)	Golub et al. 2000 Aluminum lactate	

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

b Used to derive an intermediate-duration oral minimal risk level (MRL) of 0.9 mg Al/kg/day; dose divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability).

c Used to derive a chronic-duration oral MRL of 0.3 mg Al/kg/day; dose divided by an uncertainty factor of 300 (10 for the use of a LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; CFU-E = colony-forming unit-erythroid; d = day(s); (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GW) = gavage in water; Hemato = hematological; Ld = lactation day; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; Immuno/Lymphoret = immunological/lymphoreticular; M = male; mo = month(s); NOAEL = no-observed-adverse-effect level; NR = not reported; pnd = post-natal day; Resp = respiratory; (W) = drinking water; wk = week(s); x = time(s); yr = year(s)

Figure 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral

Acute (≤14 days)

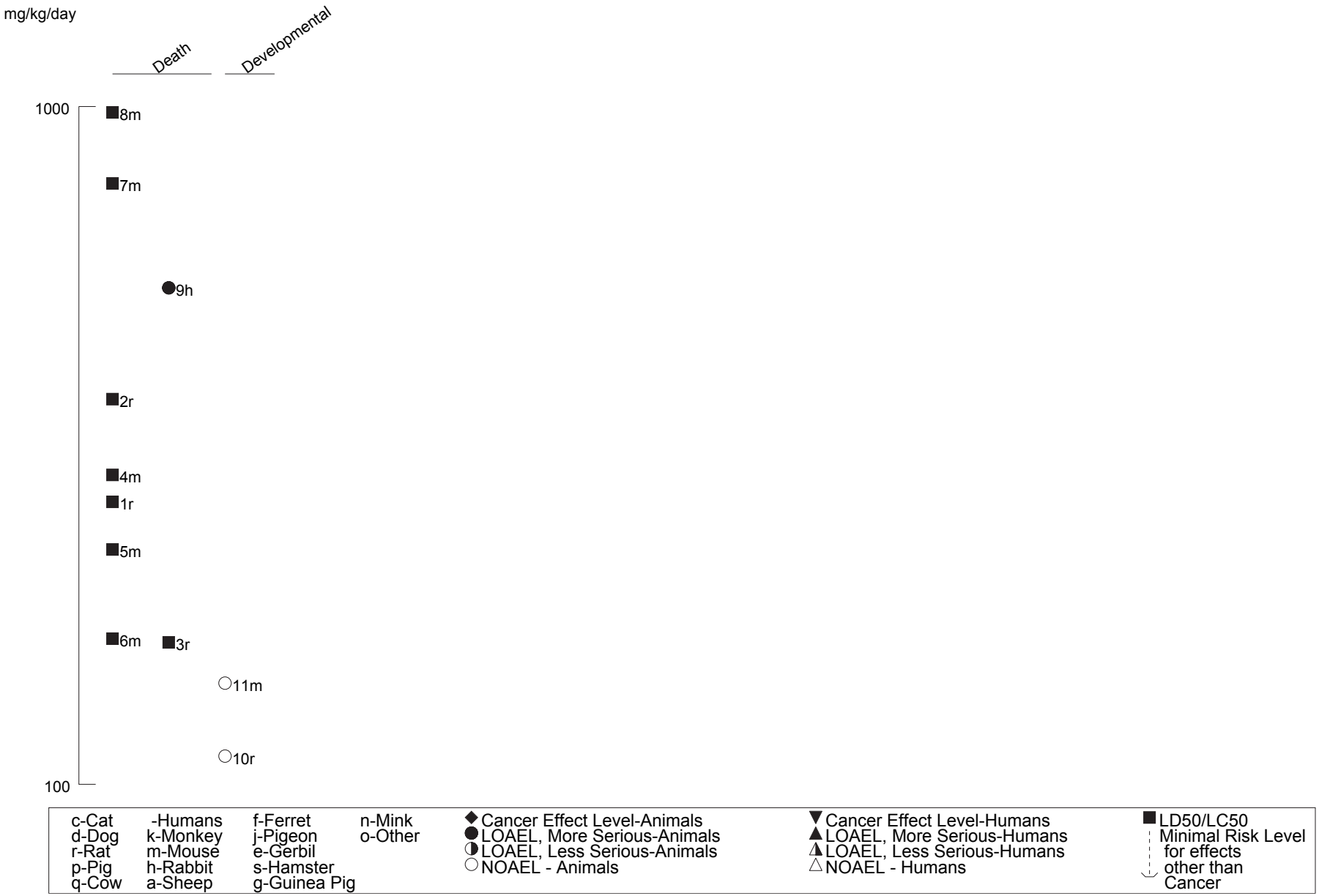


Figure 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral *(Continued)*

Intermediate (15-364 days)

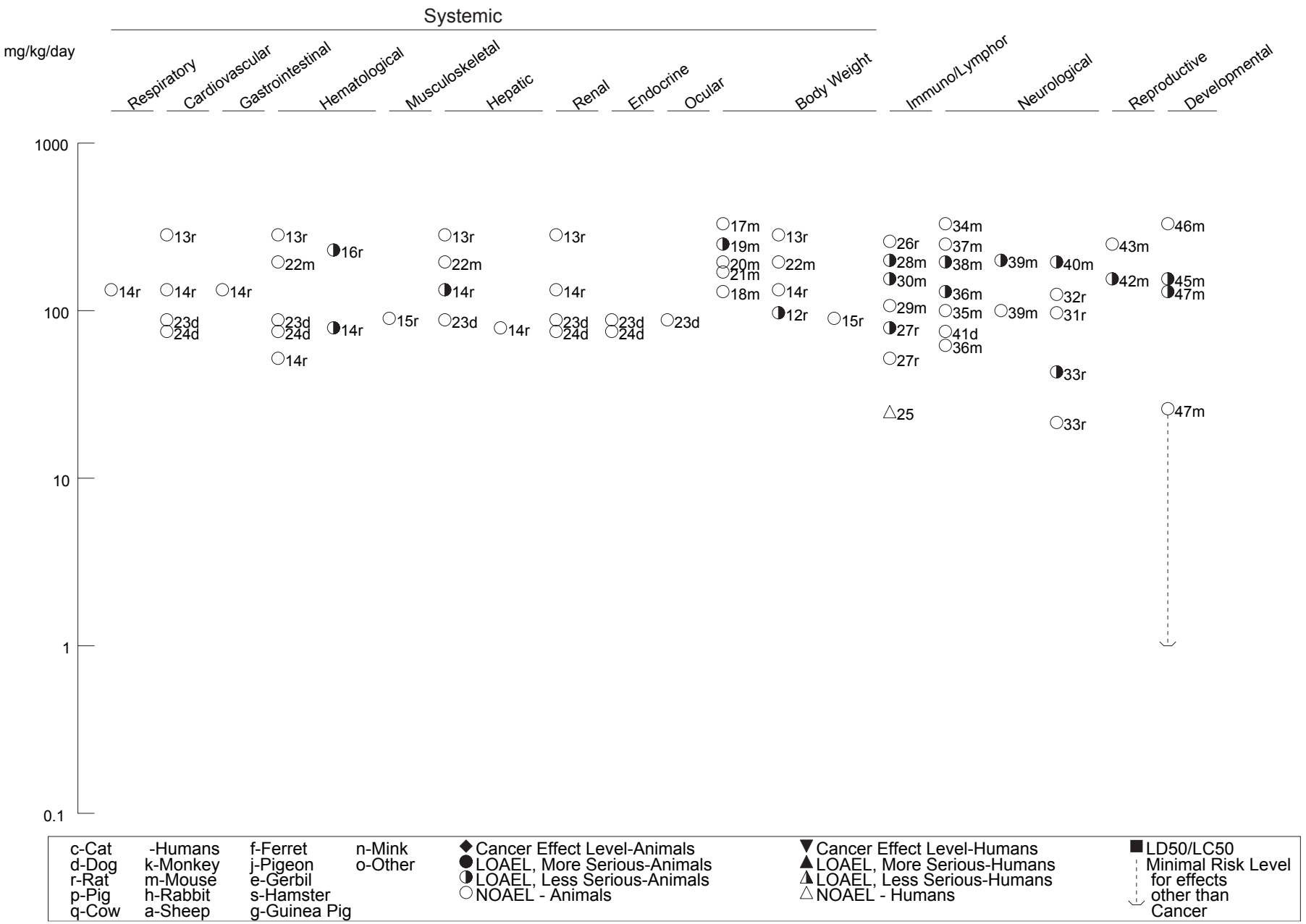


Figure 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral *(Continued)*

Intermediate (15-364 days)

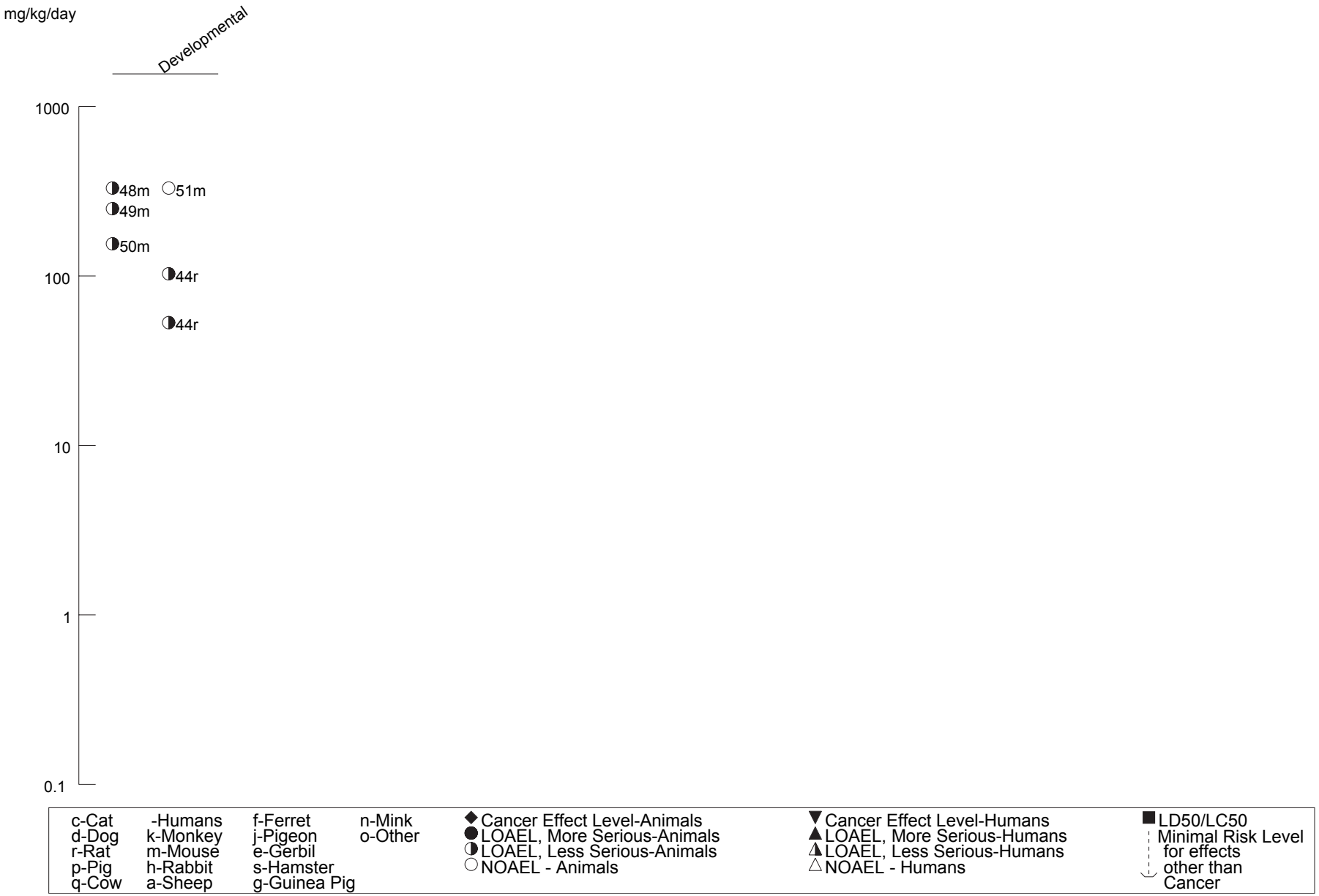
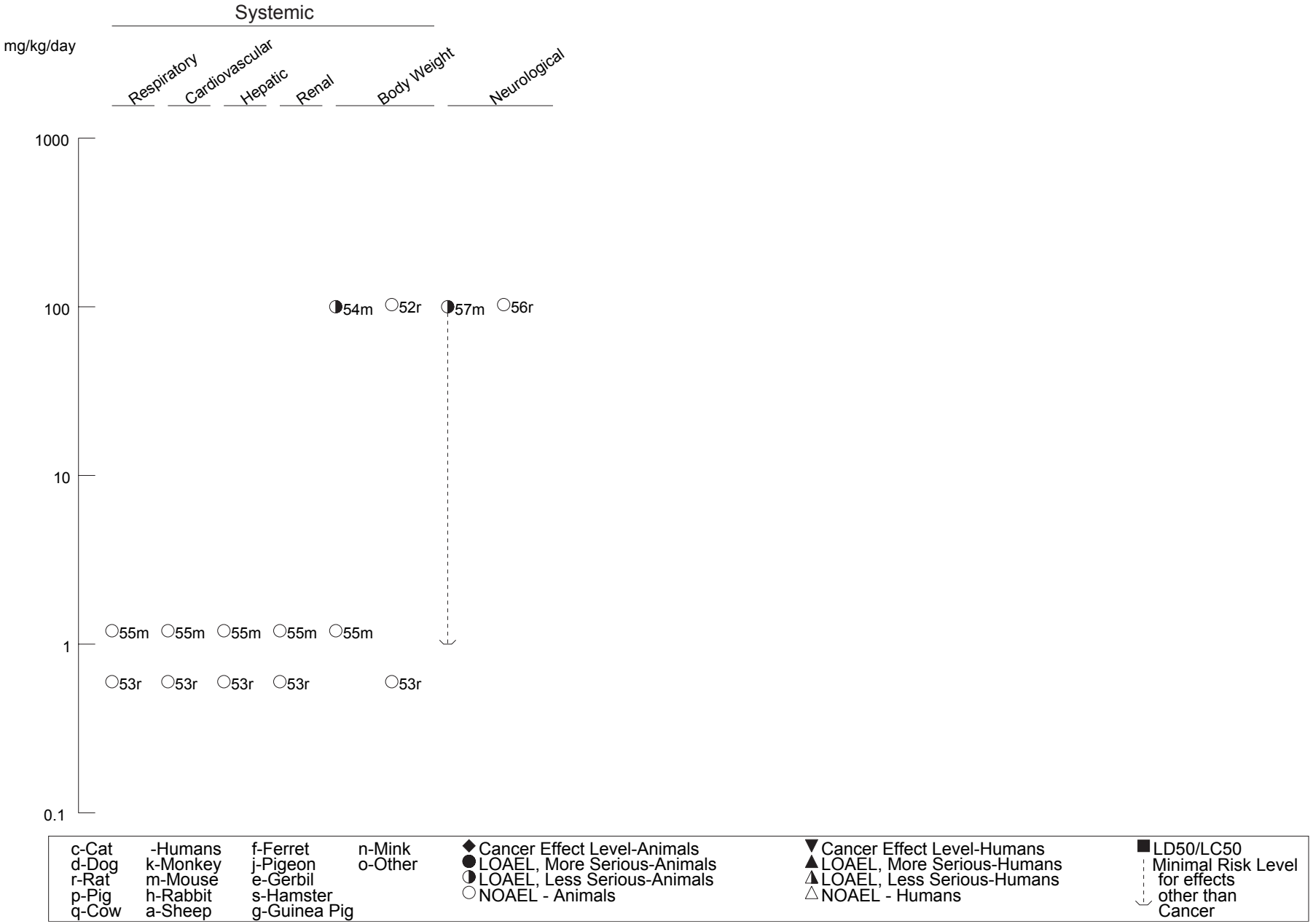


Figure 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral *(Continued)*

Chronic (≥365 days)



Although levels of human oral intake of aluminum may be characterized, it is important to recognize that the amount of aluminum ingested does not provide an actual estimate of exposure without information on bioavailability of the form of aluminum ingested. Similarly, effective doses in the animal studies, including the exact underestimate of aluminum intake in animal studies with insufficient information on aluminum in the base diet, cannot be known without information on bioavailability of the aluminum. As discussed in Section 3.3.1.2, the bioavailability of aluminum is influenced by the form in which it is ingested and the presence of other substances in the gastrointestinal tract, particularly complexing moieties in foods, which may significantly enhance or hinder absorption.

3.2.2.1 Death

No aluminum-related deaths in healthy humans have been reported after oral exposure. One aluminum compound that can be life threatening to humans is aluminum phosphide, a grain fumigant. Accidental or volitional ingestion (to commit suicide) of large amounts has caused death (Chopra et al. 1986; Khosla et al. 1988). The toxicity from this compound is due to the exposure to phosphine gas, which is produced in the gastrointestinal tract after the aluminum phosphide is ingested.

Aluminum caused death in laboratory animals only at doses that are high compared to normal human exposure. Data on acute lethality of ingested aluminum are summarized below. For aluminum bromide, LD_{50} (lethal dose, 50% kill) values of 162 and 164 mg Al/kg have been reported in Sprague-Dawley rats and Swiss Webster mice, respectively (Llobet et al. 1987). For the nitrate form, LD_{50} values of 261 and 286 mg Al/kg have been reported for Sprague-Dawley rats and Swiss Webster mice, respectively (Llobet et al. 1987). For the chloride form, LD_{50} values of 370, 222, and 770 mg Al/kg have been reported for Sprague-Dawley rats, Swiss Webster mice, and male Dobra Voda mice, respectively (Llobet et al. 1987; Ondreicka et al. 1966). The LD_{50} for aluminum sulfate in male Dobra Voda mice was reported as 980 mg Al/kg (Ondreicka et al. 1966). Time to death and clinical signs were not reported in these studies. A single gavage exposure to 540 mg Al/kg as aluminum lactate was fatal to all 5 lactating female New Zealand rabbits tested (Yokel and McNamara 1985). Time to death was reported as 8–48 hours.

Intermediate-duration oral exposure to aluminum has also been shown to cause death. Mortality occurred in female Swiss Webster mice exposed to aluminum lactate in the diet for 42 days throughout gestation and lactation at doses of 184 or 280 mg Al/kg/day (Golub et al. 1987), but not at 330 mg Al/kg/day in a different study (Donald et al. 1989) by the same group of investigators. Severe signs of neurotoxicity (ataxia, paralysis) were noted prior to the deaths. The effects in the Golub et al. (1987) study appear to be

related to semipurified diet composition. In particular, the formulation of the diet was revised by Donald et al. (1989) (and in subsequent studies by Golub and coworkers) by adding a "more generous provision" of several essential nutrients, particularly trace minerals (including calcium, magnesium, phosphate), to avoid the toxicity associated with the aluminum in the original diet. One of nine pregnant Swiss Webster mice that consumed 250 mg Al/kg/day as aluminum lactate in the revised purified diet died (Golub et al. 1992a). No mortality was observed in male Sprague-Dawley rats (7–10 per group) orally exposed to 70 mg Al/kg/day as aluminum chloride in water for 30, 60, or 90 days (Dixon et al. 1979), or up to 158 mg Al/kg/day as aluminum hydroxide in the feed for 16 days (Greger and Donnaubauer 1986); these doses do not include aluminum in the base diet. No male or female Beagle dogs (4/sex/group) died following dietary exposure to 75–80 mg Al/kg/day as sodium aluminum phosphate and base levels of aluminum in the feed for 26 weeks (Pettersen et al. 1990). In chronic-duration studies, exposure to aluminum at 100 mg Al/kg/day as aluminum lactate in the diet or 103 mg Al/kg/day as aluminum nitrate with added citric acid in drinking water did not result in significant alterations in mortality (Golub et al. 2000; Roig et al. 2006).

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

3.2.2.2 Systemic Effects

The highest NOAEL values and all LOAEL values for oral exposure from each reliable study for systemic effects in each species and duration category for aluminum are shown in Table 3-2 and plotted in Figure 3-2; only studies providing information on the levels of aluminum in the base diet are included in Table 3-2 and Figure 3-2.

Respiratory Effects. No studies were located regarding respiratory effects of various forms of aluminum following intermediate- or chronic-duration oral exposure in humans. Acute-duration oral exposure to aluminum phosphide has been shown to cause pulmonary edema in persons following accidental or volitional ingestion (Chopra et al. 1986; Khosla et al. 1988). The toxicity was probably due to the formation of highly toxic phosphine gas rather than to aluminum exposure.

No studies were located regarding respiratory effects of various forms of aluminum following acute-duration oral exposure in animals. Intermediate- and chronic-duration studies found no organ weight or histological changes in the lungs in rats exposed to 70 mg Al/kg/day as aluminum chloride in drinking

water (base dietary aluminum not reported) for 30, 60, or 90 days (Dixon et al. 1979), rats exposed to 133 mg Al/kg/day as aluminum nitrate in drinking water and base diet for 1 month (Gomez et al. 1986), rats or mice exposed to 0.6 and 1.2 mg Al/kg/day as aluminum potassium sulfate in drinking water (base dietary aluminum not reported), respectively, for 2–2.5 years (Schroeder and Mitchener 1975a, 1975b), or mice exposed to 979 mg Al/kg/day as aluminum potassium sulfate in the feed (base dietary aluminum not reported) for 20 months (Oneda et al. 1994).

Cardiovascular Effects. No studies were located regarding cardiovascular effects of various forms of aluminum following intermediate- or chronic-duration oral exposure in humans. Acute-duration oral exposure to aluminum phosphide has been shown to cause tachycardia, hypotension, cardiovascular electrocardiographic abnormalities, subendocardial infarction, and transient atrial fibrillation in persons who either ingested it accidentally or in suicide attempts (Chopra et al. 1986; Khosla et al. 1988). However, toxicity was probably due to the formation of highly toxic phosphine gas rather than to aluminum exposure.

No studies were located regarding cardiovascular effects of aluminum or its compounds following acute-duration oral exposure in animals. No histological changes were observed in the hearts of male Sprague-Dawley rats given up to 70 mg Al/kg/day as aluminum chloride in drinking water (base dietary aluminum not reported) for 30, 60, or 90 days (Dixon et al. 1979). Similarly, no organ weight or histological changes were found in the hearts of female Sprague-Dawley rats that ingested 133 or 284 mg Al/kg/day as aluminum nitrate in drinking water and base diet for up to 1 month (Gomez et al. 1986) or 100 days, respectively (Domingo et al. 1987b). No organ weight or histological changes were observed in the hearts of dogs that consumed up to 75 mg Al/kg/day (Katz et al. 1984) or 88 mg Al/kg/day (aluminum levels of base diet not provide) (Pettersen et al. 1990) as sodium aluminum phosphate in the diet for 6 months.

Cardiovascular effects were not observed in animals following chronic-duration exposure to aluminum compounds. No histological changes were observed in the hearts of male and female Long Evans rats or Swiss mice given 0.6 or 1.2 mg Al/kg/day as aluminum potassium sulfate in drinking water, respectively, for 2–2.5 years (Schroeder and Mitchener 1975a, 1975b) or B6C3F1 mice that ingested 979 mg Al/kg/day as aluminum potassium sulfate in the diet for 20 months (Oneda et al. 1994). Aluminum levels in the base diet were not reported in these rat and mouse studies, although the animals were fed a low-metal diet in metal-free environmental conditions in the Schroeder and Mitchener (1975a, 1975b) studies.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects of various forms of aluminum following intermediate- or chronic-duration exposure in humans. Unspecified gastrointestinal and bowel problems were reported by people who, for 5 days or more, may have consumed water that contained unknown levels of aluminum sulfate accidentally placed in a water treatment facility in England (Ward 1989). Forty-eight of the exposed persons were examined, but the number of people with gastrointestinal complaints was not reported. It should be noted that the water supply also contained elevated levels of copper and lead which leached from the plumbing systems due to the greater acidity of the water (pH <4). Aluminum and copper levels in body tissues were reported as elevated in scalp hair and fingernails. Acute-duration oral exposure to aluminum phosphide has been shown to cause vomiting and abdominal pain in persons who ingested it either accidentally or in suicide attempts (Chopra et al. 1986; Khosla et al. 1988). However, as noted above, toxicity was probably due to the formation of highly toxic phosphine gas rather than to aluminum exposure.

No studies were located regarding gastrointestinal effects of aluminum or its compounds following acute-duration oral exposure in animals. No organ weight or histological changes were observed in the gastrointestinal tissues of female Sprague-Dawley rats given 133 mg Al/kg/day as aluminum nitrate in drinking water and base diet for up to 1 month (Gomez et al. 1986), or in male or female B6C3F1 mice that ingested 979 mg Al/kg/day as aluminum potassium sulfate in the feed (base dietary aluminum not reported) for 20 months (Oneda et al. 1994).

Hematological Effects. No studies were located regarding hematological effects of various forms of aluminum following acute-, intermediate-, or chronic-duration exposure in humans after oral exposure to aluminum or its compounds.

Repeated exposure to aluminum appears to adversely affect the hematological system of rats and mice. Significant decreases in hemoglobin, hematocrit, and/or erythrocyte osmotic fragility were observed in rats exposed to 420 mg Al/kg/day as aluminum citrate in drinking water for 15 weeks (Garbossa et al. 1998), mice exposed to 13 mg Al/kg as aluminum citrate administered via gavage 5 days/week for 22 weeks (Garbossa et al. 1996), rats exposed to 230 mg Al/kg/day as aluminum citrate in drinking water for 8 months (Vittori et al. 1999), and rats exposed via drinking water to 54.7 mg Al/kg/day as aluminum sulfate in a sodium citrate solution for 18 months (Farina et al. 2005). Exposure to lower concentrations or for shorter durations resulted in no significant damage to the erythrocytes. No alterations in hemoglobin, hematocrit, and/or erythrocyte osmotic fragility were observed in mice exposed to 13 mg Al/kg as aluminum citrate or aluminum chloride administered via gavage 5 days/week for 2 weeks

(Garbossa et al. 1996), rats exposed to 133 mg Al/kg/day as aluminum nitrate in drinking water for 1 month (Gomez et al. 1986), mice exposed to 195 mg Al/kg/day as aluminum citrate in the diet for 5 or 7 weeks (Oteiza et al. 1993), rats exposed to 284 mg Al/kg/day as aluminum nitrate in drinking water for 100 days (Domingo et al. 1987b), rats exposed to 27 mg Al/kg as aluminum citrate administered via gavage 5 days/week for 15 weeks (Garbossa et al. 1996), or dogs exposed to 75 or 88 mg Al/kg/day as aluminum phosphate in the diet for 6 months (Katz et al. 1984; Pettersen et al. 1990). The studies conducted by Domingo et al. (1987b), Gomez et al. (1986), Oteiza et al. (1993), Pettersen et al. (1990), and Vittori et al. (1999) provided information on the levels of aluminum in the base diet; the remaining studies did not provide this information. As highlighted by the Garbossa et al. (1996) study, which used multiple durations, the erythrocytic effects appear to be duration sensitive. No alterations in hemoglobin or hematocrit levels were observed in mice exposed to 13 mg Al/kg as aluminum citrate administered via gavage for 2 weeks; however, significant decreases in these parameters were observed when the exposure was continued for 22 weeks. Additionally, aluminum can alter mature erythrocyte morphology; anisocytosis (abnormal variations in cell size), anisochromia (unequal degree of cell staining), and poikilocytosis (abnormal variation in cell shape) have been observed in rats exposed to 230 mg Al/kg/day as aluminum citrate in drinking water for 8 months (Vittori et al. 1999). Hyperemia in the red pulp of the spleen was reported in rats exposed to 79 mg Al/kg/day as aluminum nitrate in drinking water for 1 month (Gomez et al. 1986); this may be indicative of erythrocyte damage.

There is some evidence that aluminum may affect iron levels in blood; however, this has not been well studied and the results are not consistent across studies. Vittori et al. (1999) did not find significant alterations in plasma iron levels or total iron binding capacity in rats exposed to 230 mg Al/kg/day as aluminum citrate in drinking water for 8 months; however, impaired iron uptake and decreased iron incorporation into heme were measured in bone marrow cells. Farina et al. (2005) found significant decreases in blood iron concentrations and no change in total iron binding capacity in rats exposed to 54.7 mg Al/kg/day as aluminum sulfate in a sodium citrate solution in drinking water for 18 months. Florence et al. (1994) reported decreases in serum iron levels, total iron binding capacity, and transferring saturation in rats exposed to 75 mg Al/kg/day as aluminum citrate in the diet for 6 months; however, the statistical significance of these findings was not reported.

Several studies have shown that aluminum can adversely affect erythropoeisis. Intermediate-duration exposure has been associated with significant inhibition of colony forming units-erythroid (CFU-E) development in bone marrow of mice exposed to 13 mg Al/kg as aluminum citrate or aluminum chloride administered via gavage 5 days/week for 2 or 22 weeks (Garbossa et al. 1996), rats exposed to 27 mg

Al/kg as aluminum citrate administered via gavage 5 days/week for 15 weeks (Garbossa et al. 1998), rats exposed to 420 mg Al/kg/day as aluminum citrate in drinking water for 15 weeks (Garbossa et al. 1998), and rats exposed to 230 mg Al/kg/day as aluminum citrate in drinking water for 8 months (Vittori et al. 1999); the aluminum content of the base diet was not reported in the Garbossa et al. (1996, 1998) studies. Chronic-duration studies did not examine this end point.

Musculoskeletal Effects. Joint pains were common symptoms reported in people in England who, for 5 days or more, consumed unknown levels of aluminum sulfate in drinking water which also contained elevated levels of copper and lead (Ward 1989). Osteomalacia has been observed in healthy individuals following long-term use of aluminum-containing antacids and in individuals with kidney disease. There are numerous case reports of osteomalacia and rickets in otherwise healthy infants and adults using aluminum-containing antacids for the treatment of gastrointestinal illnesses (i.e., ulcers, gastritis, colic) (Carmichael et al. 1984; Chines and Pacifici 1990; Pivnick et al. 1995; Woodson 1998). The aluminum in the antacids binds with dietary phosphorus and prevents its absorption resulting in hypophosphatemia and phosphate depletion. Osteomalacia, characterized by a softening of the bone and resulting in increased spontaneous fractures and pain, has been well documented in dialyzed uremic adults and children exposed to aluminum-contaminated dialysate or orally administered aluminum-containing phosphate-binding agents (Andreoli et al. 1984; Griswold et al. 1983; King et al. 1981; Mayor et al. 1985; Wills and Savory 1989). Decreased aluminum urinary excretion caused by impaired renal function and possibly an increase in gastrointestinal absorption of aluminum (Alfrey 1993) results in increased aluminum body burden leading to markedly increased bone aluminum levels and the presence of aluminum between the junction of calcified and noncalcified bone. For more information on renal patients and aluminum, see Section 3.10.

Although long-term oral exposure to aluminum results in an increase in aluminum levels in the bone (Ahn et al. 1995; Konishi et al. 1996), there is no histological evidence that under normal physiological conditions that the accumulation of aluminum alters the bone structure. No histological alterations were observed in the tibias of male Wistar rats fed 100 mg Al/kg/day as aluminum lactate (aluminum levels in the base diet not reported) for 10 weeks (Konishi et al. 1996).

Hepatic Effects. No studies were located regarding hepatic effects of various forms of aluminum following intermediate- or chronic-duration exposure in humans. Hepatic dysfunction was reported in 1 of 15 people acutely exposed to unspecified amounts of aluminum phosphide (Khosla et al. 1988).

However, the toxicity, as noted above was probably due to the formation of highly toxic phosphine gas rather than to aluminum exposure.

Most animal studies did not find significant alterations in liver weights or liver histology following intermediate- or chronic-duration oral exposure. Hyperemia and periportal monocytic infiltrate were observed in the livers of female Sprague-Dawley rats given 133 mg Al/kg/day as aluminum nitrate in drinking water for 1 month (Gomez et al. 1986). Mild hepatocyte vacuolation was found in male dogs exposed to 75 mg Al/kg/day in the diet for 26 weeks (Pettersen et al. 1990), but the study authors concluded that the hepatic effects probably resulted from a drastic reduction in food consumption and a decrease in body weight.

The remaining studies conducting liver histopathological examinations did not find significant alterations in rats exposed to 70 mg Al/kg/day as aluminum chloride in drinking water for 30, 60, or 90 days (Dixon et al. 1979), rats exposed to 284 mg Al/kg/day as aluminum nitrate in drinking water for 100 days (Domingo et al. 1987b), mice exposed to 49 mg Al/kg/day as aluminum chloride in drinking water for 180 days (Ondreicka et al. 1966), dogs exposed to 88 mg Al/kg/day as aluminum phosphate in the diet for 6 months (Katz et al. 1984), mice exposed to 979 mg Al/kg/day as aluminum sulfate in the diet for 20 months (Oneda et al. 1994), or rats or mice exposed to 0.6 or 1.2 mg Al/kg/day as aluminum sulfate, respectively, in drinking water for a lifetime (Schroeder and Mitchener 1975a, 1975b). Only the Domingo et al. (1987b) and Ondreicka et al. (1966) studies included the levels of aluminum in the base diet.

Renal Effects. No studies were located regarding renal effects of various forms of aluminum following intermediate- or chronic-duration exposure in humans. Acute-duration oral exposure to aluminum phosphide has been shown to cause renal failure, significant proteinuria, and anuria in persons who ingested it either accidentally or in suicide attempts (Chopra et al. 1986; Khosla et al. 1988). However, toxicity was probably due to the formation of highly toxic phosphine gas rather than to aluminum exposure.

Several intermediate- or chronic-duration studies examined for possible effects on the kidneys; most studies did not find any adverse effects. Mild tubular “glomerularnephritis” was observed in dogs exposed to 75 mg Al/kg/day as sodium aluminum phosphate in the diet for 26 weeks (Pettersen et al. 1990); however, the study investigators did not consider this effect to be adverse because it was not accompanied by clinical evidence of kidney dysfunction. The effect may have been secondary to the

drastic reduction in feed intake and decreased body weight also observed in these dogs. No alterations in kidney histopathology were observed in rats exposed to 70 mg Al/kg/day as aluminum chloride in drinking water for 30–90 days (Dixon et al. 1979), rats exposed to 284 mg Al/kg/day as aluminum nitrate in drinking water for 100 days (Domingo et al. 1987b), mice exposed to 49 mg Al/kg/day as aluminum chloride in drinking water for 180 days (Ondreicka et al. 1966), dogs exposed to 88 mg Al/kg/day as aluminum phosphate in the diet for 6 months (Katz et al. 1984), mice exposed to 979 mg Al/kg/day as aluminum sulfate in the diet for 20 months (Oneda et al. 1994), or rats or mice exposed to 0.6 or 1.2 mg Al/kg/day as aluminum sulfate, respectively, in drinking water for a lifetime (Schroeder and Mitchener 1975a, 1975b). With the exception of the Domingo et al. (1987b), Pettersen et al. (1990), and Ondreicka et al. (1966) studies, information on the levels of aluminum in the base diet was not reported.

Endocrine Effects. No studies were located regarding endocrine effects of various forms of aluminum following acute-, intermediate-, or chronic-duration oral exposure in humans.

No studies were located regarding endocrine effects of aluminum or its compounds following acute-duration exposure in animals. No organ weight or histological changes were observed in the thyroid, adrenal, or pituitary glands of male and female Beagle dogs that consumed up to 75 (Pettersen et al. 1990) or 88 (Katz et al. 1984) mg Al/kg/day as sodium aluminum phosphate in the diet for 6 months; the doses in the Katz et al. (1984) study do not include aluminum in the base diet.

Dermal Effects. No studies were located regarding dermal effects of various forms of aluminum following intermediate- or chronic-duration oral exposure in humans. Skin rashes were common symptoms reported by 48 people in England who consumed drinking water containing unknown levels of aluminum sulfate for approximately 5 days (Ward 1989). The water also contained elevated levels of copper and lead.

No studies were located regarding dermal effects of aluminum or its compounds following acute-duration exposure in animals. A localized loss of fur on the tip of the snout was observed in mice that ingested 130 mg Al/kg/day as aluminum lactate and base dietary aluminum for 6 weeks, but the effect was considered to be a sign of poor condition in the colony and not clearly attributable to aluminum exposure (Golub et al. 1989).

Ocular Effects. No studies were located regarding ocular effects of various forms of aluminum following acute-, intermediate-, or chronic-duration oral exposure in humans.

No studies were located regarding ocular effects of various forms of aluminum following acute-duration exposure in animals. No adverse ocular changes were found in male and female Beagle dogs that consumed up to 88 mg Al/kg/day as sodium aluminum phosphate in the diet for 6 months (Katz et al. 1984); these doses do not include aluminum in the base diet.

Body Weight Effects. No studies were located regarding body weight effects of various forms of aluminum following acute-, intermediate-, or chronic-duration oral exposure in humans.

Most studies have not found significant alterations in body weight gain in rats or mice following acute exposure to 73–192 mg Al/kg/day as aluminum lactate or aluminum hydroxide with citric acid (Bernuzzi et al. 1986; Domingo et al. 1989; Gomez et al. 1991; Misawa and Shigeta 1992), intermediate-duration exposure to 20–399 mg Al/kg/day as aluminum lactate, aluminum chloride, aluminum hydroxide, or aluminum nitrate (Bernuzzi et al. 1989b; Bilkei-Gorzo 1993; Domingo et al. 1987b; Donald et al. 1989; Golub et al. 1989, 1992b, 1995; Gomez et al. 1986; Greger and Donnaubauer 1986; Konishi et al. 1996; Ondreicka et al. 1966; Oteiza et al. 1989), or chronic-duration exposure to 0.6–979 mg Al/kg/day as aluminum nitrate with citric acid, aluminum lactate, or aluminum sulfate (Golub et al. 2000; Oneda et al. 1994; Roig et al. 2006; Schroeder and Mitchener 1975a, 1975b). Of the studies reporting reductions of body weight gain, many involved gestational and/or lactational exposure; significant decreases in body weight gain were observed in rats administered via gavage 409 mg Al/kg/day as aluminum hydroxide with citric acid on gestation days 6–15 (Gomez et al. 1991), rats administered via gavage 38 mg Al/kg/day as aluminum nitrate on gestation days 6–14 (Paternain et al. 1988), rats administered via gavage 70 mg Al/kg/day as aluminum chloride on gestation days 0–16 (Sharma and Mishra 2006), and mice exposed to 200 or 250 mg Al/kg/day aluminum lactate in the diet on gestation day 0 through lactation day 21 (Golub et al. 1987, 1992a). A decrease in body weight was also observed in aged rats exposed to 97 mg Al/kg/day as aluminum nitrate with citric acid for 100 days (Colomina et al. 2002) and rats administered via gavage 53 mg Al/kg/day as aluminum chloride for 30 days (Rajasekaran 2000). In a lifetime exposure study, Golub et al. (2000) reported a 20% decrease in body weight gain in female mice exposed to 100 mg Al/kg/day as aluminum lactate in the diet; however, in a separate group of mice similarly exposed to 100 mg Al/kd/day as aluminum lactate, no significant alterations in body weight gain were observed (Golub et al. 2000).

3.2.2.3 Immunological and Lymphoreticular Effects

There are limited data on the potential for aluminum to induce immunological effects in humans. Intermediate-duration exposure to 25 mg Al/kg/day as aluminum hydroxide in the form of an antacid suspension for 6 weeks did not affect immunoglobulin and interleukin concentrations or production, natural killer (NK) cells, or B- and T-lymphocyte populations or proliferation; a significant reduction in, primed cytotoxic T- cells (CD8+CD45R0+ population) was observed (Gräske et al. 2000). The toxicological significance of this finding in the absence of other alterations is not known.

Very few animal studies examined the potential immunotoxicity of aluminum. Intermediate-duration exposure of mice to 13 mg Al/kg/day as aluminum citrate administered via gavage 5 days/week for 22 weeks resulted in a significantly higher proliferation of lymph node cells and had no effect on spleen cell proliferation (Lauricella et al. 2001). This suggests that while aluminum might induce alterations in cell immune response, the stimulating or suppressing effects could depend on the dose, route of administration, exposure duration, or cell population. There is some evidence that developmental exposure to aluminum may adversely affect the immune system in young animals. A 19% increase in spleen weights, depressed spleen cell concentrations of interleukin-2, interferon-γ and tumor necrosis factor-α, and a deficiency of CD4+ cells in T-cell populations were observed in Swiss Webster mice exposed to aluminum from conception through 6 months of age (Golub et al. 1993). The maternal animals consumed 200 mg Al/kg/day as aluminum lactate in the diet from conception through lactation and the offspring were subsequently fed the same diet as the dams. Susceptibility to bacterial infection was increased in offspring of Swiss-Webster mice exposed to dietary aluminum lactate in a dose of 155 mg Al/kg from conception through 10 days of age, but not in 6-week-old mice exposed to 107 mg Al/kg/day for 6 weeks (Yoshida et al. 1989). Susceptibility to infection was evaluated by assessing survival following intravenous inoculation with *Listeria monocytogenes* at the end of the exposure periods.

No organ weight or histological changes in spleen and/or thymus were observed in female Sprague-Dawley rats exposed to 284 mg Al/kg/day as aluminum nitrate in drinking water for 100 days (Domingo et al. 1987b), male Sprague-Dawley rats given 70 mg Al/kg/day as aluminum chloride in drinking water for 30, 60, or 90 days (Dixon et al. 1979), or male and female mice exposed to 979 mg Al/kg/day as aluminum potassium sulfate in the diet for 20 months (Oneda et al. 1994). The doses in all of the above studies except Lauricella et al. (2001), Dixon et al. (1979), and Oneda et al. (1994) include aluminum in the base diet.

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

3.2.2.4 Neurological Effects

The neurotoxicity of aluminum following oral exposure has been well established in humans with renal insufficiency and animals; however, it has not been adequately investigated in healthy humans. The human database consists of case reports of acute accidental or intentional exposure to aluminum, an acute exposure study in healthy individuals, studies of patients undergoing dialysis treatment, and studies examining the possible association between aluminum ingestion and Alzheimer's disease.

Memory loss, fatigue, depression, behavioral changes, and learning impairment were reported in five children who, over a 5-day period, consumed drinking water containing unknown levels of aluminum sulfate, which was accidentally placed in a water-treatment facility in England (Ward 1989). The water also contained elevated levels of copper and lead, a highly neurotoxic element, which leached from the plumbing systems due to the greater acidity of the water. Thus, the role of aluminum in the onset of the neurological symptoms is unclear. Acute-duration oral exposure to aluminum phosphide (19–157 mg Al/kg) caused altered sensorium in 4 of 16 persons who ingested it either accidentally or in suicide attempts (Khosla et al. 1988). Restlessness and loss of consciousness were observed in 10 of 15 people who ingested unknown amounts of aluminum phosphide (Chopra et al. 1986). The toxicity associated with aluminum phosphide ingestion was probably due to the formation of highly toxic phosphine gas rather than the aluminum exposure.

Uremic persons represent a population at risk for aluminum-related dementia (Alfrey 1993). Prolonged dialysis with aluminum-containing dialysates, possibly combined with oral treatment with aluminum hydroxide to control hyperphosphatemia, has produced a characteristic neurotoxicity syndrome which has been referred to as "dialysis dementia" (Alfrey 1987; King et al. 1981; Mayor et al. 1985; Wills and Savory 1989). Alfrey (1993) describes two types of aluminum neurotoxicity in uremic patients: acute and classical. The acute form is caused by high levels of aluminum in the dialysate, the co-ingestion of aluminum-containing phosphate binders and citrate, or the rapid rise in serum aluminum following desferoxamine treatment. The onset of neurotoxicity is rapid and marked by confusion, muscle twitching, grand mal seizures, coma, and death. Plasma levels of aluminum are typically >500 μg/L; normal levels are approximately 1–3 μg/L (House 1992; Liao et al. 2004). The classical type results from chronic

parenteral or oral aluminum exposures and is characterized by a gradual onset of neurobehavioral disorders and, eventually, death. These neurological effects have been observed in adults and children (Alfrey 1993; Griswold et al. 1983). Plasma levels are estimated to be 100–200 μg/L. Limiting aluminum exposure in uremic persons (for example, the use of aluminum-free dialysates and aluminum-free phosphate binding agents) essentially eliminates these neurotoxic effects.

Alzheimer's disease is a neurodegenerative disorder, which is manifested clinically as a progressive deterioration of memory and cognition. The primary neuropathological characteristics of Alzheimer's disease are neuronal loss and the formation of neurofibrillary tangles, senile plaques with amyloid deposits and neuropil threads, and cerebrovascular amyloid deposition. The etiology of Alzheimer's disease is complex, with genetics playing a critical role; there is also evidence that the environment may modify the risk. The possible association between aluminum and Alzheimer's disease was proposed over 40 years ago; however, the evidence that aluminum may or may not be a risk factor is inconsistent and inconclusive. A number of lines of evidence have been used to support the relationship between aluminum and Alzheimer's disease (Flaten 2001; Munoz 1998); these include elevated levels of aluminum in the brains of individuals with Alzheimer's disease, the well-established neurotoxicity of aluminum, and epidemiology studies finding a geographical association between aluminum levels in drinking water and Alzheimer's disease. In the last 25 years, a number of epidemiology and animal studies have investigated this possible association; an animal model that fully mimics human Alzheimer's disease has not been identified. Many of the epidemiology studies have been criticized for flawed patient selection, poor comparability of exposed and control groups, poor exposure assessment, inaccurate diagnosis of Alzheimer's disease, and weak statistical correlations (Nieboer et al. 1995; Schupf et al. 1989). A number of these studies have found significant associations between individuals living in areas with elevated aluminum levels in drinking water and the prevalence of Alzheimer's disease (or a surrogate such as dementia or cognitive impairment) (Flaten 1990; Forbes et al. 1992, 1994; Gauthier et al. 2000; Jacqmin et al. 1994; Jacqmin-Gadda et al. 1996; Martyn et al. 1989; McLachlan et al. 1996; Michel et al. 1990; Neri and Hewitt 1991; Rondeau et al. 2000, 2001); the aluminum content of the water typically exceeded 0.10 mg Al/L. The odds ratios (or relative risks) were typically <2.0 (Flaten 1990; Jacqmin et al. 1994; Martyn et al. 1989; McLachlan et al. 1996; Neri and Hewitt 1991), although some studies, particularly studies that controlled for other risk factors such as age, education level, and family history of dementia, estimated higher odds ratios (Gauthier et al. 2000; Rondeau et al. 2000). In contrast, several studies did not find significant associations between aluminum exposure and the risk of Alzheimer's disease (or cognitive impairment (Forster et al. 1995; Martyn et al. 1997; Sohn et al. 1996;

Wettstein et al. 1991; Wood et al. 1988); the levels of aluminum in the drinking water were similar to the levels in studies finding positive associations.

Additionally, there are studies that examined the possible association between Alzheimer's disease and ingestion of aluminum from sources other than drinking water, particularly tea and antacids. The aluminum levels in tea are typically 10–50 times higher than levels found in drinking water; similarly, the levels of aluminum in antacids (typically containing aluminum hydroxide) are very high compared to drinking water levels. No significant associations between tea consumption (Forster et al. 1995; McDowell et al. 1994) or antacid use (Amaducci et al. 1986; Broe et al. 1990; Colin-Jones et al. 1989; Forster et al. 1995; Graves et al. 1990; Heyman et al. 1984; McDowell et al. 1994) and Alzheimer's disease have been found. A small scale study did find a significant relationship between consumption of food containing aluminum additives and the risk of Alzheimer's disease (Rogers and Simon 1999); however, this was based on a very small number of cases. The contrast between the results of the drinking water studies, many of which found a weak association between living in areas with high aluminum levels in drinking water and Alzheimer's disease, and the tea and antacid studies may be due to the difference in aluminum bioavailability. The presence of tannins and other organic constitutes found in tea may significantly reduce aluminum absorption; the aluminum hydroxide found in antacids is poorly absorbed. Although the aluminum speciation was not provided in most drinking water studies, in a study by Gauthier et al. (2000), organic monomeric aluminum was the only aluminum species significantly associated with Alzheimer's disease. The bioavailability of organic aluminum compounds such as aluminum citrate, aluminum lactate, and aluminum maltolate is much greater than for inorganic aluminum compounds (Froment et al. 1989a; Yokel and McNamara 1988).

In conclusion, the available data suggest that aluminum is not likely the causative agent in the development of Alzheimer's disease. However, aluminum may play a role in the disease development by acting as a cofactor in the chain of pathological events resulting in Alzheimer's disease (Flaten 2001).

Amyotrophic lateral sclerosis (ALS) and Parkinsonism-dementia (PD) are neurodegenerative diseases that have also been associated with aluminum exposure. ALS is a progressive disease of the central nervous system that is characterized by an accumulation of neurofibrillary tangles. In Guam, Southwest New Guinea, and the Kii Peninsula of Honshu Island in Japan, there is an unusually high prevalence of ALS and PD. This may be related to the natural abundance of highly bioavailable aluminum compounds coupled with the virtual lack of magnesium and calcium in the areas' drinking water supplies and soil. The consumption of the neurotoxic seed of the false sago palm tree may also play a key role in the

prevalence of ALS and PD in these areas. It has been proposed that long-term dietary deficiencies of calcium, rendering a secondary hyperparathyroid state, in the presence of highly bioavailable aluminum compounds and enhanced gastrointestinal absorption of aluminum can result in neuronal degeneration. In a study designed to evaluate effects of high aluminum and low calcium levels in the diet, much like the conditions associated with Guam and other similar areas, Cynomolgus monkeys were placed on a low calcium diet either with or without supplemental aluminum and manganese (Garruto et al. 1989). Chronic calcium deficiency alone produced neurodegenerative effects, although neurofibrillary changes were most frequently seen in the monkey on a low calcium diet supplemented with aluminum and manganese.

There are limited data on the neurotoxicity of ingested aluminum in healthy individuals. An acute exposure study conducted by Molloy et al. (2007) did not find any significant alterations in performance in neurobehavioral tests with a mean aluminum blood level of 280–300 μg/L at the time of testing. Although neurotoxicity of aluminum has not been established or adequately studied in people who are healthy (i.e., have normal renal function), there is conclusive evidence that aluminum compounds are neurotoxic in orally-exposed animals. As discussed below and in Section 3.2.2.6, numerous intermediate-duration studies in mice and rats found various neurotoxic effects in exposed adults and developing offspring.

Many of the animal neurotoxicity studies are complicated by a lack of reported information on aluminum content in the base diet. This is an important issue because, as discussed in the introduction to Section 3.2.2, commercial rodent laboratory feed has a high aluminum content which can significantly contribute to total exposure. Dosages in studies with insufficient information on aluminum content in the base diet therefore must be assumed to underestimate the actual experimental dosages. The magnitude of the underestimate may be considerable, particularly for maternal dietary intake during lactation (an exposure period used in many neurobehavioral studies of aluminum in mice), which can be markedly (often 2-fold) higher than in nonlactating adults. Consequently, although aluminum studies with inadequate data on base dietary levels of aluminum provide useful information on neurotoxicity, NOAELs and LOAELs from these studies cannot be assumed to be accurate and are not suitable for comparing with effect levels from studies that used diets with known amounts of aluminum. There is particular concern for the adequacy of neurotoxicity NOAEL and LOAEL values for aluminum because sensitive neurotoxic effects may occur in rodents at aluminum intake levels close to those provided by commercial diet alone. Based on these concerns, only neurotoxicity studies providing information on base dietary aluminum content are included in Table 3-2.

In general, oral exposure to aluminum is not associated with marked signs of neurotoxicity in animals. In a study by Golub et al. (1987), ataxia, splaying and dragging of hindlimbs, and paralysis were observed in mouse dams exposed to 200 mg Al/kg/day as aluminum lactate during gestation and lactation. Other studies involving exposure to higher aluminum doses have not noted significant increases in the incidence of overt signs of neurotoxicity (Donald et al. 1989; Golub et al. 1992a). It is possible that the levels of essential trace minerals in the diet used by Golub et al. (1987) were too low and may have contributed to the severity of the observed effects. The diet formulation used by this group was revised by adding a "more generous provision" of several essential nutrients, particularly trace minerals (including calcium, magnesium, phosphate), to avoid the marked maternal neurotoxicity associated with their absence in the original diet (Donald et al. 1989). Due to the apparent nutritional insufficiency of the diet used by Golub et al. (1987), the results of this study are not included in Table 3-2. Another overt sign of toxicity is an increase in cage mate aggression in male mice exposed to 200 mg Al/kg/day from gestation day 1 through postnatal day 170 (Golub et al. 1995).

The overall weight of evidence strongly indicates that oral exposure to aluminum results in functional and cognitive alterations. Motor function and sensory function are affected by aluminum exposure. Decreases in forelimb and/or hindlimb grip strength have been observed in mice exposed to 195 mg Al/kg/day as aluminum lactate in the diet for 5–7 weeks (Oteiza et al. 1993) or 13 weeks (Golub et al. 1992b; Oteiza et al. 1993) and in mice exposed to 100 mg Al/kg/day for over 2 years (Golub et al. 2000). In contrast, no alterations in grip strength were observed in mouse dams exposed to 250 mg Al/kg/day (Golub et al. 1992a) or 330 mg Al/kg/day (Donald et al. 1989) as aluminum lactate in the diet on gestation day 1 through lactation day 21 or in mice exposed to 200 mg Al/kg/day on gestation day 1 through postnatal day 170 (Golub et al. 1995). No significant alterations have been observed for footsplay or negative geotaxis following intermediate duration exposure to 195 mg Al/kg/day or 200 mg Al/kg/day as aluminum lactate in the diet (Golub et al. 1992b, 1995; Oteiza et al. 1993) or mouse dams exposed to 250 mg Al/kg/day (Golub et al. 1992a) or 330 mg Al/kg/day as aluminum lactate in diet on gestation day 1 through lactation day 21 (Donald et al. 1989). A chronic-duration study found impaired performance on the negative geotaxis test after 18 months of exposure to 100 mg Al/kg/day as aluminum lactate in the diet, but not after 24 months of exposure (Golub et al. 2000).

Significant decreases in spontaneous motor activity have also been reported in rats and mice exposed to aluminum chloride or aluminum lactate in the diet for at least 6 weeks. Effects are typically observed at doses of 130 mg Al/kg/day and higher. A decrease in total spontaneous activity, vertical activity

(rearing), and horizontal activity were observed in mice exposed to 130 mg Al/kg/day for 6 weeks (Golub et al. 1989). In mice exposed to 195 mg Al/kg/day, decreases in total activity, horizontal activity, and percentage of intervals with high activity counts were found after 90 days of exposure, but not after 45 days of exposure (Golub et al. 1992b). Decreases in spontaneous motor activity have also been observed in rats exposed to aluminum chloride in the diet for 7 weeks or 11 months (Commissaris et al. 1982); the amounts of aluminum added to the diet were 184 and 66 mg Al/kg/day, respectively; however, the aluminum content of the basal diet was not reported. Gavage exposure to a relatively low dose (53 mg Al/kg/day as aluminum chloride; aluminum content of the diet not reported) was also associated with a decrease in spontaneous motor activity. Exposure to lower doses of aluminum lactate or aluminum nitrate (with added citric acid) has not been associated with decreases in motor activity. No alterations in motor activity (as assessed in open field tests) were found in rats exposed to 97 mg Al/kg/day for 100 days (Colomina et al. 2002), 125 mg Al/kg/day for 6.5 months (Domingo et al. 1996), or 103 mg Al/kg/day for 1 or 2 years (Roig et al. 2006). Similarly, no alterations in total activity or horizontal activity were observed in mice exposed to 100 mg Al/kg/day as aluminum lactate in the diet during gestation, lactation, and postnatally until 2 years of age (Golub et al. 2000). However, the investigators noted that the automated activity monitor used in this study did not detect vertical movement of the older rats and that their previous study (Golub et al. 1989) found that vertical movement was more sensitive than horizontal movement. Another chronic-duration study (Roig et al. 2006) found no significant alterations in the total distance traveled or the total number of rearings in rats exposed to 103 mg Al/kg/day as aluminum nitrate in drinking water (citric acid added) from gestation day 1 through 2 years of age. Exposure to doses as high as 1,252 mg Al/kg/day as aluminum hydroxide (aluminum content of the basal diet was not reported) for 30 or 60 days (Thorne et al. 1986, 1987); the poor absorption of aluminum hydroxide probably contributed to this very high NOAEL.

Several tests of sensory function have resulted in significant alterations. Decreases in thermal sensitivity were observed following chronic exposure of mice to 100 mg Al/kg/day as aluminum lactate in the diet (Golub et al. 2000). Changes in thermal sensitivity was not observed in mice exposed to 195 mg Al/kg/day as aluminum lactate for 5–7 weeks (Oteiza et al. 1993) or 13 weeks (Golub et al. 1992b) or mouse dams exposed to 250 mg Al/kg/day (Golub et al. 1992a) or 330 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through lactation day 21 (Donald et al. 1989). As with thermal sensitivity, conflicting results have been observed for startle responsiveness. Decreased responses to auditory and/or air puff stimuli were observed in mice exposed to 195 mg Al/kg/day as aluminum lactate in the diet for 5–7 weeks (Oteiza et al. 1993) or 90 days (Golub et al. 1992b). However, no changes in startle responsiveness were observed in mice exposed to 250 or 330 mg Al/kg/day as

aluminum lactate in the diet on gestation day 1 through lactation day 21 (Donald et al. 1989; Golub et al. 1992a). Impairment of post-rotatory nystagmus was observed in rats exposed to 43.1 mg Al/kg/day as aluminum chloride in drinking water (dietary aluminum levels not reported) for 3 months; no alterations were observed at 21.5 mg Al/kg/day (Mameli et al. 2006).

The potential effect of aluminum on cognitive function has been assessed in a number of studies using passive avoidance, operant training, or water maze tests. Aluminum does not appear to adversely affect performance on passive avoidance or operant training tests at lower oral doses. No significant alterations have been observed in rats exposed to 97 mg Al/kg/day as aluminum nitrate in drinking water (with added citric acid) for 100 days (Colomina et al. 2002), rats exposed to 125 mg Al/kg/day as aluminum nitrate in drinking water (with added citric acid) for 6.5 months (Domingo et al. 1996), or rats exposed to 830 mg Al/kg/day or as high as 1,252 mg Al/kg/day as aluminum hydroxide in the diet (aluminum levels of basal diet were not reported) for 60 or 30 days, respectively (Thorne et al. 1987). Another study found improved performance on operant training tasks in mice exposed to 100 mg Al/kg/day in the diet for an intermediate duration (Golub and Germann 1998); the authors attributed this to an increase in food motivation in the aluminum-exposed mice. It is not known if an increased food motivation also influenced the results of the other studies. At higher aluminum doses, performance on operant training tasks is adversely affected. Impaired retention of learned responses were observed in rats exposed to 346 mg Al/kg/day as aluminum sulfate in the drinking water (aluminum content of the diet was not reported) (Connor et al. 1989) or 70 mg Al/kg/day as aluminum chloride in drinking water (aluminum content of the basal diet was not reported) for 90 days (Zhang et al. 2003). Another study found impaired learning (more trials were needed to reach the acquisition criterion), but no effect on retention or recall in rats exposed to 66 mg Al/kg/day as aluminum chloride in the diet (aluminum content of the basal diet was not reported) (Commissaris et al. 1982).

Because maze tests did not typically involve a food reward, these studies controlled for the potential confounder of food motivation. Impaired learning in a labyrinth maze test was observed in rats receiving gavage doses of 6 mg Al/kg/day as aluminum chloride or 35 mg Al/kg/day as aluminum hydroxide with citric acid (aluminum content of the diet was not reported) for 90 days (Bilkei-Gorzo 1993). In Morris water maze tests, impaired learning and memory was observed following gavage doses of 500 mg Al/kg/day of an unreported aluminum compound for 90 days (Jing et al. 2004). In contrast, no significant alterations in performance on the water maze test were found in rats exposed to 103 mg Al/kg/day as aluminum nitrate in the drinking water for a chronic duration (Roig et al. 2006).

A number of studies have conducted histopathological examinations of the brain of rats, mice, and dogs following oral exposure to aluminum and have not found significant alterations (Dixon et al. 1979; Domingo et al. 1987b; Gomez et al. 1986; Katz et al. 1984; Oneda et al. 1994; Pettersen et al. 1990); the aluminum doses ranged from 70 to 979 mg Al/kg/day. In contrast to these results, Abd El-Rahman (2003) reported spongioform changes in the neurons of the hippocampus, nuclear deformity, neurofibrillary degeneration, and foci of demyelination in rats receiving gavage doses of 85.9 mg Al/kg/day as aluminum sulfate (aluminum content of the diet was not reported).

Neurotoxicity has been extensively studied in developing mice and rats that were exposed to aluminum during gestation, lactation, and/or directly via diet following weaning. As summarized in Section 3.2.2.6, effects on reflexes and simple motor behaviors were commonly found in aluminum-exposed developing animals, whereas effects on learning and memory have not been consistently shown.

All reliable NOAEL and LOAEL values for neurological effects in adults in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects of various forms of aluminum following acute-, intermediate-, or chronic-duration oral exposure in humans.

Several studies evaluated reproductive effects of acute-duration oral exposure to aluminum in animals. An increased incidence of resorptions occurred in female BALB/c mice treated with 41 mg Al/kg/day as aluminum chloride by gavage (aluminum in base diet not reported) on gestation days 7–16 (Cranmer et al. 1986). No reproductive effects were observed in female Sprague-Dawley rats exposed to 158 mg Al/kg/day as aluminum hydroxide or aluminum citrate by gavage and base diet from gestation day 6 to 15 (Gomez et al. 1991), or in THA rats treated with 73.1 mg Al/kg/day as aluminum chloride by gavage (aluminum in base diet not reported) from gestation day 7 to 16 (Misawa and Shigeta 1992). In a study of female reproductive system development (Agarwal et al. 1996), offspring of rats that were gavaged with aluminum lactate on gestation days 5–15 showed a transient irregularity of the estrus cycle (increased number of abnormal cycle lengths) at 250 mg Al/kg/day; doses as high as 1,000 mg Al/kg/day did not affect other end points (gonad weights, anogenital distance, time to puberty, duration of induced pseudopregnancy, or numbers of superovulated oocytes). The inconsistent findings summarized above may reflect differences in susceptibility among different strains/species of animals or compound

differences in toxicity or bioavailability. Additionally, because levels of aluminum in the base diet were not reported by Agarwal et al. (1996), Misawa and Shigeta (1992), or Cranmer et al. (1986), the doses in these studies are likely to underestimate actual aluminum intake.

In a combination acute- and intermediate-duration study, no adverse effects on fertility or other general reproductive indices were found in female rats that were exposed to 38–77 mg Al/kg/day as aluminum nitrate by gavage and base diet for 14 days prior to mating with males that were similarly treated for 60 days pre-mating (Domingo et al. 1987c). These exposures were continued throughout mating, gestation, parturition, and weaning and caused a reduction in the growth of the offspring in all treated groups, but the effects were negligible and transient (slight decreases in body weight, body length, and tail length observed on postpartum days 1 and 4 were no longer evident at time of weaning). An intermediate-duration oral study in male rats found that sperm count was decreased following exposure to 2.5 mg Al/kg/day as aluminum chloride for 6–12 months (Krasovskii et al. 1979). The method of oral exposure was not specified but is presumed to be gavage, no information on aluminum in the base diet was reported, and reproductive function was not evaluated. No adverse reproductive effects were seen in male Sprague-Dawley rats, as assessed by plasma gonadotropin levels, histopathological evaluation, and serial matings, following exposure to 70 mg Al/kg/day as aluminum chloride in drinking water for up to 90 days (Dixon et al. 1979); this dose does not include base dietary aluminum.

Mating success (numbers of litters and offspring) was not affected in a three-generation study with Dobra Voda mice that were exposed to 49 mg Al/kg/day as aluminum chloride in drinking water and base diet over a period of 180–390 days (Ondreicka et al. 1966). No reproductive effects were observed in pregnant Swiss Webster mice that consumed 250 mg Al/kg/day as aluminum lactate throughout gestation and lactation (Golub et al. 1992a). However, an alteration in gestation length was observed in pregnant Swiss Webster mice that consumed 155 mg Al/kg/day as aluminum lactate in the diet during gestation and lactation (Donald et al. 1989). The effect on gestation length was small but statistically significant; all litters in the control group (7.5 mg Al/kg/day) were born on gestation day 18, whereas 4 of 17 litters exposed to ≥155 mg Al/kg/day were born earlier or later (gestation days 17, 19, or 20).

No organ weight or histological changes were observed in the gonads of male and female Beagle dogs that consumed 93 mg Al/kg/day as acidic sodium aluminum phosphate (a common human food additive) in the diet for 6 months (Katz et al. 1984); this dose does not include base dietary aluminum. In another study with dogs, two of four male Beagles that were fed 75 mg Al/kg/day as basic sodium aluminum phosphate and base dietary aluminum for 26 weeks had decreased testicular weight and moderate

seminiferous tubule germinal epithelial cell degeneration and atrophy (Pettersen et al. 1990). No changes in reproductive tissue weight or histology occurred in the males at lower doses (≤27 mg Al/kg/day) or in female Beagles similarly exposed to ≤80 mg Al/kg/day. The investigators concluded that the testicular changes appeared to be secondary to palatability-related reductions in food consumption and body weight, and therefore, are not clearly direct effects of aluminum.

Chronic studies showed no histological changes in the testes or ovaries of male and female Wistar rats fed a diet containing unspecified levels of aluminum phosphide/ammonium carbamate for 24 months (Hackenberg 1972), or in B6C3F1 mice that ingested 979 mg Al/kg/day as dietary aluminum potassium sulfate for 20 months (Oneda et al. 1994). The doses in the latter study do not include aluminum in the base diet. Neither mouse study assessed reproductive function.

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

3.2.2.6 Developmental Effects

No studies were located regarding developmental effects of various forms of aluminum following acute- or chronic-duration oral exposure in healthy humans. The only human data on developmental effects come from infants with renal failure and premature infants. Their responses are probably not indicative of responses expected in normal infants. Osteomalacia and increased bone and serum levels of aluminum were reported in three infants with kidney failure who had been treated orally with >100 mg of Al/kg/day as aluminum hydroxide from the first or sixth month of life (Andreoli et al. 1984; Griswold et al. 1983), and in healthy infants ingesting aluminum-containing antacids (Pivnick et al. 1995). Progressive encephalopathy was also observed among children with severe renal disease ingesting aluminum-containing phosphate binders (Finberg et al. 1986; Griswold et al. 1983).

A large number of studies have examined the developmental toxicity of aluminum in rats and mice. A variety of effects have been found including decreased pup survival/increased pup mortality, decreased growth, delayed maturation, and impaired neurodevelopment. Increases in pup mortality, typically occurring within the first 4 postnatal days, have been observed in rats exposed to 155 mg Al/kg/day as aluminum chloride in the diet on gestational days 8–20 (Bernuzzi et al. 1986), 200 mg Al/kg/day as aluminum lactate administered via gavage on postnatal days (PND) 5–14 (Bernuzzi et al. 1989a), and 272 mg Al/kg/day as aluminum chloride or 378 mg Al/kg/day as aluminum lactate in the diet on gestation

days 1–20. Interpretation of the results of these studies is limited by the lack of information on the aluminum content of the basal diet. Another study found a decrease in the number of live pups per litter and an increase in the number of dead young per litter on PND 21 in the offspring of rats administered via gavage 51 mg Al/kg/day as aluminum nitrate for 14 days prior to mating, on gestation days 1–20, and lactation days 1–21 (Domingo et al. 1987c). The gavage administration route may have influenced the results of this study; other studies involving exposure to aluminum nitrate, aluminum citrate, or aluminum lactate via drinking water or diet have not reported increases in mortality at doses as high as 330 mg Al/kg/day as aluminum lactate in the diet on gestation days 1 through PND 35 (Colomina et al. 1992, 2005; Golub and Germann 1998, 2001; Golub et al. 1992a, 1995; McCormack et al. 1979).

Numerous studies have reported decreases in pup body weight gain (Bernuzzi et al. 1986, 1989a, 1989b; Colomina et al. 2005; Domingo et al. 1987a, 1987c, 1989; Golub and Germann 2001; Golub et al. 1992a; Gomez et al. 1991; Misawa and Shigeta 1992; Paternain et al. 1988; Sharma and Mishra 2006). Since some of these studies did not report the aluminum content of the basal diet, their usefulness in establishing dose-response relationships is limited. With few exceptions, most studies have shown that aluminum does not adversely affect birth weight in the absence of effects on maternal body weight (Colomina et al. 2005; Domingo et al. 1989; Donald et al. 1989; Golub and Germann 1998, 2001; Golub et al. 1992a, 1995; Gomez et al. 1991; McCormack et al. 1979). The possible exception to this finding was decreases in birth weight observed in the offspring of rats administered aluminum nitrate via gavage at doses of ≥38 mg Al/kg/day on gestation day 1 through lactation day 21 (Domingo et al. 1987c) or 77 mg Al/kg/day on gestation day 14 through lactation day 21 (Domingo et al. 1987a); neither study reported whether there were significant effects on maternal body weight gain. Paternain et al. (1988) also reported a decrease in pup body weight in rats receiving gavage doses of 38 mg Al/kg/day as aluminum nitrate on gestation days 6–14; a decrease in maternal weight gain was also reported at this dose level. Although most studies did not find effects on birth weights, several studies did find decreases in post-birth pup body weights; however, this finding was not consistent across studies. Lower pup body weights starting on PND 10 were observed in mouse pups exposed to aluminum during gestation only, during lactation only, or during gestation and lactation (Golub et al. 1992a); a decrease in maternal body weight gain was observed in the dams exposed during lactation. This study suggests that aluminum may influence growth directly and may not be only related to changes in maternal body weight during lactation. Similarly, decreases in body weights were observed on PND 12, 16, and 21 in the pups exposed to 100 mg Al/kg/day as aluminum nitrate in the drinking water (with added citric acid) on gestation day 1 through lactation day 21; a decrease in maternal food and water intake was also observed at this dose level (Colomina et al. 2005). A third study found decreases in pup body weight at PND 21 in

mice exposed to 130 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through PND 35 (Golub and Germann 2001). The lower body weights were still present at 5 months of age even though aluminum exposure was stopped on PND 35; an increase in food intake was also observed in these animals. In contrast to these studies, no adverse effects on body weight were observed in mouse pups exposed to 330 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through PND 21 or 35 (Donald et al. 1989; Golub and Germann 1998; Golub et al. 1995).

Gestational exposure to aluminum does not appear to result in an increase in the occurrence of malformation and anomalies, although reductions in ossification have been observed (Gomez et al. 1991; Sharma and Mishra 2006). Delays in ossification were observed at doses that also resulted in decreases in pup body weight. Some alterations in physical maturation have been observed in rats exposed to aluminum nitrate in drinking water (with added citric acid) on gestation day 1 through lactation day 21 (Colomina et al. 2005). The observed effects included significant delay in vagina opening at 53 or 103 mg Al/kg/day, testes descent at 103 mg Al/kg/day, and incisor eruption in males at 53 mg Al/kg/day. No effects on days to pinna detachment or eye opening were observed. No delays on pinna detachment, eye opening, or incisor eruption were observed in rats administered via gavage 73 mg Al/kg/day as aluminum chloride (aluminum content of the diet not reported) on gestation days 8–20 (Misawa and Shigeta 1992).

Animal studies provide strong evidence that gestational and/or lactational exposure to aluminum impairs the development of the nervous system. Potential neurodevelopmental effects have been evaluated using a variety of functional tests and cognitive tests. Because comparisons between studies are difficult due to differences in the exposure period, subroute of exposure, lack of information on the aluminum levels in the basal diet, and age of assessment, the results for each test will be presented separately. Significant impairment in the righting reflex and grasping reflex were observed in rat pups exposed to 272 mg Al/kg/day as aluminum chloride or 194 mg Al/kg/day as aluminum lactate in the diet (aluminum content of the basal diet was not reported) on gestation days 1–20 (Bernuzzi et al. 1989b); no reflex alterations were observed at 96 mg Al/kg/day for aluminum chloride or aluminum lactate. Impairment of the righting reflex was also observed in the offspring of rats exposed to 155 mg Al/kg/day as aluminum chloride on gestation days 8–20 (Bernuzzi et al. 1986); grasping reflex was not significantly affected at this dose level or at 192 mg Al/kg/day. Exposure of pups to gavage doses of 300 mg Al/kg/day as aluminum lactate on PND 5–14 did not adversely affect the grasping reflex (Bernuzzi et al. 1989a). Righting reflex was also not affected in pups exposed to 103 mg Al/kg/day as aluminum nitrate in drinking water (citric acid added) on gestation day 1 through lactation day 21 (Colomina et al. 2005).

Four studies examined temperature sensitivity; increases in sensitivity were observed in the offspring of mice exposed to 250 mg Al/kg/day as aluminum lactate in the diet on lactation days 1–21 (Golub et al. 1992a) or 330 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through PND 42 (Golub et al. 1995). No effects were observed in mice exposed to 330 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through lacation day 21 or to 250 mg Al/kg/day as aluminum lactate in the diet on gestation days 1–21 (Golub et al. 1992a).

A variety of motor function tests have been used to assess neurodevelopmental toxicity. Dosing pups with 300 mg Al/kg/day as aluminum lactate on PND 5–14 resulted in impairment of the suspension test and locomotor coordination (Bernuzzi et al. 1989a). Locomotor coordination was also altered in rat offspring exposed to 399 mg Al/kg/day as aluminum chloride in the diet on gestation days 1–20 (Bernuzzi et al. 1989b). No effects on the suspension test or locomotor coordination were observed in the offspring of rats exposed to 192 mg Al/kg/day as aluminum chloride in the diet on gestation days 8–20 (Bernuzzi et al. 1986). No information on the aluminum content of the basal diet was reported in the Bernuzzi studies. Alterations in the performance on the negative geotaxis test were found in mouse pups exposed to 250 mg Al/kg/day as aluminum lactate in the diet on lactation days 1–21 (Golub et al. 1992a) and in rat pups exposed to 399 mg Al/kg/day as aluminum chloride in the diet on gestation days 1–20 (Bernuzzi et al. 1989b), 200 mg Al/kg/day as aluminum lactate administered to pups on PND 5–14 (Bernuzzi et al. 1989a), or 155 mg Al/kg/day as aluminum chloride in the diet on gestation days 8–20 (Bernuzzi et al. 1986). No alterations in negative geotaxis results were found in mice exposed to 330 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through PND 21 (Donald et al. 1989; Golub et al. 1995) or in rat pups exposed to 103 mg Al/kg/day as aluminum nitrate in the drinking water (citric acid added) on gestation day 1 through lactation day 21 (Colomina et al. 2005).

Exposure to aluminum during gestation and/or lactation has consistently resulted in decreases in forelimb and/or hindlimb grip strength. Decreases in grip strength have been observed in mice exposed to 155 mg Al/kg/day as aluminum lactate in diet on gestation day 1 through lactation day 21 (Donald et al. 1989; Golub et al. 1995), 250 mg Al/kg/day as aluminum lactate on gestation days 1–21 or lactation days 1–21 (Golub et al. 1992a), or 130 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through PND 35 (Golub and Germann 2001) and in rats exposed to 103 mg Al/kg/day as aluminum nitrate in drinking water (with citric acid added) on gestation day 1 through lactation day 21 (Colomina et al. 2005). In other motor tests, increases in the number of rotations on a rotorod and a shorter latency to fall in a wire suspension test were observed in mice exposed to 260 or 130 mg Al/kg/day, respectively, as aluminum lactate in the diet on gestation day 1 through PND 35 (Golub and Germann 2001). Foot splay

has been observed in the mice exposed to 155 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through lactation day 21 (Donald et al. 1989), but not in mice exposed to 250 mg Al/kg/day as aluminum lactate in the diet on gestation days 1–21 or lactation days 1–21 (Golub et al. 1992a). In open field tests of motor activity, significant delays in pivoting, longer latencies, and more rearings were observed in the offspring of rats administered via gavage 73 mg Al/kg/day as aluminum chloride (aluminum content of the diet was not reported) (Misawa and Shigeta 1992). No effect on open field tests were observed in rat pups exposed to 103 mg Al/kg/day as aluminum nitrate in drinking water (citric acid added) on gestation day 1 through lactation day 21 (Colomina et al. 2005).

Cognitive function effects were evaluated in passive avoidance tests, operant conditioning tests and water maze tests. No adverse effects were observed in operant conditioning tests in mice exposed to 155 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through lactation day 21 (Golub et al. 1995) or 330 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through PND 35 (Golub and Germann 1998) and in passive avoidance tests in rats exposed to 103 mg Al/kg/day as aluminum nitrate in the drinking water (with added citric acid) on gestation day 1 through lactation day 21 (Colomina et al. 2005). The studies in mice noted that the aluminum-exposed pups often performed better than the controls; this may be due to an increase in food motivation in the aluminum-exposed rats rather than a direct effect on cognitive function. Impaired learning, as measured using the Morris water maze, was observed in mice exposed to 260 mg Al/kg/day as aluminum lactate in the diet from gestation day 0 to PND 21 and on PND 21–35 (tested at 90 days of age) (Golub and Germann 2001). When the salient and nonsalient cues were rotated, an increase in the escape latency was found at 130 and 260 mg Al/kg/day. The investigators found exposure to >130 mg Al/kg/day resulted in differences in how the mice used the salient and nonsalient cues; no effects were observed at 26 mg Al/kg/day. A study in rats exposed to 103 mg Al/kg/day (Colomina et al. 2005) did not find any significant effects in the water maze test. However, this study did not use probe trials; the alteration observed in the Golub and Germann studies were detected in the probe trials.

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

3.2.2.7 Cancer

No studies were located regarding cancer in humans after oral exposure to various forms of aluminum.

Animal bioassays have found no conclusive evidence for carcinogenicity of aluminum. Significantly increased incidences of gross tumors were reported for Long Evans rats (only in males) and Swiss mice (only in females) given 0.6 or 1.2 mg Al/kg/day as aluminum potassium sulfate in drinking water, respectively, for 2–2.5 years (Schroeder and Mitchener 1975a, 1975b). Aluminum levels in the base diet were not reported in these studies, although the animals were fed a low-metal diet in metal-free environmental conditions. At gross necropsy, 13/25 (52%) aluminum-treated male rats were found to have tumors compared to 4/26 (15.4%) controls. Six of the tumors in the aluminum-treated males were malignant compared to two malignancies in the control rats. The incidences of gross tumors in the female mice were 19/41 (46.3%) and 14/47 (29.8%) in exposed and control groups, respectively. The incidence of "lymphoma leukemia" was significantly increased (10/41 versus 3/47 in controls) in the female mice. A dose-response relationship could not be determined for either species because only one aluminum dose was used and the types of tumors and organs in which they were found were not specified. Very few study details were reported in this paper and it is unclear if the investigators grouped several types of tumors into the "lymphoma leukemia" category. Another study in rats (Wistar) found no increase in the incidence of neoplasms in male and female rats fed diets containing unspecified amounts of aluminum phosphide/ammonium carbamate for 24 months (Hackenberg 1972).

There were no exposure-related increased incidences of tumors, other proliferative lesions or nonneoplastic lesions in 60 male or 60 female B6C3F1 mice that ingested ≤979 mg Al/kg/day as aluminum potassium sulfate in the diet for 20 months (Oneda et al. 1994). The level of aluminum in the base diet was not reported. The incidence of spontaneous hepatocellular carcinoma was significantly decreased in the high-dose males (5.5% compared to 20.5% in controls).

3.2.3 Dermal Exposure

3.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to various forms of aluminum.

3.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, endocrine, ocular, body weight, or metabolic effects in humans or animals after dermal exposure to various forms of aluminum.

The highest NOAEL values and all LOAEL values for dermal exposure from each reliable study for systemic effects in each species and duration category for aluminum are shown in Table 3-3.

Musculoskeletal Effects. Information on potential musculoskeletal effects associated with dermal exposure of aluminum is limited to a case report of a woman reporting bone pain after a 4-year exposure to aluminum chlorhydrate in antiperspirant (Guillard et al. 2004). No osseous abnormalities were detected via radiography, and C-reactive protein levels and bone-specific serum parameters (alkaline phosphatase, γ-glutamyl transferase, calcium, phosphate) were within reference ranges; however, plasma aluminum levels were approximately 10 times higher than reference levels. Termination of aluminum exposure resulted in decreases in plasma aluminum levels and a disappearance of bone pain.

No studies were located regarding musculoskeletal effects in animals following dermal exposure to aluminum.

Dermal Effects. No studies were located regarding dermal effects in humans after dermal exposure to various forms of aluminum. Aluminum compounds are widely used in antiperspirants without harmful effects to the skin or other organs (Sorenson et al. 1974). Some people, however, are unusually sensitive to topically applied aluminum compounds. Skin irritation was reported in subjects following the application of aluminum chloride hexahydrate in ethanol used for the treatment of axillary or palmar hyperhidriosis (excessive sweating) (Ellis and Scurr 1979; Goh 1990) or the use of a crystal deodorant containing alum (Gallego et al. 1999).

No studies were located regarding dermal effects in animals following intermediate- or chronic- duration dermal exposure to various forms of aluminum.

Skin damage has been observed in female TF_1 Carworth mice, New Zealand rabbits, and Large White pigs following the application of 10% aluminum chloride (0.005–0.1 g Al) or aluminum nitrate (0.006–0.013 g Al) for 5 days; but not from aluminum sulfate, hydroxide, acetate, or chlorhydrate (Lansdown 1973). The damage consisted of hyperplasia, microabscess formation, dermal inflammatory cell infiltration, and occasional ulceration. These results suggest that the development of adverse dermal effects from exposure to aluminum depends upon its chemical form.

Table 3-3 Levels of Significant Exposure to Aluminum and Compounds - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL				Reference Chemical Form	Comments
				Less Serious		Serious			
ACUTE EXPOSURE									
Systemic									
Mouse (TFI)	5 d 1 x/d	Dermal	2.5 F Percent (%)	5 F Percent (%)	(slight to moderate hyperplasia)	25 F Percent (%)	(severe hyperplasia with focal ulceration)	Lansdown 1973 Aluminum chloride	
Mouse (TFI)	5 d 1 x/d	Dermal	25 F Percent (%)					Lansdown 1973 Aluminum chlorhydrate	
Mouse (TFI)	5 d 1 x/d	Dermal	10 F Percent (%)					Lansdown 1973 Aluminum sulfate	
Mouse (TFI)	5 d 1 x/d	Dermal		10 F Percent (%)	(epidermal damage; hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)			Lansdown 1973 Aluminum chloride	
Mouse (TFI)	5 d 1 x/d	Dermal	10 F Percent (%)					Lansdown 1973 Aluminum hydroxide	
Mouse (TFI)	5 d 1 x/d	Dermal	10 F Percent (%)					Lansdown 1973 Aluminum acetate	

Table 3-3 Levels of Significant Exposure to Aluminum and Compounds - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL			Reference Chemical Form	Comments
				Less Serious		Serious		
Mouse (TFI)	5 d 1 x/d	Dermal		10 F Percent (%)	(epidermal change: hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)		Lansdown 1973 Aluminum nitrate	
Rabbit (New Zealand)	5 d 1 x/d	Dermal		10 Percent (%)	(epidermal damage; hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)		Lansdown 1973 Aluminum chloride	
Rabbit (New Zealand)	5 d 1 x/d	Dermal	25 Percent (%)				Lansdown 1973 Aluminum acetate	
Rabbit (New Zealand)	5 d 1 x/d	Dermal	10 Percent (%)				Lansdown 1973 Aluminum sulfate	
Rabbit (New Zealand)	5 d 1 x/d	Dermal	10 Percent (%)				Lansdown 1973 Aluminum hydroxide	

Table 3-3 Levels of Significant Exposure to Aluminum and Compounds - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL			Reference Chemical Form	Comments
				Less Serious		Serious		
Rabbit (New Zealand)	5 d 1 x/d	Dermal	10 Percent (%)				Lansdown 1973 Aluminum acetate	
Rabbit (New Zealand)	5 d 1 x/d	Dermal		10 Percent (%)	(epidermal change: hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)		Lansdown 1973 Aluminum nitrate	
Pig (Large White)	5 d 1 x/d	Dermal		10 Percent (%)	(epidermal damage; hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)		Lansdown 1973 Aluminum chloride	
Pig (Large White)	5 d 1 x/d	Dermal	25 Percent (%)				Lansdown 1973 Aluminum chlorhydrate	
Pig (Large White)	5 d 1 x/d	Dermal	10 Percent (%)				Lansdown 1973 Aluminum sulfate	
Pig (Large White)	5 d 1 x/d	Dermal	10 Percent (%)				Lansdown 1973 Aluminum hydroxide	

Table 3-3 Levels of Significant Exposure to Aluminum and Compounds - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL			Reference Chemical Form	Comments
				Less Serious		Serious		
Pig (Large White)	5 d 1 x/d	Dermal	10 F Percent (%)				Lansdown 1973 Aluminum acetate	
Pig (Large White)	5 d 1 x/d	Dermal		10 Percent (%)	(epidermal change: hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)		Lansdown 1973 Aluminum nitrate	

d = day(s); F = female; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; x = time(s)

3.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological/lymphoreticular effects in humans after intermediate- or chronic-duration dermal exposure to various forms of aluminum.

Several children and one adult who had previous injections of vaccines or allergens in an aluminum-based vehicle showed hypersensitivity to aluminum chloride in a patch test (Böhler-Sommeregger and Lindemayr 1986; Veien et al. 1986). Dermal hypersensitivity to aluminum appears to be rare in humans.

No studies were located regarding immunological/lymphoreticular effects in animals after dermal exposure to various forms of aluminum.

3.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans after acute- or intermediate-duration dermal exposure to various forms of aluminum. Graves et al. (1990) examined the association between Alzheimer's disease and the use of aluminum-containing antiperspirants in a case-control study using 130 matched pairs. The Alzheimer's disease was clinically diagnosed at two geriatric psychiatric centers; the controls were friends or nonblood relatives of the Alzheimer patients. Information on lifetime use of antiperspirants/deodorant was collected via a telephone interview with the subject's spouse. No association was found between Alzheimer's disease and antiperspirant/deodorant use, regardless of aluminum content (odds ratio of 1.2; 95% confidence interval of 0.6–2.4). When only users of aluminum-containing antiperspirants/deodorants were examined, the adjusted odds ratio was 1.6 (95% confidence interval of 1.04–2.4). A trend (p=0.03) toward a higher risk of Alzheimer's with increasing use of aluminum-containing antiperspirants/ deodorants was also found.

No studies were located regarding the following health effects in humans or animals after dermal exposure to various forms of aluminum:

3.2.3.5 Reproductive Effects
3.2.3.6 Developmental Effects
3.2.3.7 Cancer

3.3 GENOTOXICITY

Although aluminum complexes with deoxyribonucleic acid (DNA), particularly at lower pHs (Dyrssen et al. 1987; Karlik et al. 1980), negative results have been observed in *in vitro* assays (summarized in Table 3-4) for reverse mutations in *Salmonella typhimurium* (Marzin and Phi 1985), DNA damage in *Escherichia coli* (Olivier and Marzin 1987), rec assay using *Bacillus subtilis* (Kada et al. 1980; Kanematsu et al. 1980; Nishioka 1975), forward mutations in the thymidine kinase locus of L5178Y mouse lymphoma cells (Oberly et al. 1982), and morphological transformation in Syrian hamster cells (DiPaola and Casto 1979). However, other studies have shown that aluminum can induce DNA cross-linking in rat ascites hepatoma cells (Wedrychowski et al. 1986), micronuclei formation in human peripheral blood lymphocytes (Banasik et al. 2005; Migliore et al. 1999; Roy et al. 1990), and chromosome aberrations in human peripheral blood lymphocytes (Roy et al. 1990). Using FISH analysis, Migliore et al. (1999) was unable to conclude whether the micronuclei resulted from clastogenic and aneuploidogenic mechanism, although a higher (not statistically significant) percentage of micronuclei contained whole chromosomes. An *in vivo* study also found significant increases in chromosome aberrations in the mone marrow cells of mice receiving an intraperitoneal dose of aluminum chloride (Manna and Das 1972). There was a significant increase in chromatid-type aberrations over the controls, and these occurred in a nonrandom distribution over the chromosome complement; no dose-response relationship could be demonstrated, although the highest dose of aluminum chloride did produce the greatest number of aberrations.

3.4 TOXICOKINETICS

Aluminum is poorly absorbed following either oral or inhalation exposure and is essentially not absorbed dermally. Approximately 0.1–0.6% of ingested aluminum is usually absorbed, although absorption of less bioavailable forms, such as aluminum hydroxide, can be on the order of 0.1%. The unabsorbed aluminum is excreted in the feces. The bioavailability of aluminum is strongly influenced by the aluminum compound and the presence of dietary constituents which can complex with aluminum and

Table 3-4. Genotoxicity of Aluminum *In Vitro*

Species (test system)	End point	Results	Reference
Salmonella typhimurium	Gene mutation	–	Marzin and Phi 1985
Escherichia coli	DNA damage	–	Olivier and Marzin 1987
Bacillus subtilis	Rec assay	–	Kada et al. 1980; Kanematsu et al. 1980; Nishioka 1975
L5178Y mouse lymphoma cells	Forward mutation	–	Oberly et al. 1982
Syrian hamster embryo cells	Transformation assay	–	DiPaola and Casto 1979
Rat ascites hepatoma cells	DNA cross-linking	+	Wedrychowski et al. 1986
Human peripheral blood lymphocytes	Micronuclei formation	+	Banasik et al. 2005; Migliore et al. 1999; Roy et al. 1990
Human peripheral blood lymphocytes	Chromosome abberrations	+	Roy et al. 1990

– = negative result; + = positive result

thereby enhance or inhibit its absorption. The main mechanism of absorption is probably passive diffusion through paracellular pathways. Aluminum binds to various ligands in the blood and distributes to every organ, with highest concentrations found in bone and lung tissues. Absorbed aluminum is excreted principally in the urine and, to a lesser extent, in the bile. Studies on aluminum uptake and elimination rates indicate that a near steady-state is maintained in most healthy adults, with aluminum body burdens varying slightly up and down over time with an overall small rate of increase over the lifespan. Nevertheless, blood and tissue aluminum levels are increased in persons exposed to high levels of aluminum, such as those associated with long-term use of antacids. The levels return to normal upon cessation of exposure. Under certain atypical conditions (e.g., poor renal function with increased aluminum load), levels of aluminum in the body may raise high enough to cause toxicity in humans. The main target organs under these conditions appear to be the central nervous system and bone. The molecular mechanism of aluminum bone and neurotoxicity has not been established.

Aluminum can form complexes with many molecules in the body (organic acids, amino acids, nucleotides, phosphates, carbohydrates, macromolecules). Many aluminum compounds have low solubility products, so their "free" aluminum ions (e.g., hydrated $Al(H_2O)_6^{3+}$) occur in very low concentrations. The toxicokinetics of aluminum can vary, depending on the nature of these complexes. For example, aluminum bound in a low-molecular-weight complex could be filtered at the renal glomeruli and excreted, while aluminum in a high-molecular-weight complex (aluminum transferrin) would not.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Evidence for absorption of aluminum after inhalation exposure in humans is available from several occupational studies. Occupational exposure to aluminum fumes, dusts, and flakes has resulted in increases in serum, tissue, and urinary levels of aluminum. Significantly higher serum aluminum levels were observed in 279 workers exposed to aluminum powder as compared to unexposed workers; the preshift plasma levels were 4.92 and 3.60 µg/L, respectively (Gitelman et al. 1995); no significant differences in postshift plasma levels were found between the aluminum workers (5.12 µg/L) and unexposed controls (4.16 µg/L). Results of an autopsy on a stone mason presumably exposed to aluminum showed that tissue levels of aluminum were substantially higher than those of a group of 24 individuals presumably not exposed to aluminum in the workplace (Teraoka 1981). Following an 8-hour exposure to a time-weighted average (TWA) concentration of 2.4 mg/m^3 aluminum, urinary levels in 3 previously unexposed volunteers rose from 3 to 4–414 µg/L (Sjögren et al. 1985). Increased urinary

aluminum levels have also been observed in workers exposed to 0.025 (median respirable concentration) or 5 mg/m^3 (TWA concentrations) aluminum dust (Gitelman et al. 1995; Mussi et al. 1984) or 2.4 or 5 mg/m^3 (TWA concentrations) aluminum fumes (Mussi et al. 1984; Sjögren et al. 1985). Indirect evidence for inhalation absorption of aluminum was reflected in a fall in urinary aluminum levels from 82 to 29 μg/L in workers following a 16–37-day exposure-free interval (Sjögren et al. 1988).

The percentage of aluminum absorbed following inhalation exposure was not reported in occupational toxicokinetic studies (Gitelman et al. 1995; Mussi et al. 1984; Pierre et al. 1995; Sjögren et al. 1985, 1988). However, a fractional absorption of 1.5–2% was estimated based on the relationship between urinary aluminum excretion and the airborne soluble aluminum to which workers were exposed (Yokel and McNamara 2001). Data from Mussi et al. (1984) suggest that the fractional absorption of aluminum from lung to blood is higher in individuals exposed to aluminum fumes as compared to aluminum dust. This is consistent with knowledge that particle size influences the deposition pattern in the lungs and absorption.

It is considered that systemic absorption of airborne aluminum occurs via the lungs, gastrointestinal tract after mucociliary clearance from the respiratory tract (ICRP 1994), or intranasal absorption via olfactory neurons. Gitelman et al. (1995) found a better correlation between respirable aluminum air concentrations and urinary aluminum output than between total aluminum air concentrations and urinary aluminum output, suggesting that some of the aluminum was absorbed through the lungs. Studies by Perl and Good (1987) and Zatta et al. (1993) have demonstrated that aluminum may directly enter the brain via the olfactory tract; the aluminum crosses the nasal epithelium and reaches the brain via axonal transport.

Several animal studies indicate that aluminum is retained in the lung after inhalation exposure to aluminum oxide (Christie et al. 1963; Thomson et al. 1986) and aluminum chlorhydrate (Steinhagen et al. 1978; Stone et al. 1979). However, no significant increases in aluminum in tissues other than the lungs or serum were seen, indicating that lung retention rather than absorption was taking place (Steinhagen et al. 1978; Stone et al. 1979).

3.4.1.2 Oral Exposure

Aluminum present in food and drinking water is poorly absorbed through the gastrointestinal tract. Several small scale human studies estimated aluminum absorption efficiencies of 0.07–0.39% following administration of a single dose of the radionuclide aluminum-26 (^{26}Al) in drinking water (Hohl et al.

1994; Priest et al. 1998; Stauber et al. 1999; Steinhausen et al. 2004). Fractional absorption was estimated by measuring aluminum levels in urine; it is likely that most of these studies (with the exception of Stauber et al. 1999) underestimated gastrointestinal absorption because the amount of aluminum retained in tissues or excreted by non-renal routes was not factored into the absorption calculations. Several animal studies also utilized ^{26}Al to estimate aluminum bioavailability from drinking water. When aluminum levels in urine and bone were considered, absorption rates of 0.04–0.06% were estimated in rats (Drueke et al. 1997; Jouhanneau et al. 1993); when liver and brain aluminum levels were also considered, an absorption rate of 0.1% was estimated (Jouhanneau et al. 1997). Another study that utilized a comparison of the area under the plasma aluminum concentration-time curve after oral and intravenous administration of ^{26}Al estimated an oral aluminum bioavailability of 0.28% (Yokel et al. 2001a).

Two human studies examined the bioavailability of aluminum in the diet. An absorption efficiency of 0.28–0.76% was estimated in subjects ingesting 3 mg Al/day (0.04 mg Al/kg/day) or 4.6 mg Al/day (0.07 mg Al/kg/day) (Greger and Baier 1983; Stauber et al. 1999). When 125 mg Al/day (1.8 mg Al/kg/day) as aluminum lactate in fruit juice was added to the diet, aluminum absorption decreased to 0.094% (Greger and Baier 1983). Yokel and McNamara (2001) suggested that the bioavailability of aluminum from the diet is 0.1% based on daily urinary excretion levels of 4–12 µg and average aluminum intakes by adults in the United States of 5,000–10,000 µg/day.

The bioavailability of aluminum is dependent on the form in which it is ingested and the presence of dietary constituents with which the metal cation can complex (see Section 3.5.1). Ligands in food can have a marked effect on absorption of aluminum, as they can either enhance uptake by forming absorbable (usually water soluble) complexes (e.g., with carboxylic acids such as citric and lactic), or reduce it by forming insoluble compounds (e.g., with phosphate or dissolved silicate). Evidence strongly suggests that the complexing agent of most importance to aluminum uptake in humans is citric acid (or its conjugate base citrate), which is a constituent of many foods and beverages and can be present in the gut in high concentrations (Reiber et al. 1995). It is well-documented in both human and animal studies that blood and tissue levels of aluminum can be increased by simply increasing the consumption of citric acid (i.e., with no concurrent increase in aluminum ingestion), or other dietary chelators such as ascorbic acid and lactic acid (DeVoto and Yokel 1994; Domingo et al. 1991; Florence et al. 1994; Molitoris et al. 1989; Partridge et al. 1989; Slanina et al. 1984, 1985, 1986; Testolin et al. 1996; Weberg and Berstad 1986). The amount of a 976 mg (approximately 14 mg/kg) dose of aluminum as aluminum hydroxide in antacid tablets absorbed by 7–10 volunteers were estimated as 0.004, 0.03, or 0.2% when the antacids were

suspended in tap water (pH 9.2), orange juice (pH 4.2), or citric acid (pH 2.4), respectively (Weberg and Berstad 1986). Absorption was estimated as the amount excreted in urine in 72 hours divided by the amount ingested. A more recent study using ^{26}Al estimated aluminum absorption rates of 0.523, 0.0104, and 0.136% in two subjects receiving a single dose of aluminum citrate, aluminum hydroxide, or aluminum hydroxide dissolved in a citrate solution, respectively (Priest et al. 1996). This is consistent with another study reporting absorption levels of 0.37–0.57% in humans ingesting 280 mg Al as aluminum hydroxide in sodium citrate and citric acid (Taylor et al. 1998). A fourth study reported a higher absorption level (1%) in one subject administered ^{26}Al in a sodium citrate solution (Day et al. 1991).

A comparison of the bioavailability of different aluminum compounds was conducted by Yokel and McNamara (1988). Bioavailability in rabbits following a single maximum safe dose was estimated by comparing areas under the plasma concentration-time curves after oral and intravenous dosing. The estimated bioavailability of the water-soluble compounds aluminum chloride (333 mg Al/kg), aluminum nitrate (934 mg Al/kg), aluminum citrate (1,081 mg Al/kg), and aluminum lactate (2,942 mg Al/kg) in rabbits was 0.57, 1.16, 2.18, and 0.63%, respectively. Aluminum absorption in rabbits similarly treated with the water-insoluble compounds aluminum hydroxide (780 mg Al/kg), aluminum borate (2,736 mg Al/kg), aluminum glycinate (1,351 mg Al/kg), and aluminum sucrose sulfate (20,867 mg Al/kg) was 0.45, 0.27, 0.39, and 0.60%, respectively (Yokel and McNamara 1988). Similarly, Schönholzer et al. (1997) examined aluminum absorption following oral exposure to ^{26}Al in rats. The bioavailability of aluminum hydroxide, aluminum citrate, aluminum citrate with added sodium citrate, or aluminum maltolate following a single gavage dose was 0.1, 0.7, 5.1, and 0.1%, respectively.

The presence of food in the stomach appeared to delay the absorption of ^{26}Al, but did not significantly alter the amount of aluminum absorbed in rats (Yokel et al. 2001a). Aluminum bioavailability was 0.23% with no food in the stomach and 0.21% when food was present. Similarly, there were no differences in absorption when the ^{26}Al was added to hard water (300 mg calcium carbonate/L added) or soft water.

Considering the available human and animal data as discussed above, it is likely that the oral absorption of aluminum can vary 10-fold based on chemical form alone. Although bioavailability appears to generally parallel water solubility, insufficient data are available to directly extrapolate from solubility in water to bioavailability. Additionally, due to available dietary ligands such as citrate, lactate, and other organic carboxylic acid complexing agents, the bioavailability of any particular aluminum compound can be markedly different in the presence of food than under empty stomach conditions.

3.4.1.3 Dermal Exposure

There are limited human data on the dermal absorption of aluminum. Aluminum compounds are common additives in underarm antiperspirants. The active ingredient is usually an aluminum chlorhydrate salt, which is thought to form an obstructive plug of aluminum hydroxide within the sweat duct (Hostynek et al. 1993; Reiber et al. 1995). Using ^{26}Al labeled aluminum chlorohydrate applied to the underarm of two subjects, Flarend et al. (2001) estimated that 0.012% of the applied aluminum was absorbed through the skin. The study investigators cautioned against using these results to extrapolate dermal absorption following repeated exposure to aluminum.

Dermal absorption studies were not located for animals; however a study by Anane et al. (1995) found increased levels of aluminum in the urine of mice exposed to 0.1 or 0.4 μg/day aluminum chloride (0.01–0.04 μg Al/day) applied daily to a 4 cm^2 shaved area for 130 days. Interpretation of this study is limited due to the lack of control measures to prevent the animals from licking their fur and thus ingesting aluminum.

3.4.1.4 Other Routes of Exposure

Flarend et al. (1997) estimated aluminum absorption in rabbits following intramuscular injection of ^{26}Al labelled aluminum hydroxide or aluminum phosphate adjuvants used for vaccines. Aluminum from both solutions was absorbed, appearing in the blood as early as 1 hour after injection. Three times as much aluminum from the aluminum phosphate adjuvant was absorbed during the first 28 days after exposure; since the terminal phase of the blood concentration curve was not reached by that time, this difference may be due to differences in the rate of absorption.

3.4.2 Distribution

Aluminum occurs normally in all body tissues of humans (Ganrot 1986). The total body burden of aluminum in healthy human subjects is approximately 30–50 mg (Alfrey 1981, 1984; Alfrey et al. 1980; Cournot-Witmer et al. 1981; Ganrot 1986; Hamilton et al. 1973; Tipton and Cook 1963). Normal levels of aluminum in serum are approximately 1–3 μg/L (House 1992; Liao et al. 2004). Of the total body burden of aluminum, about one-half is in the skeleton, and about one-fourth is in the lungs (Ganrot 1986). The normal level of aluminum in adult human lungs is about 20 mg/kg wet weight (w/w) and increases with age due to an accumulation of insoluble aluminum compounds that have entered the body via the

airways (Ganrot 1986). Most of the aluminum in other parts of the body probably originates from food intake. Reported normal levels in human bone tissue range from 5 to 10 mg/kg (Alfrey 1980; Alfrey et al. 1980; Cournot-Witmer et al. 1981; Flendrig et al. 1976; Hamilton et al. 1973; Tipton and Cook 1963). Aluminum is also found in human skin (Alfrey 1980; Tipton and Cook 1963), lower gastrointestinal tract (Tipton and Cook 1963), lymph nodes (Hamilton et al. 1973), adrenals (Stitch 1957; Tipton and Cook 1963), and parathyroid glands (Cann et al. 1979). Low aluminum levels (0.3–0.8 mg/kg w/w) are found in most soft tissue organs, other than the lungs (Hamilton et al. 1973; Tipton and Cook 1963).

The normal level of aluminum in the human brain ranges from 0.25 to 0.75 mg/kg w/w, with gray matter containing about twice the concentration found in the white matter (Alfrey et al. 1976; Arieff et al. 1979; McDermott et al. 1978; Roider and Drasch 1999). There is evidence that with increasing age of humans, aluminum concentrations may increase in the brain tissue (Alfrey 1980; Crapper and DeBoni 1978; Markesbery et al. 1981; McDermott et al. 1979; Stitch 1957; Tipton and Shafer 1964); aluminum levels in serum may also increase with aging (Zapatero et al. 1995).

3.4.2.1 Inhalation Exposure

Limited information is available regarding the distribution of aluminum following inhalation exposure in humans or animals. Results of an autopsy of a stone mason presumed to have been exposed to aluminum by inhalation indicated elevated concentrations of aluminum in the lungs (2,000 ppm), hilar lymph nodes (3,200 ppm), liver (130 ppm), and spleen (520 ppm) (Teraoka 1981). The aluminum levels in the tissues of control subjects were 230, 2,000, 19, and 22 ppm, respectively. Rats and guinea pigs given intermediate or chronic inhalation exposures to aluminum chlorhydrate accumulated aluminum primarily in the lungs (Steinhagen et al. 1978; Stone et al. 1979). The only other organs with significant accumulation of aluminum were the adrenal glands (Stone et al. 1979) and the peribronchial lymph nodes (Steinhagen et al. 1978; Stone et al. 1979). No appreciable aluminum accumulation was observed in the brain, heart, spleen, kidneys, or liver of either species.

During inhalation exposure to aluminum and its compounds, the lungs distribute and deposit the material based on particle size (ICRP 1994). A portion of the particles are exhaled, some are trapped in the nasopharyngeal and upper respiratory areas and deposited in the gastrointestinal tract by mucosal movement and mucocilliary action, and a portion of the small particles reach the alveoli where they can be transferred to blood (especially for soluble compounds), or taken up by alveolar macrophages through

phagocytosis and transported to pulmonary lymph nodes for insoluble compounds. Pulmonary concentration of aluminum increases with age.

3.4.2.2 Oral Exposure

There are limited data on the distribution of aluminum in humans. Clearance of ^{26}Al from the blood was assessed in two male volunteers orally exposed to 100 mg aluminum as aluminum chloride (Hohl et al. 1994). Plots of the serum and urine concentrations showed several slope changes, indicating that the clearance from blood involves one central and three peripheral compartments with turnover rates ranging from 0.003 to 9 h^{-1}.

The distribution of aluminum in animals after oral exposure has been evaluated in a number of studies (Cranmer et al. 1986; Deng et al. 2000; Dlugaszek et al. 2000; Domingo et al. 1993; Gomez et al. 1997a, 1997b; Greger and Donnaubauer 1986; Julka et al. 1996; Ogasawara et al. 2002; Santos et al. 1987; Sutherland and Greger 1998; Walton et al. 1995; Yokel and McNamara 1985; Yokel et al. 1999; Zafar et al. 1997). These studies are particularly informative because they demonstrate that, although bioavailability of aluminum is low, aluminum tissue concentrations can increase substantially following oral exposure, and provide information on distribution of aluminum in various tissues. Aluminum is not equally distributed throughout the body following oral exposure. Aluminum accumulation was typically higher in the spleen, liver, bone, and kidneys than in the brain, muscle, heart, or lung (Greger and Sutherland 1997). Eight days after a single gavage dose of 2.6 mg of ^{26}Al as aluminum chloride, the descending order of aluminum levels was bone>spleen>liver>kidney (Zafar et al. 1997). To evaluate the retention of aluminum in tissues following oral exposure, rats were fed a diet supplemented with aluminum hydroxide for an intermediate-duration exposure period (Greger and Donnaubauer 1986). Relative to controls, treated rats had increased aluminum concentrations in bone, muscle, and kidneys. Aluminum concentrations in these tissues decreased significantly 3 days after withdrawal of aluminum hydroxide from the diet. Tissue concentrations of aluminum were similar for treated and control rats 7 days after withdrawal.

Once into the blood, aluminum is believed to be present almost exclusively in the plasma where it is bound mainly to transferrin (Ganrot 1986; Harris and Messori 2002; Martin 1986); recent data suggest that over 90% of the aluminum in serum is bound to transferrin (Harris and Messori 2002). There is *in vitro* evidence indicating that aluminum can bind to the iron-binding sites of transferrin (Moshtaghie and Skillen 1986), and that Al^{+3} may compete with similar ions in binding to transferrin (Ganrot 1986). As

reviewed by Priest (2004), approximately 10% of the aluminum in blood is found in the erythrocytes; peak levels occur 1 day after peak serum aluminum levels were reached. The half-life of aluminum in the erythrocytes appears to longer than the half-life in plasma. In addition to binding with transferrin, Al^{+3} is also known to bind to a considerable extent to bone tissue, primarily in the metabolically active areas of the bone (Ganrot 1986).

Cellular uptake of aluminum by organs and tissues is believed to be relatively slow and most likely occurs from the aluminum bound to transferrin (Ganrot 1986). It is likely that the density of transferrin receptors in different organs influences the distribution of aluminum to organs (Morris et al. 1989). Within cells, Al^{+3} accumulates in the lysosomes, cell nucleus, and chromatin. In organs composed of postmitotic cells, this accumulation would be expected to lead to an increase of the Al^{+3} concentration; however, in other organs, a steady state is expected to be reached between the Al^{+3} accumulation and the elimination of dead cells that are replaced by cells with a lower Al^{+3} content. The cells that accumulate the most aluminum are large, long-lived postmitotic cells, such as in neurons (Ganrot 1986).

In addition to distribution of aluminum to the brain (hippocampus), bone, muscle, and kidneys of orally exposed animals, there is evidence in animals that aluminum crosses the placenta and accumulates in the fetus and distributes to some extent to the milk of lactating mothers (Cranmer et al. 1986; Golub et al. 1996; Yokel 1985; Yokel and McNamara 1985). Aluminum levels were increased in both fetuses and placentas of mice treated throughout gestation with aluminum chloride (Cranmer et al. 1986). The concentration of aluminum in milk of rats that ingested 420 mg Al/kg/day as aluminum lactate in the diet during gestation and lactation increased at least 4-fold beginning on postnatal day 12 (Golub et al. 1996). Peak concentrations of aluminum were detected in the milk of lactating rabbits 12–24 hours after a single large gavage dose of aluminum lactate; however, the amount of aluminum in milk as a percentage of the total oral dose was not reported (Yokel and McNamara 1985). Aluminum levels of rabbit pups exposed during lactation were not significantly different from levels in control pups, suggesting that only a small amount of the aluminum in breast milk is absorbed by the offspring (Yokel 1985).

Age-related differences in the distribution of aluminum has been observed in rats exposed to 0, 50, or 100 mg Al/kg/day as aluminum nitrate in the drinking water with added citrate (Gomez et al. 1997a). The levels of aluminum in the brain and bone were significantly higher in the older rats (16 months of age at study beginning) compared to young (21 days of age) or adult (8 months of age) rats; this was observed in the control and aluminum-treated rats. Liver aluminum levels were significantly higher in adult and older rats as compared to the young rats.

3.4.2.3 Dermal Exposure

No studies were located regarding distribution in humans after dermal exposure to aluminum or its compounds. Elevated levels of aluminum have been observed in the liver, brain, lung, and kidneys of Swiss mice dermally exposed to 0.4 μg/day aluminum chloride (0.04 μg Al/day) for 20 days during gestation (Anane et al. 1997). Elevated levels of aluminum were also observed in the fetus, providing evidence of transplacental transfer of aluminum. As noted previously, this study did not prevent the mice from licking their fur.

3.4.2.4 Other Routes of Exposure

When there is inadequate elimination of aluminum from the body, as in nondialyzed uremic patients, increased aluminum concentrations are detected in serum, bone tissue, liver, spleen, brain, and skeletal muscle (Alfrey et al. 1980; Arieff et al. 1979). In hemodialysis patients exposed by infusion to large amounts of aluminum over long periods of time (with inadequate removal of aluminum by the kidneys and dialysis machines), increased aluminum concentrations are observed mostly in the spleen, followed by the liver and skeletal system (Alfrey 1980; Alfrey et al. 1980). A study in rabbits found a significantly lower serum half-life in renally-impaired animals, as compared to renally-intact animals (27 hours versus 14 hours); this is likely due to the diminished volume of distribution in the renally-impaired rabbits (Yokel and McNamara 1988).

The distribution of aluminum following intravenous, subcutaneous, intraperitoneal, and intramuscular exposure has been evaluated in studies with experimental animals (Cranmer et al. 1986; Du Val et al. 1986; Flarend et al. 1997; Leblondel and Allain 1980; Yokel and McNamara 1985, 1989; Yokel et al. 2001b). Results of these animal studies indicate that aluminum distributes to a number of tissues, organs, and biological fluids (Du Val et al. 1986; Leblondel and Allain 1980; Yokel and McNamara 1989).

In rabbits given a single intravenous dose of aluminum lactate, aluminum concentrations did not increase above controls in the cerebellum, white brain tissue, hippocampus, spinal cord, adrenal glands, bone, heart, testes, or thyroid (Yokel and McNamara 1989). Treated animals did have significant increases of aluminum in the liver, serum, bile, kidneys, lungs, and spleen. Throughout the 128 day study, the liver of exposed rabbits had over 80% of the total body burden of aluminum. Persistence of aluminum in the various tissues, organs, and fluids varied. Estimated half-times of aluminum were 113, 74, 44, and 42 days in the spleen, liver, lungs, and serum, respectively. The kidneys of treated rabbits demonstrated

two half-times with an initial time of 4.2 and 2.3 days for the renal cortex and renal medulla, respectively, and a second half-time of >100 days for kidney in general; the relative amounts subject to each half-time were not addressed. The half-life of aluminum in the brain of rats receiving an intravenous dose of aluminum citrate was approximately 150 days (Yokel et al. 2001b).

Subcutaneous injection of rabbits with aluminum chloride daily for 28 days was associated with significant accumulation of aluminum (measured at the end of the exposure period) in bone, followed in order by significantly increased aluminum concentrations in renal cortex, renal medulla, liver, testes, skeletal muscle, heart, brain white matter, hippocampus, and plasma (Du Val et al. 1986). Because the brain tissue of treated rabbits had the lowest aluminum concentrations of the tissues evaluated, the authors suggested that there was a partial blood-brain barrier to entry of aluminum.

Distribution of aluminum to tissues following intraperitoneal exposure depends in part on the type of aluminum compound administered and on the aluminum concentration in blood (Leblondel and Allain 1980). Mice were administered 54 mg Al/kg as aluminum chloride, nitrate, lactate, or gluconate by a single intraperitoneal injection. The blood concentrations of aluminum, which reached a peak within 20 minutes, increased significantly with gluconate (99.5 mg/L), increased to high levels with lactate (4.5 mg/L), and increased marginally with nitrate and chloride (0.3 mg/L). Aluminum concentrations in the brain tissue of treated mice significantly increased only with aluminum gluconate and only at extremely high blood aluminum concentrations of 20–100 mg/L; the half-life of aluminum in the brain was approximately 90 minutes. At blood aluminum concentrations of 2–4 mg/L, there was no increase in brain aluminum with any of the compounds evaluated. Interpretation of this study is limited by the short monitoring period (apparently 80 minutes); thus, the study does not take into consideration possible differences in absorption rate between aluminum compounds. Differences in brain aluminum levels following administration of different aluminum compounds may also be due to the presence of carrier systems that can transport aluminum into or out of the brain; this has been demonstrated for aluminum citrate (Allen et al. 1995).

Following intramuscular administration of aluminum hydroxide or aluminum phosphate vaccine adjuvants in rabbits, increased levels of ^{26}Al were found in the kidney, spleen, liver, heart, lymph nodes, and brain (in decreasing order of aluminum concentration) (Flarend et al. 1997).

There is also evidence from animal studies indicating that aluminum administered parenterally accumulates to a small extent in the milk of lactating mothers, and that aluminum crosses the placenta and

accumulates in fetal tissue (Cranmer et al. 1986; Yokel and McNamara 1985; Yumoto et al. 2000). Intraperitoneal exposure of pregnant mice to aluminum chloride on gestation days 7–16 has been associated with significantly increased concentrations of aluminum in both placental and fetal tissues (Cranmer et al. 1986). Following a single subcutaneous injection of ^{26}Al on gestation day 15, 0.2 and 0.21% of the dose was detected in the placenta and fetus, respectively, 5 days after the injection (Yumoto et al. 2000). Within the fetus, the level of ^{26}Al in the brain was as high as 30% of that in the fetal liver; in contrast, the level of ^{26}Al in the brain of the dam was only 1% of the level in the liver. Intravenous, intraperitoneal, or subcutaneous exposure of lactating rats, rabbits, or mice to aluminum lactate or aluminum chloride has been associated with increased concentrations of aluminum in milk (Muller et al. 1992; Yokel and McNamara 1985). The amount of aluminum detected in milk 24 hours after exposure was estimated to be 2.4% of the intravenous dose and 3.3% of the subcutaneous dose (Yokel and McNamara 1985). Subcutaneous injection of ^{26}Al in rats on lactation day 1 through 20, resulted in significant elevation in aluminum levels in the suckling rats (Yumoto et al. 2000, 2003). On lactation day 2, elevated levels of ^{26}Al were detected in the liver, but not in the kidney, brain, or blood; ^{26}Al was detected in these tissues on lactation day 9 (Yumoto et al. 2000).

3.4.3 Metabolism

As an element, aluminum is always found attached to other chemicals, and these affinities can change within the body. In living organisms, aluminum is believed to exist in four different forms: as free ions, as low-molecular-weight complexes, as physically bound macromolecular complexes, and as covalently bound macromolecular complexes (Ganrot 1986). The free ion, Al^{+3}, is easily bound to many substances and structures; therefore, its fate is determined by its affinity to each of the ligands and their relative amounts and metabolism. Aluminum may also form low-molecular-weight complexes with organic acids, amino acids, nucleotides, phosphates, and carbohydrates. These low-molecular-weight complexes are often chelates and may be very stable. The complexes are metabolically active, particularly the nonpolar ones. Because aluminum has a very high affinity for proteins, polynucleotides, and glycosaminoglycans, much of the aluminum in the body may exist as physically bound macromolecular complexes with these substances. Metabolically, these macromolecular complexes would be expected to be much less active than the smaller, low-molecular-weight complexes. Aluminum may also form complexes with macromolecules that are so stable that they are essentially irreversible. For example, evidence suggests that the nucleus and chromatin are often sites of aluminum binding in cells (Crapper McLachlan 1989; Dyrssen et al. 1987; Ganrot 1986; Karlik et al. 1980).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

Urinary excretion is the primary route of elimination of absorbed aluminum after inhalation exposure in humans. Elevated levels of aluminum in urine have been detected in aluminum welders and aluminum flake workers (Letzel et al. 1996; Ljunggren et al. 1991; Mussi et al. 1984; Pierre et al. 1995; Rossbach et al. 2006; Schaller et al. 2007; Sjögren et al. 1985, 1988). Six volunteers had urinary levels of 14–414 μg/L aluminum compared to concentrations of <3 μg/L prior to a 1-day exposure to 0.3–10.2 mg Al/m^3 in welding fumes (Sjögren et al. 1985). The urinary aluminum levels of 7 welders exposed occupationally to aluminum fumes or dust for 6 months were increased 3-fold after an 8-hour workshift compared to concentrations at the beginning of the day (Mussi et al. 1984). Several investigators (Letzel et al. 1996; Rossbach et al. 2006; Sjögren et al. 1988) have found a linear relationship between post-shift urinary aluminum levels and levels of aluminum in air among welders.

Occupational exposure studies suggest that the urinary excretion of aluminum is biphasic. The excretion half-time for the first phase ranged from 7.5 to 9 days among workers exposed to welding fumes or aluminum dust (Pierre et al. 1995; Sjögren et al. 1985, 1988). The half-times for the second phase ranged from 6.8 to 24 weeks (Schaller et al. 2007; Sjögren et al. 1988, 1991); the wide range of half-times may reflect the character of the inhaled aluminum (welding fume particles or aluminum flake particles) and the duration of exposure.

No studies were located regarding excretion in animals after inhalation exposure to aluminum or its compounds.

3.4.4.2 Oral Exposure

Following ingestion in humans, absorbed aluminum from the blood is eliminated in the kidney and excreted in the urine (Gorsky et al. 1979; Greger and Baier 1983; Kaehny et al. 1977; Recker et al. 1977; Sutherland and Greger 1998). The unabsorbed aluminum is excreted primarily in the feces. An acute exposure of 4 days to 54.3 mg Al/kg as aluminum carbonate produced peak concentrations ranging from 4- to 10-fold elevation in base-line urinary levels; the average urinary excretion rate being 495 μg/day during exposure (Recker et al. 1977). In humans, 0.09 and 96% of the aluminum intake per day was cleared through the urine and feces, respectively, during exposure to 1.71 mg Al/kg/day as aluminum lactate in addition to 0.07 mg Al/kg/day in basal diet for 20 days (Greger and Baier 1983). Urinary

aluminum concentrations were significantly elevated in volunteers who received aluminum hydroxide and aluminum carbonate (Kaehny et al. 1977). Patients taking aluminum antacids in the diet had only a 3-fold increase in urinary aluminum levels (Gorsky et al. 1979), suggesting that most of the aluminum hydroxide was not absorbed and was excreted directly into the feces.

Excretion of aluminum may be lower in premature compared to full-term infants (Bougle et al. 1991). Plasma levels of aluminum in premature infants were 14.6 μg/L compared to 7.8 μg/L in full-term infants, and absolute urinary excretion was reduced. The aluminum-creatinine ratio in the urine was similar in both groups, indicating that the lower excretion in the premature infants may be due to lower metabolic and glomerular filtration rates, thus increasing the risk of aluminum accumulation in this group.

Excretion data collected in animal studies are consistent with the results from human studies. A single oral dose of 11 mg aluminum resulted in a 14-fold increase in urine aluminum levels, as compared to baseline levels, in healthy Sprague-Dawley rats (Ittel et al. 1987). The aluminum was primarily excreted during the first 24-hour period, and was comparable to baseline levels 5 days postexposure. Similarly exposed uremic rats excreted more aluminum than the healthy rats; the study authors postulated that this increase in excretion was probably due to increased gastrointestinal absorption. Rats administered a single dose of one of eight aluminum compounds (all contained 35 mg aluminum) excreted in the urine 0.015–2.27% of the initial dose (Froment et al. 1989b). The range most likely reflects differences in gastrointestinal absorption. Following administration of a single dose of 6.7–27 mg Al/kg, 1.3–2.8% of the dose was excreted within the first 3 hours; the percent of the dose excreted in the urine did not differ among the three dose groups (Sutherland and Greger 1998).

Fecal aluminum represents unabsorbed aluminum as well as aluminum excreted via bile. Within 15 minutes of rats receiving a gavage dose of 6.7–27 mg Al/kg, the levels of aluminum in bile were significantly higher than in controls (Sutherland and Greger 1998). The percentage of the total dose excreted in bile during the first 3 hours after dosing ranged from 0.06 to 0.14%. In the control group, 25.0 mmol aluminum were excreted in the bile compared to 7.9 mmol in the urine.

3.4.4.3 Dermal Exposure

No studies were located regarding the excretion in humans and animals after dermal exposure to aluminum or its compounds.

3.4.4.4 Other Routes of Exposure

Human and animal studies have investigated the aluminum retention in the body. Within the first day of receiving a single injection of ^{26}Al citrate, approximately 59% of the dose was excreted in the urine of six subjects; 72 and 1.2% was excreted in the urine and feces, respectively, during the first 5 days (Talbot et al. 1995). At the end of 5 days, it was estimated that 27% of the dose was retained in the body (Priest et al. 1995; Talbot et al. 1995). When ^{26}Al levels were monitored more than 3 years after a single subject received the injection, a half-life of approximately 7 years was calculated (Priest et al. 1995). However, when the subject was re-examined approximately 10 years after the injection, a half-life of about 50 years was estimated (Priest 2004).

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 and Krishnan 1994; Andersen et al. 1987). 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 parameterization, (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.

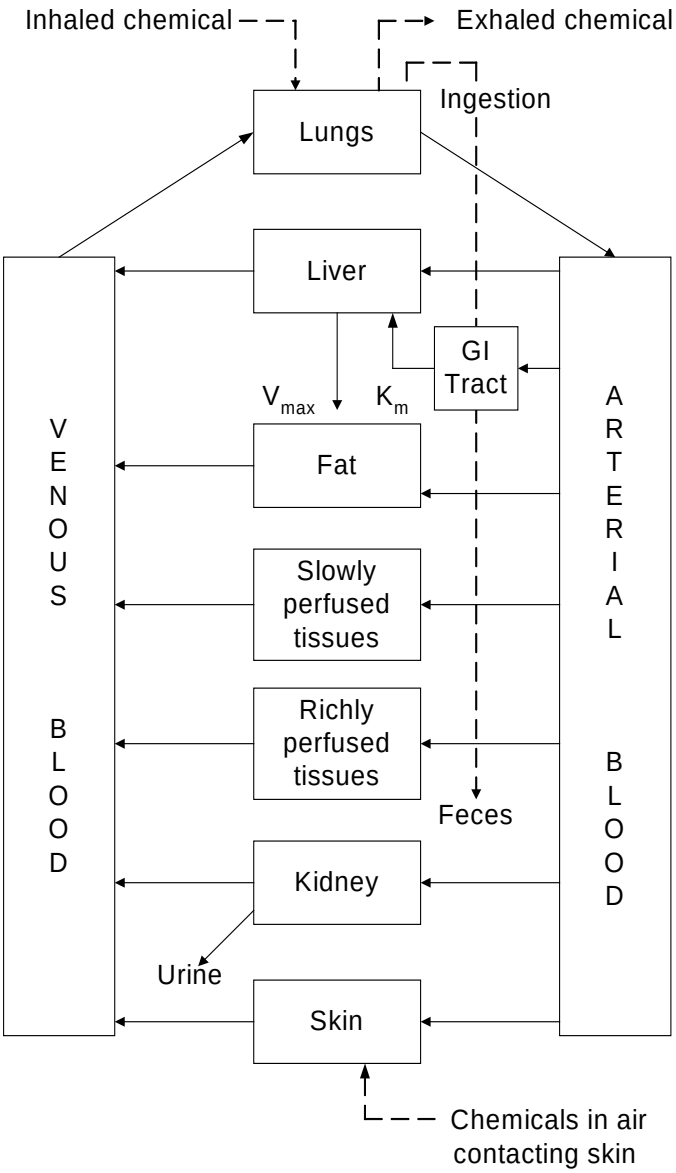
The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many 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 3-3 shows a conceptualized representation of a PBPK model.

If PBPK models for aluminum exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

A PBPK/PD model that can be used in risk assessment to predict the concentrations of aluminum delivered to target tissues (particularly the brain) or to examine the relationship between target tissue dose and the observed responses was not located. However, a biokinetic model has been developed to describe the absorption, distribution, and excretion of aluminum (Kislinger et al. 1997; Nolte et al. 2001; Steinhausen et al. 2004). This model allows for the prediction of aluminum levels under different physiological conditions such as renal failure or iron deficiency/overload. The model is an open compartment model comprised of a central compartment, three peripheral compartments, additional compartments for the gastrointestinal tract (stomach, duodenum, and residual intestinal tract), and excretion primarily via kidney output into urine. The central compartment comprises the blood plasma and interstitial fluid; in both compartments, the aluminum is bound to large proteins such as transferrin

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



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.

Source: adapted from Krishnan et al. 1994

and to small soluble molecules such as citrate. The peripheral compartments are: (1) the liver and spleen, which are supplied by aluminum from plasma transferrin (this compartment is characterized by a rapid exchange with the central compartment and no significant long-term storage of aluminum); (2) the muscles, heart, and kidney tissues, which are supplied aluminum from interstitial transferrin; and (3) the bones, which are supplied by aluminum from interstitial tissue citrate (this compartment is characterized by rapid accumulation of aluminum and long-term storage). Aluminum is primarily excreted via ultrafilterable citrate-bound aluminum of plasma via the kidneys into the urine; a minor excretion path is transport of transferrin-bound aluminum of plasma via the liver into the residual intestinal tract.

3.5 MECHANISMS OF ACTION

The mechanism of action for aluminum toxicity is not known, but the element is known to compete in biological systems with cations, especially magnesium (Macdonald and Martin 1988) despite an oxidation state difference, and to bind to transferrin and citrate in the blood stream (Ganrot 1986). It may also affect second messenger systems and calcium availability (Birchall and Chappell 1988), and irreversibly bind to cell nucleus components (Crapper McLachlan 1989; Dyrssen et al. 1987). Aluminum has also been shown to inhibit neuronal microtubule formation. However, much more work is needed before a mechanism can be proposed.

3.5.1 Pharmacokinetic Mechanisms

Gastrointestinal absorption of aluminum is low, generally in the range of 0.01–0.6% in humans as discussed in Section 3.3.1.2. Absorption of aluminum compounds is largely determined by its ionic availability in the aqueous conditions of the gut, which is mainly related to pH, the presence of complexing ligands with which the metal can form absorbable aluminum species, and the chemical form (type of anion) of the ingested compound (DeVoto and Yokel 1994; Reiber et al. 1995). In acidic aqueous conditions such as in the stomach (pH≈2) aluminum primarily occurs as a monomolecular hexahydrate, $Al(H_2O)_6^{+3}$, which is generally abbreviated Al^{+3} and referred to as “free” aluminum (Reiber et al. 1995). The acidic conditions and mixing/residence time in the stomach appear to ensure that the majority of consumed aluminum will be solubilized to monomolecular species (most likely free Al^{+3}), regardless of the compound and form (e.g., food, drinking water or antacid tablets) in which it was ingested. The solubilized aluminum that is in the stomach can recomplex with the anion from the original aluminum compound that was ingested or form new complexes with dietary ligands. The dietary constituents that appear to play a particularly important role in the complexation process include simple mono-, di-, and tricarboxylic acids (particularly citric acid). The vast majority of the solubilized

aluminum is not complexed. As pH increases in the duodenum, a series of aluminum hydroxy complexes are formed by successive deprotonation so that in near-neutral conditions such as in the intestines, the predominant form is aluminum hydroxide ($[Al(OH)_3]$), which is rapidly precipitated as insoluble by the near-neutral pH conditions, and is ultimately excreted in the feces.

The mechanism by which aluminum is absorbed and the chemical forms of aluminum able to pass through the intestinal wall are not completely understood (DeVoto and Yokel 1994; Exley et al. 1996; Lione 1985a; Priest 1993; Reiber et al. 1995; van der Voet 1992; Wilhelm et al. 1990). Available data, mainly results of *in vitro* (everted gut) and *in situ* (intestinal perfusion) studies in rats (e.g., Feinroth et al. 1982; Froment et al. 1989b; Provan and Yokel 1990), suggest that aluminum is mainly absorbed as neutral complexes by passive diffusion through intercellular tight junction (paracellular channel) pathways (i.e., via spaces between cells rather than through the cells themselves). However, adequate information is not available to rule out transcellular transport (cellular internalization), and both paracellular and transcellular pathways may be involved. Transcellular transport is also likely to be a passive process; possible mechanisms include cell-mediated endocytosis, simple diffusion of neutral and possibly lipophilic aluminum complexes, and facilitative diffusion via cation-specific channels (Exley et al. 1996). Active transport of Al^{+3} via iron absorption pathways may also contribute to the absorption of aluminum, but the role of iron pathways in aluminum absorption is incompletely elucidated (DeVoto and Yokel 1994) and complicated by the primary differences in oxidation states (2+ and 3+), which would argue against the two following an identical pathway. The predominant uptake mechanism remains unresolved due to insufficient data in the existing studies, particularly failure to characterize or control for intraluminal conditions affecting aluminum absorption, especially pH differences which can influence aluminum speciation, presence of dietary and other gut substances that can influence solubility of aluminum via formation of complexes, and quantity of available aluminum. These data insufficiencies complicate reconciling different results and postulated mechanisms between studies, and extrapolating to human *in vivo* physiochemical conditions (i.e., identifying the chemical form and mechanism of aluminum absorption in humans).

As previously discussed, absorption of aluminum is markedly increased by the presence of citrate. The mechanism is not fully characterized, but it is thought that citrate enhances gut bioavailability by increasing the permeability of the paracellular channels, possibly via disruption in calcium homeostasis (DeVoto and Yokel 1994; Exley et al. 1996; Froment et al. 1989b; Molitoris et al. 1989; Provan and Yokel 1988). It currently appears that aluminum is not absorbed across the gastrointestinal epithelium as a citrate complex, but that citrate expedites the absorption of aluminum by maintaining the aluminum in a

form that can be readily incorporated into one or more mechanisms of absorption (Exley et al. 1996). This mechanism may be unique to the aluminum-citrate complex, which would be consistent with the apparent greater bioavailability of aluminum citrate compared to other carboxylic acid chelates. Other factors such as parathyroid hormone (through stimulation of $1,25(OH)_2D_3$ production) and vitamin D have also been suggested to enhance the absorption of aluminum, but the data are largely inconclusive.

Mechanisms of inhalation absorption of aluminum are not well characterized, although it seems likely that relatively large aluminum-containing particles retained in the respiratory tract are cleared to the gastrointestinal tract by ciliary action. As has been observed with typical particulates (ICRP 1994), it is hypothesized that aluminum particles that are small enough (<5 μm diameter) to penetrate the lung's protective removal mechanisms may contribute to overall body levels by dissolution and direct uptake from alveoli into the blood stream, or by macrophage phagocytosis (Priest 1993; Reiber et al. 1995).

3.5.2 Mechanisms of Toxicity

In the cases in which human aluminum toxicity has occurred, the target organs appear to be the lung, bone, and the central nervous system. No specific molecular mechanisms have been elucidated for human toxicity to aluminum. In animal models, aluminum can also produce lung, bone, and neurotoxicity, as well as developmental effects in offspring.

Bone Toxicity. Two types of osteomalacia have been associated with aluminum exposure. The first type has been observed in healthy individuals using aluminum-containing antacids to relieve the symptoms of gastrointestinal disorders such as ulcers, colic, or gastritis. The aluminum in the antacids binds with dietary phosphorus and impairs gastrointestinal absorption of phosphorus. The observed osteomalacia and rickets is directly related to the decreased phosphate body burden. Osteomalacia is well documented in dialyzed uremic patients exposed to aluminum via dialysis fluid or orally administered aluminum used to control hyperphosphatemia. In the case of the uremic patient, bone aluminum levels are markedly increased and the aluminum is present between the junction of calcified and noncalcified bone (Alfrey 1993). The osteomalacia is characterized by increased mineralization lag time, osteoid surface, and osteoid area, relatively low parathyroid hormone levels, and mildly elevated serum calcium levels.

Neurotoxicity. Various neurotoxic effects of aluminum have been induced in animals, ranging from neurobehavioral and neurodevelopmental alterations following repeated oral exposures in mice and rats to neurodegenerative pathological changes in the brain caused by acute parenteral administration in

nonrodent species. Numerous mechanistic studies of aluminum neurotoxicity have been performed, but no single unifying mechanism has been identified (Erasmus et al. 1993; Jope and Johnson 1992; Strong et al. 1996); it is likely that more than one mechanism is involved. The main sites of action of aluminum are difficult to discern because the studies have been performed using a variety of exposure methods (including a number of different *in vivo* injections and *in vitro* systems) and animal species, and a number of typical effects are not common to all species and exposure circumstances (i.e., are only expressed using certain models of neurotoxicity). Although insufficient data are available to fully understand the mechanism(s) of aluminum toxicity, some general processes that are involved have been identified. Changes in cytoskeletal proteins, manifested as hyperphosphorylated neurofilamentous aggregates within the brain neurons, is a characteristic response to aluminum in certain species (e.g., rabbits, cats, ferrets, and nonhuman primates) and exposure situations (e.g., intracerebral and intracisternal administration). Similar neurofibrillary pathological changes have been associated with several neurodegenerative disorders, suggesting that the cause of aluminum-related abnormal neuronal function may involve changes in cytoskeletal protein functions in affected cells. The neurofilamentous aggregates appear to mainly result from altered phosphorylation, apparently by posttranslational modifications in protein synthesis, but may also involve proteolysis, transport and synthesis (Jope and Johnson 1992; Strong et al. 1996). Interactions between these processes probably contribute to the induction of the phosphorylated neurofilaments. Each of the processes can be influenced by kinases, some of which are activated by second messenger systems. For example, aluminum appears to influence calcium homeostasis and calcium-dependent processes in the brain via impairment of the phosphoinositide second messenger-producing system (which modulates intracellular calcium concentrations); calcium-activated proteinases may be affected, which could alter the distribution and concentration of cytoskeletal proteins and other substates (Gandolfi et al. 1998; Jope and Johnson 1992; Julka and Gill 1995; Kaur and Gill 2005; Kaur et al. 2006; Mundy et al. 1995; Nostrandt et al. 1996; Sarin et al. 1997; Shafer and Mundy 1995). Another process that may contribute to neurodegeneration is apoptosis (Fu et al. 2003; Ghribi et al. 2001; Johnson et al. 2005; Suarez-Fernandez et al. 1999).

The species (rodents) in which aluminum-induced neurobehavioral effects (e.g., changes in locomotor activity, learning and memory) have been observed fail to develop significant cytoskeletal pathology, but exhibit a number of neurochemical alterations following *in vivo* or *in vitro* exposure (Erasmus et al. 1993; Strong et al. 1996). Studies in these animals indicate that exposure to aluminum can affect permeability of the blood-brain barrier (Yokel et al. 2002; Zheng 2001), cholinergic activity (Kaizer et al. 2005; Kohila et al. 2004; Zatta et al. 2002), signal transduction pathways (Montoliu and Felipo 2001), lipid peroxidation (Deloncle et al. 1999; El-Demerdash 2004; Fraga et al. 1990; Khanna and Nehru 2007;

Nehru and Anand 2005), and impair neuronal glutamate nitric oxide-cyclic GMP pathway (Cucarella et al. 1998; Hermenegildo et al. 1999; Llansola et al. 1999; Rodella et al. 2004), as well as interfere with metabolism of essential trace elements (e.g., iron) because of similar coordination chemistries and consequent competitive interactions.

3.5.3 Animal-to-Human Extrapolations

The appropriateness of extrapolating health effects of aluminum in animals to humans cannot be conclusively determined due to limitations of the human database. Information on toxicity of aluminum in humans is not extensive because the preponderance of studies are in patients with reduced renal function who accumulated aluminum as a result of long-term intravenous hemodialysis therapy with aluminum-containing dialysis fluid and, in many cases, concurrent administration of high oral doses of aluminum to regulate phosphate levels. No clinical studies on health effects of aluminum medicinals in people with normal renal function have been performed, largely due to the fact that exposures typically consist of over-the-counter products such as antacids and buffered aspirins that have been assumed to be safe in healthy individuals at recommended doses based on historical use. The assumed safety of aluminum is also partly due to the FDA-approved GRAS status of aluminum-containing food additives. Other human data largely consist of studies of aluminum-exposed workers that are limited by the lack of quantitative exposure data and/or co-exposure to other chemicals. Subtle neurological effects have been observed in workers chronically exposed to aluminum dust or aluminum fumes, but these studies only provide suggestive evidence that there may be a relationship between chronic aluminum exposure and neurotoxic effects in humans. Aluminum is generally considered to be neurotoxic in animals, and there is an adequate basis to conclude that neurotoxicity/neurodevelopmental toxicity is the critical effect of oral exposure in animals. Whether the subtle neurotoxic effects seen in adult and developing animals exposed to relatively low doses of aluminum would definitely manifest in humans under similar exposure conditions remains to be determined.

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 Thomas and Colborn (1992), was also used in 1996 when Congress mandated the 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), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in humans and/or animals after exposure to aluminum. No *in vitro* studies were located regarding endocrine disruption of aluminum.

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).

There is a limited amount of information available on the toxicity of aluminum in children. As with adults, neurological and skeletal (osteomalacia) effects have been observed in children with impaired renal function (Andreoli et al. 1984; Griswold et al. 1983). These effects are related to an abnormal accumulation of aluminum due to exposure to aluminum-contaminated dialysate, use of aluminum containing phosphate binding gels, and impaired renal excretion of aluminum. These effects are not likely to occur in children with normal renal function. Skeletal effects have also been observed in children on long-term total parenteral nutrition containing elevated levels of aluminum. Another subpopulation of children that may be particularly sensitive to the toxicity of aluminum is preterm infants. The observed elevated plasma aluminum levels may be due to the higher aluminum content of premature infant formula and/or limited renal capacity of preterm infants to excrete aluminum (Tsou et al. 1991). Bougle et al. (1991) reported plasma aluminum levels of 14.6 μg/L in preterm infants compared to 7.8 μg/L in full-term infants; decreased urinary aluminum levels at comparable creatinine normalized rates were also found. Bishop et al. (1997) found significant decreases in the Bayley Mental Development Index in pre term infants receiving a standard intravenous feeding solution compared to pre term infants receiving an aluminum-depleted feeding solution. Growth reduction, hypotonia, muscle weakness, and craniosynostosis (premature ossification of the skull and obliteration of the sutures) have been observed in healthy infants following prolonged used of oral antacids for the treatment of colic (Pivnick et al. 1995). These effects were related to secondary hypophosphatemia caused by aluminum binding to phosphate in the gut and markedly reduced phosphate absorption.

Most of the available data come from animal studies that examined the distribution, neurotoxicity, and skeletal toxicity of aluminum at several ages (e.g., gestationally exposed, neonatal, young, adult, and older animals). Yokel and McNamara (1985) did not find any age-related differences in the systemic clearance or half-time of aluminum lactate in rabbits following intravenous, oral, or subcutaneous exposure. Oral exposure to aluminum nitrate resulted in higher brain aluminum levels in young rats as compared to older rats, but there was no difference in toxicity between young and adult rats (Gomez et al. 1997a). In other tissues examined, the aluminum levels in the young rats tended to be lower than in the adult or older animals (Gomez et al. 1997b). Fetal exposure may result in a higher distribution of aluminum to the brain, as compared to adults. In the fetuses of rats receiving a single subcutaneous injection of aluminum on gestation day 5, the amount of the radiolabelled aluminum in the brain was 30%

higher than in the liver; in the dams, brain aluminum levels were only 1% of the levels found in the liver (Yumoto et al. 2000).

Aluminum is distributed transplacentally, and elevated levels of aluminum have been measured in the fetus and placenta following oral, dermal, or parenteral exposure to aluminum (Anane et al. 1997; Cranmer et al. 1986; Yumoto et al. 2000). There is also evidence that oral or parenteral exposure to aluminum can result in elevated levels in breast milk (Golub et al. 1996; Muller et al. 1992; Yokel 1985; Yokel and McNamara 1985; Yumoto et al. 2000, 2003); the form of aluminum in breast milk was not reported. Although levels of aluminum in breast milk were elevated in aluminum-exposed rabbit does, the concentrations in the pups were not significantly different from control levels, suggesting that the aluminum was poorly absorbed (Yokel 1985). In contrast, subcutaneous injection of ^{26}Al in rats on lactation day 1 through 20 resulted in significant elevation in aluminum levels in the suckling rats (Yumoto et al. 2000).

The most sensitive known effect following oral exposure to aluminum is neurotoxicity. Neurotoxic effects have been observed in adult animals, weanling animals, and in animals exposed during gestation, gestation and lactation, and lactation-only (Colomina et al. 2005; Donald et al. 1989; Golub and Germann 1998, 2001; Golub et al. 1987, 1992a, 1992b, 1994, 1995; Oteiza et al. 1993). When neurological tests were performed in adult mice exposed to aluminum during development (gestation and lactation exposure) (Golub et al. 1995), the pattern of neurological effects (alterations in grip strength and startle response) was similar to those observed in mice exposed to aluminum as adults (Golub et al. 1992b; Oteiza et al. 1993) and in mice exposed to aluminum during development and adulthood (Golub et al. 1995). Additionally, the LOAELs for these effects were similar in the three groups, thus suggesting that the developing fetus and children may have a similar sensitivity as adults to the neurotoxic effects of aluminum.

A series of studies in which rabbits received subcutaneous doses of aluminum lactate suggest that the neurotoxicity of aluminum may be age-dependent. Subcutaneous administration of aluminum lactate resulted in alterations in learning and memory in gestationally-exposed rabbits and adult rabbits. A biphasic effect (enhancement after low doses and attenuation after high doses) on learning and memory was observed in the *in utero*-exposed rabbits (treatment on gestational days 2 through 27) (Yokel 1985) and an attenuated effect was observed in the adults (Yokel 1987), but no effects were observed in neonatal or immature rabbits (Yokel 1987). The apparent age-dependence of the toxicity of aluminum in

this study may be a reflection of the different ages at evaluation rather than age of exposure (Golub et al. 1995).

Another aluminum effect which appears to be age-related is skeletal toxicity. Increased carpal joint width, suggestive of poor bone calcification, was observed in immature rabbits receiving 20 subcutaneous doses of aluminum lactate, but was not seen in neonatal or adult rabbits (Yokel 1987).

A study by Sanchez et al. (1997) found significant age-related effects on aluminum interactions with essential elements (e.g., calcium, magnesium, zinc). Decreases in concentration of some essential elements in a number of tissues were observed in young rats orally exposed to aluminum lactate (as compared to adults); the decreases included liver and spleen calcium levels, bone magnesium levels, and brain manganese levels.

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, 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 aluminum 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 aluminum 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 Aluminum

Aluminum can be measured in the blood, bone, urine, and feces (see Chapter 7 for description of available methods). Since aluminum is found naturally in a great number of foods, it is found in everyone. Unfortunately, exposure levels cannot be related to serum or urine levels very accurately, primarily because aluminum is very poorly absorbed by any route and its oral absorption in particular can be quite affected by other concurrent intakes. There is an indication that high exposure levels are reflected in urine levels, but this cannot be well quantified as much of the aluminum may be rapidly excreted. Aluminum can also be measured in the feces, but this cannot be used to estimate absorption.

3.8.2 Biomarkers Used to Characterize Effects Caused by Aluminum

There are no known simple, noninvasive tests which can be used as biomarkers of effects caused by aluminum. D’Haese et al. (1995) proposed the use of the DFO (deferoxamine) test to identify individuals with aluminum-related bone disease/aluminum overload. This test involves administering a challenge dose of the chelator deferoxamine to individuals with suspected aluminum-induced bone disease. However, iron supplementation may interfere with the test results (Huang et al. 2001).

For more information on biomarkers for renal and hepatic effects of chemicals see *ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage* (Agency for Toxic Substances and Disease Registry 1990) and for information on biomarkers for neurological effects see OTA (1990).

3.9 INTERACTIONS WITH OTHER CHEMICALS

It is well documented that citrate, a common component of food, markedly enhances the gastrointestinal absorption of concurrently ingested aluminum (Alfrey 1993; Day et al. 1991; DeVoto and Yokel 1994; Froment et al. 1989b; Molitoris et al. 1989; Priest et al. 1996; Provan and Yokel 1988; Slanina et al. 1986; Weberg and Berstad 1986; Yokel and McNamara 1988). The effect has been shown with a variety of aluminum compounds and several forms of citrate in both experimental and clinical studies. The combination of citrate and aluminum has been responsible for a number of deaths in uremic patients, and the clinical implications of the interaction has led some investigators to advise against concomitant exposure to aluminum and citrate in any form (e.g., antacids and orange juice), especially to patients with impaired renal function. As discussed in Sections 3.3.1.2 and 3.5.1, citrate complexes with aluminum to form a species that is particularly bioavailable in the near-neutral pH conditions of the intestines.

Unlike citrate, it is likely that the presence of silicic acid in food and drink will decrease the bioavailability of aluminum by providing a strong competitive binding site for it within the gut contents, thus making the metal less available for absorption (Priest 1993). This is supported by two studies that show a decrease in retention of aluminum in response to higher doses of silicon when human volunteers ingested both chemicals together (Bellia et al. 1996; Edwardson et al. 1993; Jugdaohsingh et al. 2000); Jugdaohsingh et al. (2000) only found this effect when oligometric silica was administered (monomeric silica did not affect aluminum absorption). As discussed in Section 3.5.1, there are some data that suggest that aluminum absorption can be enhanced by parathyroid hormone and vitamin D, but the data are inconclusive.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

The major population at risk for aluminum loading and toxicity consists of individuals with renal failure. In a study by Alfrey (1980), 82% of nondialyzed uremic patients and 100% of dialyzed uremic patients had an increased body burden of aluminum. The decreased renal function and loss of the ability to excrete aluminum, ingestion of aluminum compounds to lessen gastrointestinal absorption of phosphate, the aluminum present in the water used for dialysate, and the possible increase in gastrointestinal absorption of aluminum in uremic patients can result in elevated aluminum body burdens. The increased body burdens in uremic patients has been associated with dialysis encephalopathy (also referred to as dialysis dementia), skeletal toxicity (osteomalacia, bone pain, pathological fractures, and proximal myopathy), and hematopoietic toxicity (microcytic, hypochromic anemia). Preterm infants may also be particularly sensitive to the toxicity of aluminum due to reduced renal capacity (Tsou et al. 1991).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to aluminum. 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 aluminum. 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 aluminum:

Schonwald S. 2004. Aluminum. In: Dart RC, ed. Medical toxicology. 3rd ed. New York, NY: Lippincott, Williams, and Wilkins, 1387-1390.

Haddad, CM, Shannon MW, Winchester, JF. 1998. Clinical management of poisoning and drug overdose. 3rd ed. Philadelphia, PA: WB Saunders, 186.

Leikin JB, Paloucek FP. 2002. Leikin and Paloucek's poisoning and toxicology handbook. 3rd ed. Hudson, OH: Lexi-Comp, Inc., 214-217.

3.11.1 Reducing Peak Absorption Following Exposure

There are limited data on reducing aluminum absorption following exposure. There is good evidence that aluminum is absorbed by a pericellular energy-independent and sodium-dependent process (Provan and Yokel 1988). If this is correct, then treatments that block pericellular processes can be used to minimize or prevent intestinal uptake of aluminum. Ranitidine may also decrease aluminum absorption (Leikin and Paloucek 2002).

3.11.2 Reducing Body Burden

In persons with normal renal function, the body burden can be reduced simply by limiting exposure (Schonwald 2004). Avoidance of aluminum-containing products, such as aluminum-containing phosphate binding gels, dialysate, and parenteral solutions, is recommended for patients with renal failure. Avoidance of co-administration of aluminum compounds and citrate compounds is also advised. Administration of a chelator such as desferrioxamine (DFO) may also help reduce aluminum body burden. DFO is a chelating agent that competes with complexing ligands such as transferrin and citrate that might deliver aluminum to tissues or otherwise redistribute it within the body. For example, DFO treatment has been used to facilitate the removal of aluminum from bone and its entry into the blood where it can be removed by hemodialysis (Haddad et al. 1998). DFO is also used in dialyzed uremic patients for the treatment of neurological, hematopoietic, and skeletal toxicity. In rats, administration of DFO resulted in a large reduction in the half life of aluminum in the brain; 55 days in the DFO-treated rats versus 150 days in controls (Yokel et al. 2001b). It should be noted that the clinical usefulness of DFO is limited by a variety of toxic effects including hypotension, skin rashes, stimulation of fungal growth, and possibly cataract formation. There is some evidence that other chelators may also be effective in reducing aluminum body burden. 1,2-Dimethyl-3-hydroxypyrid-4-one was shown to enhance urinary aluminum excretion in aluminum-loaded rats (Gomez et al. 1999; Yokel et al. 1997). Another study showed that (4-methyl-6-trifluoromethyl-6-pyrimidin-2-il)-hydrazine was effective in decreasing the levels of aluminum in the brains of mice (Missel et al. 2005), although DFO was more effective in lowering the brain aluminum levels. Tiron (4,5-dihydroxy-1,3-benzene disulfonic acid di-sodium salt) administered during aluminum exposure to pregnant rats resulted in significant decreases in aluminum levels in the blood, brain, placenta, and fetus (Sharma and Mishra 2006). Another chelator tested in this study, 4-tricloromethyl-1-H-pyrimidin-2-one, was not effective. Administration of folic acid, melatonin, silicic acid, and beer (due to its silicon content) has been shown to decrease accumulated aluminum in tissues including bone, kidney, and brain in rats or mice (Abd-Elghaffar et al. 2005; Baydar et al. 2005; Gonzalez-Muñoz et al. 2007).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanism of action for aluminum toxicity is not fully understood; thus, there are no known ways of interfering with its mechanism of action. Some pathways of aluminum chloride toxicity include induced lipid peroxidation, altered enzyme activity, overexpression of hippocampal Aβ immunoreactivity, and biochemical parameters. These toxic effects were shown to be improved in rats or mice when

administered vitamin E, vitamin C, selenium, beer (due to its silicon content), centrophenoxine (an anti-aging drug), and the herbal medicines *Dipsacus asper Wall* extract and *Bacopa moniera* (Chinoy et al. 2004; El-Demerdash 2004; Gonzalez-Muñoz et al. 2007; Jyoti and Sharma 2006; Nedzvetsky et al. 2006; Nehru and Bhalla 2006; Nehru et al. 2007; Saba-El Rigal 2004; Zhang et al. 2003).

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 aluminum 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 aluminum.

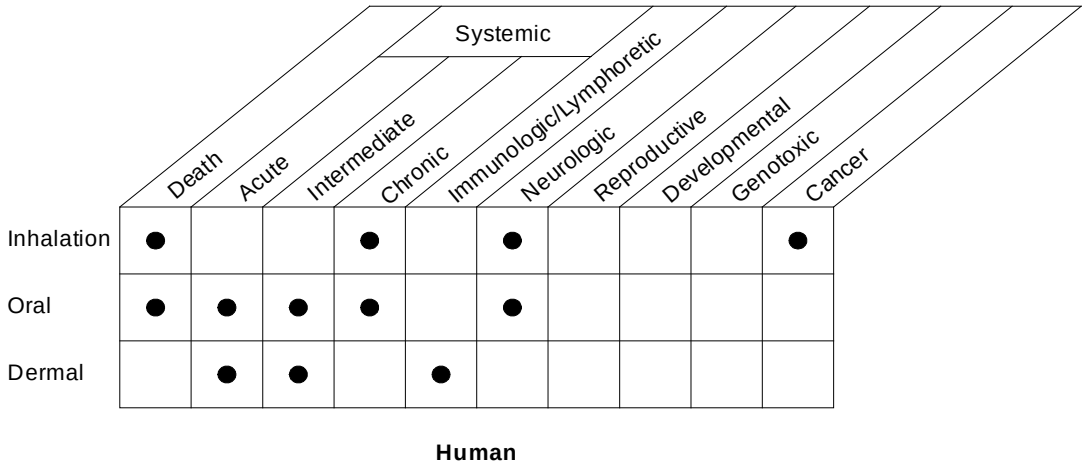
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean 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 Aluminum

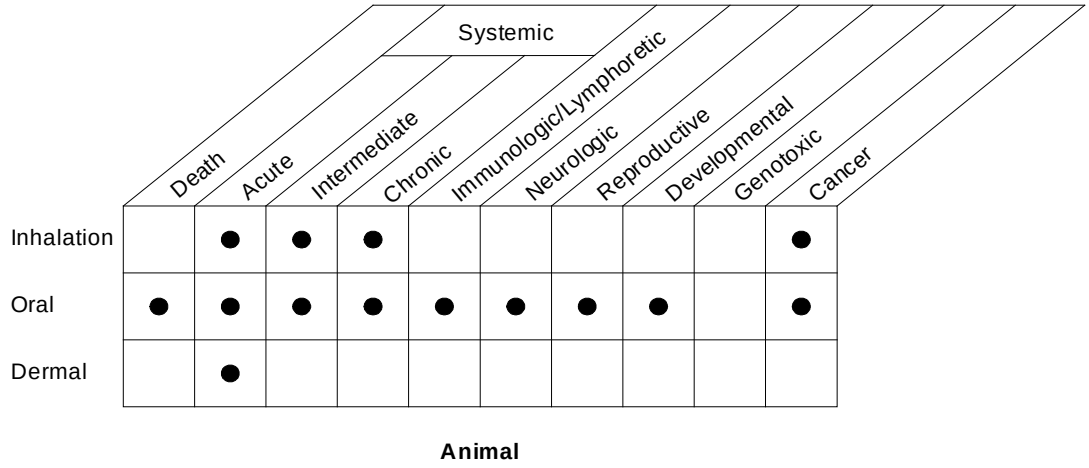
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to aluminum are summarized in Figure 3-4. The purpose of this figure is to illustrate the existing information concerning the health effects of aluminum. Each dot in the figure indicates that one or more 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.

Information on human health effects from inhaled aluminum is available from epidemiological studies and case studies of aluminum workers. This includes data on death, chronic effects, and cancer.

Figure 3-4. Existing Information on Health Effects of Aluminum



Human



Animal

● Existing Studies

Information on oral exposure is available only from specialized cases, such as people who consumed a grain fumigant to try to commit suicide, individuals consuming large doses of aluminum-containing antacids, and dialyzed and nondialyzed uremic patients consuming aluminum compounds prescribed as phosphate binding agents. Information on dermal effects in humans is available from patch tests.

In animals, information on effects from inhalation exposure is available for pure aluminum flakes, aluminum chlorhydrate antiperspirants, and a propylene glycol complex of aluminum chlorhydrate. Effects following oral exposure to several aluminum salts are available for adults and newborn animals. One acute dermal study is available.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. There are no studies that examined the acute toxicity of aluminum following inhalation, oral, or dermal exposure. A small number of animal studies have examined the acute toxicity of inhaled aluminum. The results of these inhalation studies suggest that the lung may be a sensitive target for toxicity (Drew et al. 1974; Thomson et al. 1986); the observed effects are similar to those that would occur with dust overload. The data are insufficient to determine if these effects are solely due to dust overload or to an interaction between aluminum and lung tissue; thus, an inhalation MRL was not derived. Additional inhalation studies are needed to evaluate whether the respiratory tract is a target of aluminum toxicity; these studies should also examine potential neurological effects, another sensitive target of aluminum toxicity. The acute systemic toxicity of orally administered aluminum has not been well investigated; most of the available data examined the developmental toxicity of aluminum (Bernuzzi et al. 1986, 1989a; Cranmer et al. 1986; Domingo et al. 1989; Gomez et al. 1991; McCormack et al. 1979; Misawa and Shigeta 1992; Paternain et al. 1988) or aluminum lethality (Llobet et al. 1987; Ondreicka et al. 1966). Two studies examining potential effects other than developmental toxicity only examined a small number of end points (Garbossa et al. 1996; Ondreicka et al. 1966). The Ondreicka et al. (1966) study examined potential body weight effects and Garbossa et al. (1996) examined hematological indices; neither study examined for potential neurological effects, which has been shown to be the most sensitive end point following intermediate- or chronic-duration exposure. Oral exposure studies that examined a wide range of potential effects, including neurotoxicity, are needed to identify the critical target of toxicity and establish dose-response relationships. There are limited data on the dermal toxicity of aluminum. A mouse study conducted by Lansdown (1973) found skin damage following application of a number of aluminum compounds. Because aluminum is found in a number of topical

products, additional dermal exposure studies would be useful to fully assess the potential toxicity of aluminum following dermal exposure.

Intermediate-Duration Exposure. There is a limited amount of intermediate-duration human data on the toxicity of aluminum. Neurological and skeletal effects have been observed in uremic patients (Alfrey 1987; King et al. 1981; Mayor et al. 1985; Wills and Savory 1989); however, it is not likely that individuals with normal renal function would experience these effects. Intermediate-duration inhalation studies in animals identified the lung as a sensitive target of toxicity (Drew et al. 1974; Steinhagen et al. 1978; Stone et al. 1979). It is not known if these effects, particularly the granulomatous lesions, are a response to dust overload or an interaction of aluminum with lung tissue; thus, an intermediate-duration inhalation MRL was not derived for aluminum. Additional inhalation studies are needed to evaluate the mechanisms of lung toxicity to determine whether the effects are due to dust overload or aluminum; inhalation studies examining a wide-range of potential end points, including the nervous system, would be useful for identifying the most sensitive effect of inhaled aluminum. A fair number of studies have examined the toxicity of aluminum following intermediate-duration oral exposure. Although most of the studies focused on the neurotoxicity and neurodevelopmental toxicity of aluminum, the available studies have examined potential systemic (Dixon et al. 1979; Domingo et al. 1987b; Farina et al. 2005; Garbossa et al. 1996, 1998; Gomez et al. 1986; Katz et al. 1984; Ondreicka et al. 1966; Oteiza et al. 1993; Pettersen et al. 1990; Vittori et al. 1999), immunological (Golub et al. 1993; Lauricella et al. 2001; Yoshida et al. 1989), and reproductive (Dixon et al. 1979; Donald et al. 1989; Katz et al. 1984; Krasovskii et al. 1979; Ondreicka et al. 1966; Pettersen et al. 1990) end points. A series of studies conducted by Mahieu and associates (Mahieu et al. 1998, 2003, 2005, 2006) found small changes in sodium and phosphate excretion and urine concentrating ability (under conditions of water deprivation), but no changes in overall renal function (glomerular filtration rate or clearance), in rats administered aluminum hydroxide or aluminum lactate via intraperitoneal injection. Although several oral exposure studies did not find histological alterations in the kidneys, none of these studies examined renal function; the results of the Mahieu studies suggest the need for a study examining renal function following oral exposure to aluminum. The available intermediate-duration studies clearly identify the nervous system as the most sensitive target of aluminum toxicity (Colomina et al. 2005; Donald et al. 1989; Golub and Germann 2001; Golub et al. 1989, 1992a, 1992b, 1995; Oteiza et al. 1993). An intermediate-duration oral MRL was derived based on Golub and Germann (2001) and Colomina et al. (2005) co-principal studies; the critical effect was neurodevelopmental effects and delays in physical maturation. No studies have examined the dermal toxicity of aluminum; animal studies would provide useful information on

aluminum's potential to induce dermal effects following repeated exposure and whether it can cause systemic or neurological effects.

Chronic-Duration Exposure and Cancer. Aluminum has been implicated in causing neurological (Banks et al. 1988; Liss and Thornton 1986), musculoskeletal, (Alfrey 1987; King et al. 1981; Mayor et al. 1985; Wills and Savory 1989), and hematopoietic (Jeffery et al. 1996) effects in individuals with impaired renal function. Respiratory and neurological effects have been observed in workers exposed to finely ground aluminum and aluminum welding fumes. Impaired lung function has been observed in workers employed in various aluminum industries including potrooms, foundry, and welders (Abbate et al. 2003; Al-Masalkhi and Walton 1994; Bast-Pettersen et al. 1994; Bost and Newman 1993; Burge et al. 2000; Chan-Yeung et al. 1983; Hull and Abraham 2002; Jederlinic et al. 1990; Korogiannos et al. 1998; Miller et al. 1984b; Radon et al. 1999; Simonsson et al. 1985; Vandenplas et al. 1998). Other studies have provided some suggestive evidence that aluminum exposure can result in occupational asthma (Abramson et al. 1989; Akira 1995; Al-Masalkhi and Walton 1994; Burge et al. 2000; Vandenplas et al. 1998) or pulmonary fibrosis (De Vuyst et al. 1986; Edling 1961; Gaffuri et al. 1985; Jederlinic et al. 1990; Jephcott 1948; McLaughlin et al. 1962; Mitchell et al. 1961; Musk et al. 1980; Riddell 1948; Shaver 1948; Shaver and Riddell 1947; Ueda et al. 1958; Vallyathan et al. 1982). A common limitation of most of these occupational exposure studies is co-exposure to other compounds, such as silica, which can also damage the respiratory tract. Subtle neurological effects have been observed in workers exposed to aluminum dust in the form of McIntyre powder, aluminum dust and fumes in potrooms, and aluminum fumes during welding (Bast-Pettersen et al. 1994; Buchta et al. 2003, 2005; Dick et al. 1997; Hänninen et al. 1994; Hosovski et al. 1990; Iregren et al. 2001; Rifat et al. 1990; Riihimäki et al. 2000; Polizzi et al. 2001; Sim et al. 1997; Sjögren et al. 1990, 1996; White et al. 1992). Inhalation animal studies have focused on the pulmonary toxicity of aluminum (Pigott et al. 1981; Stone et al. 1979). Data were considered inadequate for derivation of a chronic-duration inhalation MRL. Additional inhalation studies are needed to identify the critical target of aluminum toxicity following inhalation exposure. Several studies have examined the systemic toxicity of aluminum following chronic oral exposure (Farina et al. 2005; Golub et al. 2000; Oneda et al. 1994; Roig et al. 2006; Schroeder and Mitchener 1975a, 1975b). These studies identified two potential targets of toxicity: the nervous system (Golub et al. 2000) and the hematopoeitic system (Farina et al. 2005). A chronic-duration oral MRL was derived based on the neurotoxicity observed in the Golub et al. (2000) study. A comparison between the dose-response relationship of neurotoxicity and the alterations in hematological parameters cannot be conducted because the Farina et al. (2005) study did not provide information on the level of aluminum in the base diet and both studies only utilized one aluminum-exposure group. Additional studies on the toxicity of aluminum

following chronic-duration exposure utilizing multiple dose levels would be useful in comparing the sensitivity of these two effects.

The available data do not indicate that aluminum is a potential carcinogen. It has not been shown to be carcinogenic in epidemiological studies in humans, nor in animal studies using inhalation, oral, and other exposure routes (Oneda et al. 1994; Ondreicka et al. 1966; Pigott et al. 1981; Schroeder and Mitchener 1975a, 1975b). Although these studies have limitations ranging from use of only one species to a single exposure level and limited histological examinations, the evidence strongly suggests that aluminum is not carcinogenic, indicating that additional carcinogenicity testing is not warranted at this time.

Genotoxicity. Several *in vitro* studies have found significant increases in the occurrence of micronuclei formation (Banasik et al. 2005; Migliore et al. 1999; Roy et al. 1990) and chromosome aberrations (Roy et al. 1990) in human lymphocytes; no human *in vivo* studies were identified. One study examined the *in vivo* genotoxicity of aluminum and found clastogenic changes in mice receiving an intraperitoneal injection of aluminum chloride (Manna and Das 1972). *In vitro* studies in mammalian and bacterial systems have not found mutagenic alterations (DiPaola and Casto 1979; Kada et al. 1980; Kanematsu et al. 1980; Marzin and Phi 1985; Nishioka 1975; Oberly et al. 1982; Olivier and Marzin 1987). Further genotoxicity studies, particularly *in vivo* exposures, would be useful for verifying the results of the Manna and Das (1972) study and for evaluating other potential end points of genotoxicity.

Reproductive Toxicity. No studies were located regarding reproductive effects of various forms of aluminum following inhalation, oral, or dermal exposure in humans. No histological alterations were observed in the reproductive tissues of rats or guinea pigs exposed to airborne aluminum chlorhydrate (Steinhagen et al. 1978); this study did not examine reproductive function. A number of oral-exposure studies examining reproductive end points in several animal species were identified. In general, the results of these studies suggest that aluminum is not associated with alterations in fertility (Dixon et al. 1979; Domingo et al. 1987c), mating success (Dixon et al. 1979; Ondreicka et al. 1966), or number of implantations, implantation losses, or litter size (Bernuzzi et al. 1989b; Domingo et al. 1987c, 1989; Golub et al. 1992a; Gomez et al. 1991; Misawa and Shigeta 1992). Further studies in this area do not appear to be necessary at this time.

Developmental Toxicity. No studies human studies examining the potential of aluminum to induce developmental effects in humans exposed to aluminum via inhalation, ingestion, or dermal contact were located. Developmental toxicity studies in animals have shown that oral gestational exposure to

aluminum induced skeletal variations such as delayed ossification in rats and mice under conditions that enhanced its uptake, particularly maternal intake of compounds that are highly bioavailable (e.g., aluminum citrate and nitrate), concurrent exposure to dietary constituents that contribute to increased absorption of aluminum (e.g., citrate), and/or bolus administration by gavage (Colomina et al. 1992; Gomez et al. 1991; Paternain et al. 1988). There is some evidence that oral developmental exposure to aluminum affected the immune system in young mice (Golub et al. 1993; Yoshida et al. 1989) and may delay physical maturation (Colomina et al. 2005). Neurobehavioral deficits have been observed in oral studies of weanling and young developing mice and rats exposed to aluminum by gestation, combined gestation and lactation, combined gestation and lactation followed by postweaning ingestion, or postweaning ingestion alone (Bernuzzi et al. 1986, 1989a, 1989b; Colomina et al. 2005; Donald et al. 1989; Golub and Germann 1998, 2001; Golub et al. 1987, 1992a, 1992b, 1994, 1995; Misawa and Shigeta 1992; Muller et al. 1990). The most frequently affected neurobehavioral effects in the exposed weanlings and young mice included increases in grip strength and landing foot splay and decreased thermal sensitivity. The effects most commonly found in mice exposed during development and tested as adults, or tested only as adults, included decreases in spontaneous motor activity, grip strength, and startle responsiveness, indicating that the pattern of neurobehavioral impairment in developing animals was different from adults.

Although the neurodevelopmental toxicity of aluminum is well-documented in animals, there are a number of data needs that preclude fully assessing the significance of the findings to human health (Golub and Domingo 1996). An important issue not adequately addressed in the existing studies is the potential for effects on more complex central nervous system functions, including learning and memory and sensory abilities. This type of animal testing would help determine the generality or specificity of aluminum neurodevelopmental toxicity and provide a better basis for its assessment in children. Additional information that is needed to more fully characterize the neurodevelopmental toxicity of aluminum includes data on whether effects are transient and reversible or whether they persist and cause permanent changes after exposures are terminated. Additionally, it would be informative to verify that the central nervous system is the critical developmental end point for aluminum by obtaining data on effects in noncentral nervous system organs known to be targets of aluminum toxicity in adults. Additional investigations of the skeletal component of the aluminum developmental toxicity syndrome are particularly needed because permanent effects on bone growth and strength could occur during periods of rapid mineralization not investigated in existing studies, such as early infancy and adolescence. New developmental toxicity studies should include a range of low oral doses that encompasses the

neurotoxicity NOAEL on which the intermediate-duration MRL is based, as well adequately characterized levels of aluminum in the base diet.

Additional information on compound bioavailability is also needed to better evaluate the developmental toxicity of aluminum. Because the developmental effects of orally administered aluminum appear to be dependent on the bioavailability of the form in which it is administered and the presence of dietary components that promote aluminum uptake, additional information on compound-related differences in aluminum uptake and effectiveness during pregnancy and postnatal development would help in assessing the relevance of the animal data to oral exposures in humans. For example, gavage administration of low doses of aluminum (38–77 mg Al/kg/day) as aluminum nitrate during gestation induced skeletal variations in rats (Paternain et al. 1988), indicating that the LOAEL for this effect is below the neurotoxicity NOAEL of 62 mg Al/kg/day for aluminum lactate in adult mice used to derive the MRL. The Paternain et al. (1988) LOAEL was not considered to be appropriate for MRL consideration due to concern that gavage does not realistically represent environmental aluminum intake (i.e., the LOAEL could be unnaturally low compared to dietary exposure because the skeletal effects could be related to phosphate binding caused by the bolus administration), and that nitrate represents an unusually bioavailable form of aluminum. Additional information on the bioavailability of different forms and amounts of aluminum exposure would help establish how well oral aluminum exposure regimens in animals (e.g., gavage as tested by Paternain et al. [1988]) approximate the oral bioavailability of aluminum from water or food in humans. This kind of information is needed to verify that the MRL is based on the most appropriate end point (i.e., neurotoxicity in adults rather than skeletal developmental toxicity), especially considering that no NOAEL has been identified for either skeletal developmental effects (Paternain et al. 1988) or neurodevelopmental effects (Donald et al. 1989; Golub and Germann 1998; Golub et al. 1992a, 1992b, 1994, 1995). Information on fetal uptake of aluminum administered in forms that have been already evaluated for prenatal developmental toxicity could indicate if the aluminum nitrate in the Paternain et al. (1988) study was effective because it is the most available to the fetus.

Immunotoxicity. A few reports indicate hypersensitivity in children and adults who have received aluminum-containing vaccines (Bergfors et al. 2005; Böhler-Sommeregger and Lindemayr 1986; Castelain et al. 1988; Veien et al. 1986). A human oral exposure study (Gräske et al. 2000) did not find alterations in the concentrations of immunoglobulin, interleukin, natural killer cells, or B- or T-lymphocyte populations in humans ingesting an antacid suspension for 6 weeks. No other human exposure studies examining immunological end points were located. Histological alterations have been observed in the lymphoreticular system, particularly granulomas in the hilar lymph nodes, of animals

exposed to airborne aluminum (Steinhagen et al. 1978; Thomson et al. 1986); these effects were probably secondary to the pulmonary effects rather than the result of direct damage to lymphoreticular tissue. The available inhalation studies did not conduct function tests. Histopathological examination of lymphoreticular tissues has shown no effect after oral administration of aluminum in rats (Dixon et al. 1979; Domingo et al. 1987b; Gomez et al. 1986; Katz et al. 1984; Ondreicka et al. 1966). Alteration in lymph node proliferation was observed in rats (Lauricella et al. 2001), and there is some evidence that developmental exposure to aluminum can affect the immune system in young mice (Golub et al. 1993; Yoshida et al. 1989). A battery of immune function tests following developmental and intermediate- or chronic-duration oral exposure may provide important information on characterizing the immunotoxic potential of aluminum, especially the age-sensitivity of effects. Aluminum-related dermal sensitivity appears to be very rare in humans; further studies do not appear to be necessary.

Neurotoxicity. There are suggestive data that the nervous system may be a sensitive target in humans. Subtle neurological effects, such as impaired performance on neurobehavioral tests and increases in objective symptoms, have been observed in workers exposed to aluminum dust and fumes, McIntyre powder, or welding fumes (Bast-Pettersen et al. 1994; Buchta et al. 2003, 2005; Dick et al. 1997; Hänninen et al. 1994; Hosovski et al. 1990; Iregren et al. 2001; Rifat et al. 1990; Riihimäki et al. 2000; Polizzi et al. 2001; Sim et al. 1997; Sjögren et al. 1990, 1996; White et al. 1992). Although a number of studies have examined the possible association between aluminum exposure and Alzheimer's disease (Flaten 1990; Forbes et al. 1992, 1994; Forster et al. 1995; Gauthier et al. 2000; Graves et al. 1998; Jacqmin et al. 1994; Jacqmin-Gadda et al. 1996; Martyn et al. 1989, 1997; McLachlan et al. 1996; Michel et al. 1990; Neri and Hewitt 1991; Polizzi et al. 2002; Rondeau et al. 2000, 2001; Salib and Hillier 1996; Sohn et al. 1996; Wettstein et al. 1991; Wood et al. 1988), a causal link between aluminum exposure and Alzheimer's disease has not been shown, and a number of factors may influence the risk of developing Alzheimer's disease. Nevertheless, continued monitoring of aluminum intake and incidence of neurological disease in humans is important to clarify aluminum's role in the Alzheimer's disease process.

The neurotoxicity of aluminum is well-documented in animals and has been manifested following oral or parenteral routes of exposure; however, there are very limited data on neurotoxicity following inhalation or dermal exposure. Inhalation studies have conducted histological examinations of the brain (Steinhagen et al. 1978; Stone et al. 1979), but have not conducted neurobehavioral function tests; no dermal exposure neurotoxicity studies were located. Studies are needed by these routes of exposure to establish whether it is a sensitive target following inhalation or dermal exposure. In rats and mice orally exposed to aluminum for intermediate or chronic durations, the neurotoxicity is manifested in neuromotor,

behavioral, and cognitive changes (Bilkei-Gorzo 1993; Commissaris et al. 1982; Connor et al. 1989; Donald et al. 1989; Golub and Germann 1998; Golub et al. 1987, 1989, 1992a, 1992b, 1995, 2000; Jing et al. 2004; Oteiza et al. 1993; Zhang et al. 2003). Additional low-dose studies in which levels of aluminum in the base diet are adequately characterized would be useful in establishing the NOAEL/LOAEL boundary. Oral exposure studies are also needed to evaluate the potential neurotoxicity of aluminum following acute-duration exposure and to confirm or refute the potential for aluminum to induce cognitive effects. Additionally, neurotoxicology studies measuring blood aluminum levels would be useful in determining the relevance of the animal data to humans. Research issues related to neurodevelopmental effects of aluminum are discussed in the Data Needs section on Developmental Toxicity.

Epidemiological and Human Dosimetry Studies. There are numerous reports of adverse health effects, primarily respiratory and neurological effects, in workers exposed to airborne aluminum (Abbate et al. 2003; Abramson et al. 1989; Akira 1995; Al-Masalkhi and Walton 1994; Bast-Pettersen et al. 1994; Bost and Newman 1993; Buchta et al. 2003, 2005; Burge et al. 2000; Chan-Yeung et al. 1983; De Vuyst et al. 1986; Dick et al. 1997; Edling 1961; Gaffuri et al. 1985; Hänninen et al. 1994; Hosovski et al. 1990; Hull and Abraham 2002; Iregren et al. 2001; Jederlinic et al. 1990; Jephcott 1948; Korogiannos et al. 1998; McLaughlin et al. 1962; Miller et al. 1984b; Mitchell et al. 1961; Musk et al. 1980; Polizzi et al. 2001; Radon et al. 1999; Riddell 1948; Rifat et al. 1990; Riihimäki et al. 2000; Shaver 1948; Shaver and Riddell 1947; Sim et al. 1997; Simonsson et al. 1985; Sjögren et al. 1990, 1996; Ueda et al. 1958; Vallyathan et al. 1982; Vandenplas et al. 1998; White et al. 1992). However, a common limitation of the occupational exposure data is that the exposure levels have not been well quantified and workers were often exposed to a number of other chemicals. A number of studies have examined the possible association between Alzheimer's disease and aluminum exposure in air (Polizzi et al. 2002; Salib and Hillier 1996) and drinking water (Flaten 1990; Forbes et al. 1992, 1994; Forster et al. 1995; Gauthier et al. 2000; Graves et al. 1998; Jacqmin et al. 1994; Jacqmin-Gadda et al. 1996; Martyn et al. 1989, 1997; McLachlan et al. 1996; Michel et al. 1990; Neri and Hewitt 1991; Rondeau et al. 2000, 2001; Sohn et al. 1996; Wettstein et al. 1991; Wood et al. 1988). These studies have reported conflicting results and have been criticized for poor subject selection, exposure assessment, and diagnosis of Alzheimer's disease. Further studies are important in helping to determine whether there is a cause-and-effect relationship between chronic aluminum exposure and the development of Alzheimer's disease. There are also a number of studies reporting bone damage and neurological effects in individuals with chronic renal failure (Alfrey 1993); however, kidney failure increases the risk for developing aluminum-related effects; thus, these data have limited usefulness in predicting health effects in the general population. Aluminum is found in a number of over-the-counter products, such as antacids; however, controlled studies

examining potential adverse effects in healthy individuals ingesting these products long-term have not been located and are needed.

Biomarkers of Exposure and Effect. Reliable methods for determining tissue and plasma levels of aluminum exist. The mechanism of action for aluminum toxicity is not known, hence it is not known whether biomarkers of effect exist or not.

Exposure. Although aluminum can be measured in blood (Alfrey et al. 1980; Arieff et al. 1979; Ganrot 1986), urine (Gorsky et al. 1979; Greger and Baier 1983; Kaehny et al. 1977; Mussi et al. 1984; Recker et al. 1977; Sjögren et al. 1985, 1988), and feces (Greger and Baier 1983), the aluminum body burden rapidly declines upon termination of exposure (except in the lungs, where retention takes place). Also, tissue levels do not correlate with exposure except that higher-than-average tissues levels of aluminum correlate with increased exposure. There is some suggestive evidence that erythrocyte aluminum levels may be reflective of long-term aluminum exposure (Priest 2004), but a possible relationship between ingestion and erythrocyte aluminum levels has not been established. Additional studies examining the possible relationship between urine, blood, or other tissue levels and aluminum exposure would be useful in establishing biomarkers of exposure.

Effect. No biomarkers of effect have been identified for aluminum. The mechanisms of action for aluminum toxicity is not known and there is considerable research in identifying the mechanism(s) of neurotoxicity (Cucarella et al. 1998; Deloncle et al. 1999; El-Demerdash 2004; Fraga et al. 1990; Hermenegildo et al. 1999; Kaizer et al. 2005; Kohila et al. 2004; Llansola et al. 1999; Montoliu and Felipo 2001; Nehru and Anand 2005; Rodella et al. 2004; Yokel et al. 2002; Zatta et al. 2002; Zheng 2001). Studies on the mechanism of action of aluminum may lead to biochemical tests that can be used in the early identification of aluminum toxicity.

Absorption, Distribution, Metabolism, and Excretion. Available data indicate that the gastrointestinal absorption of aluminum is often in the range of 0.1–0.6% in humans, although absorption of poorly available aluminum compounds such as aluminum hydroxide can be <0.01% (Day et al. 1991; DeVoto and Yokel 1994; Ganrot 1986; Greger and Baier 1983; Hohl et al. 1994; Jones and Bennett 1986; Nieboer et al. 1995; Priest 1993; Priest et al. 1998; Stauber et al. 1999; Steinhausen et al. 2004). Bioavailability of aluminum varies mainly due to differences in the form of the ingested compound and dietary constituents (i.e., the kinds and amounts of ligands in the stomach with which absorbable aluminum species can be formed). The apparent 10-fold range in aluminum absorption has not been

systematically documented using a variety of aluminum compounds and the most suitable analytical techniques. Radiochemical studies are desired because they facilitate accurate quantitation of the small percentages of ingested aluminum that are absorbed and provide a means to distinguish endogenous aluminum from administered aluminum and from aluminum contamination of samples (Priest 1993). Additional toxicokinetic studies using ^{26}Al would help to better characterize the likely range of aluminum bioavailability. This kind of information is needed because an amount of aluminum ingested does not provide an estimate of exposure without information on bioavailability of the form in which it is ingested. In particular, if bioavailability in a particular human scenario differs from bioavailability in the MRL study, or is not known, extrapolation may not be appropriate because exposure depends on bioavailability as well as intake. Information on the bioavailability of aluminum in rodent laboratory feed would also be useful for extrapolating from animal to human exposure. Studies investigating the extent of absorption of aluminum into the placenta and fetal blood circulation would be useful in assessing the relevance of developmental effects in animals to human exposures.

There are limited data on the distribution of aluminum following inhalation or dermal exposure, although it is likely that the distribution would be similar to distribution following oral exposure. Ingested aluminum is not equally distributed throughout the body; higher levels are found in the bone, spleen, liver, and kidney (Greger and Donnaubauer 1986; Greger and Sutherland 1997; Zafar et al. 1997). In the blood, aluminum is primarily found in the plasma bound to transferrin (Ganrot 1986; Harris and Messori 2002; Martin 1986). Metabolism of the element does not occur (Ganrot 1986). Absorbed aluminum is primarily excreted in the urine with a small amount of absorbed aluminum excreted in the feces (Gorsky et al. 1979; Greger and Baier 1983; Kaehny et al. 1977; Recker et al. 1977; Sjögren et al. 1985, 1988). A main deficiency is whether aluminum can cross into the brains of healthy humans in sufficient amounts to cause neurological diseases. Further animal experiments, possibly using ^{26}Al as a tracer, would be useful in determining which, if any, levels and routes of exposure may lead to increased aluminum uptake in the brain.

Comparative Toxicokinetics. The animal data indicate that the nervous system is a sensitive target of toxicity for aluminum following oral exposure, as summarized in the Data Needs sections on Neurotoxicity and Developmental Toxicity. Human data also suggest that the nervous system is a sensitive target; a number of neurological effects have been observed in aluminum workers (Bast-Pettersen et al. 1994; Buchta et al. 2003, 2005; Dick et al. 1997; Hänninen et al. 1994; Hosovski et al. 1990; Iregren et al. 2001; Polizzi et al. 2001; Rifat et al. 1990; Riihimäki et al. 2000; Sim et al. 1997; Sjögren et al. 1990, 1996; White et al. 1992). The toxicokinetic properties of aluminum have been

studied in human and animals. The results of these studies suggest that the absorption, distribution, and excretion properties of aluminum are similar across species. There are very few comparative studies examining the toxicokinetic properties of different aluminum compounds; these studies would be useful in extrapolating toxicity data across species.

Methods for Reducing Toxic Effects. The mechanisms of absorption of aluminum have not been established. Studies that elucidated these mechanisms would be useful for establishing methods or treatments for reducing absorption and distribution of aluminum to sensitive targets. The chelating agent DFO has been used to reduce the aluminum body burden (Haddad et al. 1998; Yokel et al. 2001b); however, the clinical usefulness of DFO is limited by a variety of toxic effects. Other chelators such as 1,2-dimethyl-3-hydroxypyrid-4-one and (4-methyl-6-trifluoromethyl-6-pyrimidin-2-il)-hydrazine have also been shown to reduce the aluminum body burden (Gomez et al. 1999; Missel et al. 2005;Yokel et al. 1997). Studies that identify other methods for reducing aluminum body burden would be useful. The mechanism of toxicity has not been established for most of the toxic end points. Additional information on the mechanisms of toxicity would be useful for developing methods for reducing the toxicity of aluminum.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

The available data suggest that the targets of aluminum toxicity in children would be similar to those in adults. However, there is conflicting evidence on whether the threshold of toxicity, particularly neurotoxicity, would be lower in children. Multiple species studies using a relevant route of exposure, such as ingestion, and examining a wide range of effects in immature, mature, and older animals would be useful in assessing the children's susceptibility to the toxicity of aluminum. Additionally, there are no studies on the influence of immature renal function on aluminum retention in the body and no studies on the long-term effects of aluminum exposure on skeletal maturation or neurotoxicity. There are some data suggesting age-related differences in the toxicokinetic properties of aluminum. A study in rats found higher levels of aluminum in the brain and bone of aged rats (aged 18 months) compared to young rats (aged 21 days) (Gomez et al. 1997a); similar findings were observed in the controls and aluminum-treated rats.

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

There are a large number of ongoing studies covering many aspects of aluminum toxicity. Studies supported by the federal government are listed in Table 3-5.

Table 3-5. Ongoing Studies on Aluminum

Investigator	Study Topic	Institution	Sponsor
Longnecker M	Use of aluminum in toenails as a biomarker of exposure		National Institute of Environmental Health Sciences
Yokel R	Aluminum bioavailability from foods	University of Kentucky	National Institute of Environmental Health Sciences
Bondy S	Aluminum/iron interactions in neurodegenerative disease	University of California Irvine	National Institute of Environmental Health Sciences
DeWitt DA	Mechanism of aluminum-induced neurodegeneration in Alzheimer's disease	Liberty University	National Institutes of Health
Swyt-Thomas CR	Role of aluminum in Alzheimer's disease		National Institutes of Health

Source: FEDRIP 2006

This page is intentionally blank.

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Aluminum is a naturally occurring element that appears in the second row of Group 13 (IIIA) of the periodic table (O'Neil et al. 2001). Table 4-1 lists common synonyms and other pertinent identification information for aluminum and selected aluminum compounds.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Aluminum is a silvery-white, malleable, and ductile metal. In moist air, a protective oxide coating of aluminum oxide is formed on its surface. In compounds, aluminum typically occurs in its +3 oxidation state (Lide 2005; O'Neil et al. 2001). Table 4-2 lists important physical and chemical properties of aluminum and selected aluminum compounds.

Table 4-1. Chemical Identity of Aluminum and Compounds[a]

Characteristic	Information		
Chemical name	Aluminum	Aluminum chloride	Aluminum chlorohydrate (anhydrous)
Synonym(s)	Aluminium[b]; alumina fibre; metana; aluminium bronze; aluminum dehydrated; aluminium flake; aluminum powder; aluminum-27; Noral aluminum; PAP-1	Aluminum trichloride; aluminum chloride (1:3); Pearsall	Aluminol ACH; aluminum chloride hydroxide oxide, basic; aluminum chloride oxide; aluminum oxychloride; PAC 250A; Astringen; Chlorhydrol; Locron
Chemical formula	Al	$AlCl_3$	Unspecified[d]
Chemical structure	Al	$Al^{3+}(Cl^-)_3$	Unspecified
Identification numbers:			
CAS registry	7429-90-5	7446-70-0	1327-41-9
EINECS	231-072-3	231-208-1	215-477-2
NIOSH RTECS	BD330000	BD0525000	No data
EPA hazardous waste code	No data	D003	No data
EPA Pesticide Chemical Code	000111	013901	No data
DOT/UN/NA/IMCO shipping	UN 1309; UN 1396; IMO 4.1; IMO 4.3; NA 9260	UN 1726; UN 2581; IMO 8.0	No data
HSDB	507	607	No data

Table 4-1. Chemical Identity of Aluminum and Compounds[a]

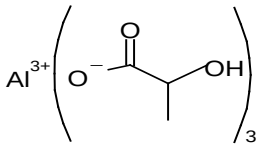
Characteristic	Information		
Chemical name	Aluminum hydroxide	Aluminum lactate	Aluminum nitrate
Synonym(s)	alpha-Alumina trihydrate; alumina hydrate; alumina hydrated; aluminum oxide trihydrate; aluminum oxide hydrate; aluminum (III) hydroxide; hydrated alumina; hydrated aluminum oxide; aluminum hydrate; aluminum trihydrate; hydrated alumina; Alcoa 331/C 30BF/C 330/C 333; Alugel; Alumigel; BACO AF260; British Aluminum AF260; Calmogastrin; Higilite H 31S/ H 32/ H 42; Hychol 705; Hydrafil; Hydral 705/710; Martinal A/A-S/F-A; Reheis F 1000	Aluminum, tris (2-hydroxypropanoato-O^1,O^2); propanoic acid, 2-hydroxy-, aluminum complex; aluminum tris (α-hydroxypropionate)	Aluminum trinitrate; aluminum (III) nitrate (1:3); nitric acid, aluminum salt; nitric acid, aluminum (3+) salt
Chemical formula	$Al(OH)_3$	$C_9H_{15}AlO_9$	$Al(NO_3)_3$
Chemical structure	$Al^{3+}\ (OH^-)_3$		$Al^{3+}\ (NO_3^-)_3$
Identification numbers:			
CAS registry	21645-51-2	18917-91-4	13473-90-0[f]
EINECS	244-492-7	242-670-9	236-751-8
NIOSH RTECS	BD0940000	No data	No data
EPA hazardous waste code	No data	No data	No data
EPA Pesticide Chemical Code	No data	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	UN 1438; IMO 5.1
HSDB	575	No data	574

Table 4-1. Chemical Identity of Aluminum and Compounds[a]

Characteristic	Information		
Chemical name	Aluminum oxide	Aluminum phosphate	Aluminum phosphide
Synonym(s)	Activated aluminum oxide; α-alumina; aluminum sesquioxide; aluminum trioxide; β-aluminum oxide; γ-alumina; Almite; Alon; Aloxite; Alumite; Alundum; Campalox; Dispal Alumina; Exolon XW 60; Faserton; Hypalox II; Ludox CL; Martoxin; Microgrit WCA; Poraminar	Aluminum ortho-phosphate; phosphoric acid; aluminum salt (1:1); Aluphos; Phosphaljel; Phosphalugel; aluminum monophosphate	Aluminum monophosphide; AL-Phos; AlP; Celphos; Delicia; Delicia Gastoxin; Detia; Phostoxin; Quickphos
Chemical formula	Al_2O_3	$AlPO_4$	AlP
Chemical structure	$(Al^{3+})_2\ (O^{2-})_3$	$Al^{3+}\ PO_4^{3-}$	$Al\equiv P$
Identification numbers:			
CAS registry	1344-28-1	7784-30-7	20859-73-8
EINECS	215-691-6	232-056-9	244-088-0
NIOSH RTECS	BD1200000	TB6450000	BD1400000[c]
EPA hazardous waste code	No data	No data	P006
EPA Pesticide Chemical Code	No data	No data	066501
DOT/UN/NA/IMCO shipping	No data	No data	UN 1397; UN 3048; IMO 4.3; IMO 6.1
HSDB	506	No data	6035

Table 4-1. Chemical Identity of Aluminum and Compounds[a]

Characteristic	Information		
Chemical name	Aluminum fluoride	Aluminum sulfate anhydrous	Aluminum carbonate
Synonym(s)	Aluminum trifluoride	Alum; aluminum sulfate (2:3); cake alum; filter alum; papermaker's alum; pearl alum; pickle alum; aluminum trisulfate; sulfuric acid, aluminum salt (3:2)	Carbonic acid, aluminium salt
Chemical formula	AlF_3	$Al_2(SO_4)_3$	$Al_2O_3 \bullet CO_2$; normal aluminum carbonate $Al_2(CO_3)_3$ is not known as an individual compound[e]
Chemical structure	$Al^{3+}\ (F^-)_3$	$(Al^{3+})_2\ (SO_4{}^{2-})_3$	No data
Identification numbers:			
CAS registry	7784-18-1	10043-01-3	53547-27-6
EINECS	232-051-1	233-135-0	238-440-2
NIOSH RTECS	BD0725000	BD1700000	No data
EPA hazardous waste code	No data	No data	No data
EPA Pesticide Chemical Code	No data	013906	No data
DOT/UN/NA/IMCO shipping	No data	NA 9078; NA 1760	No data
HSDB	600	5067	No data

Table 4-1. Chemical Identity of Aluminum and Compounds[a]

Characteristic	Information	
Chemical name	Aluminum potassium sulfate	Alchlor
Synonym(s)	Alum potassium; burnt alum; sulfuric acid, aluminum potassium salt (2:1:1); Tai-Ace K 150; Tai-Ace K 20	Aluminum chloride hydroxide propylene glycol complex
Chemical formula	$AlKO_8S_2$	Unspecified
Chemical structure	$K^+ Al^{3+} (SO_4^{2-})_2$	Unspecified
Identification numbers:		
CAS registry	10043-67-1	52231-93-3
EINECS	233-141-3	No data
NIOSH RTECS	No data	No data
EPA hazardous waste code	No data	No data
EPA pesticide chemical code	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data
HSDB	No data	No data

[a]All information obtained from ChemIDplus 2006, ChemFinder 2008, and HSDB 2008, except where noted.
[b]British spelling (Lewis 2001)
[c]NIOSH 1997
[d]Aluminum chlorohydrate: CAS No. 12042-91-0; Chemical formula: $Al_2ClH_5O_5.xH_2O$ (ChemIDplus 2006)
[e]Lewis 2001
[f]Aluminum nitrate nonahydrate (CAS No. 7784-27-2)

CAS = Chemical Abstracts Service; DOT/UN/NA/IMO = Department of Transportation/United Nations/North America/ Intergovernmental Maritime Dangerous Goods Code; EINECS = European Inventory of Existing Commercial Chemical Substances; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Physical and Chemical Properties of Aluminum and Compounds[a]

Property	Information		
Chemical name	Aluminum	Aluminum chloride	Aluminum chlorohydrate
Molecular weight	26.98	133.34	No data
Color	Silver white	White when pure, ordinarily gray or yellow to greenish	Glassy[b]
Physical state	Malleable, ductile metal; cubic crystal	White hexagonal deliquescent or moisture sensitive plates	Solid[b]
Melting point	660 °C	192.6 °C	No data
Boiling point	2,327 °C	182.7 °C at 752 mm Hg (sublimation temperature)	No data
Density (g/cm^3)	2.70	2.48	No data
Odor	Odorless	Strong odor of hydrogen chloride	No data
Odor threshold:			
Water	No data	0.5 mg/L (calculating on the aluminum ion)	No data
Air	No data	No data	No data
Solubility:			
Water	Insoluble in water	Reacts violently with water producing hydrochloric acid and heat	Dissolves in H_2O, forming slightly turbid colloidal solutions (up to 55% w/w)[b]
Other solvents	Soluble in HCl, H_2SO_4, hot water, and alkalies	Soluble in benzene, carbon tetrachloride, chloroform	No data
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
pH	No data	No data	~4.3 (15% aqueous solution)[b]
Vapor pressure	1 mm Hg at 1,284 °C	1 mm Hg at 100 °C	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability	Finely divided aluminum dust is easily ignited	Not combustible, but heating may produce irritants and toxic gases	No data
Explosive limits	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Aluminum and Compounds[a]

Property	Information		
Chemical name	Aluminum hydroxide	Aluminum lactate	Aluminum nitrate
Molecular weight	78.01	294.19[b]	213.00
Color	White	Colorless[c]	Colorless[d]
Physical state	Bulky, amorphous powder	Powder[c]	Rhombic crystals[d]
Melting point	300 °C	No data	73 °C[d]
Boiling point	No data	No data	Decomposes at 135 °C[d]
Density (g/cm^3)	2.42	No data	No data
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	Insoluble in water	Freely soluble in water[b]	Very soluble in water[d]
Other solvents	Soluble in alkaline or acid solutions	No data	Very soluble in alcohol; very slightly soluble in acetone; almost insoluble in ethyl acetate, pyridine[d]
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
pH	No data	No data	Aqueous solution is acidic[d]
Vapor pressure	No data	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability	No data	No data	No data
Explosive limits	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Aluminum and Compounds[a]

Property	Information		
Chemical name	Aluminum oxide	Aluminum phosphate	Aluminum phosphide
Molecular weight	101.94	121.95[b]	57.95
Color	White	White[b]	Dark gray or dark yellow
Physical state	Crystalline powder	Infusible powder[b]	Cubic crystals
Melting point	approximately 2,000 °C	>1,460 °C[b]	2,550 °C
Boiling point	2,980 °C	No data	No data
Density (g/cm^3)	4.0 at 20 °C	2.56[b]	2.85 at 15 °C
Odor	Odorless	No data	Garlic odor
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	Soluble in cold water, 0.000098 g/100 cc; insoluble in hot water	Practically insoluble in water[b]	Decomposes[b]
Other solvents	Very slightly soluble in acid, alkali	Practically insoluble in acetic acid; very slightly soluble in concentrated HCl and HNO_3 acids[b]	No data
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
pH	No data	No data	No data
Vapor pressure	1 mm Hg at 2,158 °C	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability	No data	No data	No data
Explosive limits	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Aluminum and Compounds[a]

Property	Information		
Chemical name	Aluminum fluoride	Aluminum sulfate	Aluminum carbonate
Molecular weight	83.98	342.14	No data
Color	White	White, lustrous	White[c]
Physical state	Hexagonal crystals	Crystals, pieces, granules or powder	Lumps or powder[c]
Melting point	1,291 °C	Decomposes at 770 °C	No data
Boiling point	Sublimes at 1,272 °C and 760 mm Hg	No data	No data
Density (g/cm^3)	3.10	1.61	No data
Odor	No data	Odorless	No data
Odor threshold:			No data
Water	No data	No data	
Air	No data	No data	
Solubility:			
Water	0.559 g/100 mL at 25 °C	Soluble in 1 part H_2O	Insoluble[c]
Other solvents	Sparingly soluble in acids and alkalies; insoluble in alcohol and acetone	Insoluble in ethanol	Dissolves in hot HCl or H_2SO_4 acid[c]
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
pH	No data	Aqueous solution (1 g/mL) not less than 2.9	No data
Vapor pressure	1 mm Hg at 1,238 °C	Essentially zero	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability	No data	No data	No data
Explosive limits	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Aluminum and Compounds[a]

Property	Information	
Chemical name	Aluminum potassium sulfate	Alchlor
Molecular weight	258.20	No data
Color	White	No data
Physical state	Powder	No data
Melting point	92 ºC[e]	No data
Boiling point	Loses 18 H_2O at 64.5 °C; anhydrous at 200 °C[e]	No data
Density (g/cm^3)	1.75[e]	No data
Odor	Odorless[e]	No data
Odor threshold:		
Water	No data	No data
Air	No data	No data
Solubility:		
Water	1 gram dissolves in about 20 mL of cold water, about 1 mL of boiling water	No data
Other solvents	Practically insoluble in alcohol	No data
Partition coefficients:		
Log K_{ow}	No data	No data
Log K_{oc}	No data	No data
pH	Aqueous solutions are acidic	No data
Vapor pressure	No data	No data
Henry's law constant	No data	No data
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	Noncombustible[e]	No data
Explosive limits	No data	No data

[a]All information obtained from HSDB 2008, except where noted.
[b]O'Neil et al. 2001
[c]Lewis 2001
[d]Aluminum nitrate nonahydrate (CAS No. 7784-27-2)
[e]$Al_2(SO_4)_3 \cdot K_2SO_4 \cdot 24H_2O$ (Lewis 2001)

This page is intentionally blank.

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

5.1 PRODUCTION

Aluminum is the most abundant metal and the third most abundant element in the earth's crust, comprising about 8.8% by weight (88 g/kg). It is rarely found free in nature and is found in most rocks, particularly igneous rocks, which contain aluminum as aluminosilicate minerals (Staley and Haupin 1992). Bauxite is a naturally occurring, heterogeneous material consisting of primarily one or more aluminum hydroxide minerals in addition to a variety of aluminosilicates, iron oxide, silica, titania, and other impurities in trace amounts. It is the most important raw material for the production of aluminum. More than 90% of the bauxite consumed in the United States in 2006 was converted to alumina (Al_2O_3) for the production of aluminum (USGS 2007d). Other raw materials sometimes used in the production of aluminum include cryolite, aluminum fluoride, fluorspar, corundum, and kaolin minerals (Browning 1969; Dinman 1983; IARC 1984; Lide 2005; O'Neil et al. 2001; USGS 2007a).

In 2006, primary aluminum was produced in 42 countries, with China, Russia, Canada, and the United States, in decreasing order of metal produced, accounting for 53% of the total world production of 31.9 million metric tons. In 2006, 5 U.S. companies, operating 13 primary aluminum smelters, produced an estimated 2.3 million metric tons of aluminum metal. Six smelters were temporarily idled. In the United States, about 3 million metric tons of aluminum were recovered from purchased scrap in 2006, with 64% of this coming from new (manufacturing) scrap and 36% from old scrap (discarded aluminum products) (USGS 2007b, 2007c).

In 2006, Australia, Brazil, and China accounted for approximately 58% of the total world bauxite product of 178 million metric tons. World production of alumina was estimated to be 69.2 million metric tons in 2006, with Australia and China as leading producers, accounting for 46% of the world's alumina production. U.S. production of alumina, which is nearly all derived from imported metallurgical-grade bauxite, was 4.61 million metric tons in 2006 (USGS 2007a, 2007d).

The principal method used in producing aluminum metal involves three major steps: refining of bauxite by the Bayer process to produce alumina, electrolytic reduction of alumina by the Hall-Héroult process to produce aluminum, and casting of aluminum into ingots (Browning 1969; Dinman 1983; IARC 1984).

In the first step (Bayer process), bauxite ($Al_2O_3 \cdot H_2O$) is digested at high temperature and pressure in a strong solution of caustic soda. The resulting hydrate is then crystallized and calcined in a kiln to produce

alumina (aluminum oxide). In the second step (Hall-Héroult process), alumina is reduced to aluminum metal by an electrolytic process involving carbon electrodes and cryolite flux ($3NaF \cdot AlF_3$). The electrolytic reduction process of transforming alumina into aluminum is carried out in electrolytic cells or pots. The areas where this occurs are called potrooms. Two types of electrolytic cells may be used, a prebake or a Söderberg cell. Their design differs, but the principle is the same. Alumina is dissolved in the cell in an electrolyte at a high temperature (950–970 °C) and a low voltage (4–6 volts). A high current is applied to the melted fraction. The alumina is reduced to aluminum at the cathode and the metal sinks to the bottom of the electrolytic cell. The aluminum is then removed by siphoning. The oxygen from the alumina migrates to the carbon anode of the cell, where it reacts to form carbon dioxide and carbon monoxide. The aluminum produced using the Hall-Héroult electrolytic reduction process may be refined to a maximum purity of 99.9%. In the third step (casting), aluminum is taken from the cell to holding furnaces from which it is poured into molds and cast into aluminum ingots (IARC 1984; Lewis 2001; Staley and Haupin 1992). Current U.S. manufacturers of aluminum are given in Table 5-1.

Aluminum is also an integral part of a variety of aluminum compounds used in industrial, domestic, consumer, and medicinal products. The methods of production for these compounds are described in the following section. Current U.S. manufacturers of selected aluminum compounds are given in Table 5-2.

Aluminum chloride can be produced by the reaction of purified gaseous chlorine with molten aluminum, as well as by the reaction of bauxite with coke and chlorine at about 875 °C (Lewis 2001).

Aluminum fluoride can be produced by heating ammonium hexafluoroaluminate to red heat in a stream of nitrogen. Other methods include the action of hydrogen fluoride gas on aluminum trihydrate; the reaction of hydrogen fluoride on a suspension of aluminum trihydrate followed by calcining the hydrate formed; fusion of cryolite or sodium fluoride with aluminum sulfate; or the reaction of fluosilicic acid on aluminum hydrate (HSDB 2007; Lewis 2001; O'Neil et al. 2001).

Aluminum hydroxide is produced from bauxite. The bauxite ore is first dissolved in a solution of sodium hydroxide, and then the aluminum hydroxide is precipitated from the sodium aluminate solution by neutralization (as with carbon dioxide) or by autoprecipitation (Bayer process) (Lewis 2001).

Aluminum nitrate as the nonahydrate is formed by dissolving aluminum or aluminum hydroxide in dilute nitric acid and allowing the resulting solution to crystallize (Grams 1992; Lewis 2001).

Table 5-1. U.S. Manufacturers of Aluminum[a]

Company	Location
Alcan Aluminum Corporation, Alcan Specialty Aluminas	Sebree, Kentucky
Alcoa, Inc., Alcoa Primary Metals	Alcoa, Tennessee
	Badin, North Carolina
	Goose Creek, South Carolina
	Massena, New York
	Wenatchee, Washington
Alcoa Intalco Works	Ferndale, Washington
Century Aluminum	Hawesville, Kentucky
	Ravenswood, West Virginia
Columbia Falls Aluminum Company	Columbia Falls, Montana
Eastalco Aluminum Company	Frederick, Maryland
Noranda Aluminum Inc.	New Madrid, Missouri
Northwest Aluminum Company	The Dalles, Oregon
Ormet Primary Aluminum Corporation	Hannibal, Ohio

[a]Derived from SRI 2007

Table 5-2. U.S. Producers of Selected Aluminum Compounds[a]

Company	Location	Annual capacity (10^3 metric tons)[b]
Alumina, calcined (Aluminum oxide)		
Alcoa, Inc., Alcoa World Alumnia	Point Comfort, Texas	
Almatis, Inc.	Bauxite, Arkansas	
Gramercy Alumina LLC	Gramercy, Louisiana	
Ormet Primary Aluminum Corporation	Burnside, Louisiana	
Sherwin Alumina Company	Corpus Christi, Texas	
Aluminas (specialty grades)		
Albemarle Corporation	Pasadena, Texas	
Almatis, Inc.	Bauxite, Arkansas	
AluChem, Inc.	Cincinnati, Ohio	
Axens North America	Savannah, Georgia	
BASF Catalysts LLC, Adsorbents and Catalysts	Port Allen, Louisiana	
	Vidalia, Louisiana	
Huber Engineered Materials	Fairmount, Georgia	
Porocel Corporation	Little Rock, Arkansas	
Saint-Gobain Ceramics & Plastics, Inc., Grains & Powders Division	Worcester, Massachusetts	
Sasol North America Inc., Ceralox Division	Westlake, Louisiana	
	Tucson, Arizona	
SPI Pharma Group	Lewes, Delaware	
Treibacher Schleifmittel North America, Inc.	Niagara Falls, New York	
UOP, LLC	Baton Rouge, Louisiana	
Washington Mills Electro Minerals Company	Niagara Falls, New York	
Aluminum ammonium sulfate		
Holland Company, Inc.	Adams, Massachusetts	
Aluminum chlorhydrate (aluminum chloride, basic)		
GEO Specialty Chemicals, Inc., Aluminum Products Group	Baltimore, Maryland	
	Bastrop, Louisiana	
	Counce, Tennessee	
The Gillette Company, North Chicago Manufacturing Center	North Chicago, Illinois	
Gulbrandsen Companies, Gulbrandsen Chemicals, Inc.	Orangeburg, South Carolina	
Gulbrandsen Companies, Gulbrandsen Technologies, Inc.	La Porte, Texas Phillipsburg, New Jersey	
Puerto Rico Alum Corporation	Penuelas, Puerto Rico	
Reheis, Inc.	Berkeley Heights, New Jersey	

Table 5-2. U.S. Producers of Selected Aluminum Compounds[a]

Company	Location	Annual capacity (10^3 metric tons)[b]
Summit Research Labs	Huguenot, New York	
	Phoenix, Arizona	
	Somerset, New Jersey	
Thatcher Company	Salt Lake City, Utah	
Aluminum chloride (anhydrous)[c]		
Gulbrandsen Companies, Gulbrandsen Chemicals, Inc.	Orangeburg, South Carolina	25
Toth Aluminum Corporation	Vacherie, Louisiana	10[d]
Vanchlor Company, Inc.	Lockport, New York	15
Aluminum chloride (hydrous)[e]		
Arkema, Inc., Specialty Chemicals Division	Axis, Alabama	2
Chattem, Chemicals, Inc.	Chattanooga, Tennessee	1
Delta Chemical Corporation	Ashtabula, Ohio	10
	Baltimore, Maryland	50
GEO Specialty Chemicals, Inc., Aluminum Products Group	Baltimore, Maryland	9
	Bastrop, Louisiana	6
The Gillette Company, North Chicago Manufacturing Center	North Chicago, Illinois	Not applicable
Gulbrandsen Companies, Gulbrandsen Technologies, Inc.	Phillipsburg, New Jersey	9
Holland Company, Inc.	Adams, Massachusetts	Not applicable
Puerto Rico Alum Corporation	Penuelas, Puerto Rico	1
Reheis, Inc.	Berkeley Heights, New Jersey	3
Southern Ionics, Inc.	Westlake, Louisiana	60
Summit Research Labs	Huguenot, New York	Not applicable
	Phoenix, Arizona	Not applicable
	Somerset, New Jersey	Not applicable
Aluminum chloride (aluminum trichloride)		
Mallinckrodt, Inc., Pharmaceuticals Group	St. Louis, Missouri	
Aluminum chlorohydrate (polyaluminum chloride)		
Delta Chemical Corporation	Ashtabula, Ohio	
	Baltimore, Maryland	
GEO Specialty Chemicals, Inc., Aluminum Products Group	Baltimore, Maryland Bastrop, Louisiana	
Gulbrandsen Companies, Gulbrandsen Chemicals, Inc.	Orangeburg, South Carolina	
Gulbrandsen Companies, Gulbrandsen Technologies, Inc.	La Porte, Texas Phillipsburg, New Jersey	
Holland Company, Inc.	Adams, Massachusetts	

Table 5-2. U.S. Producers of Selected Aluminum Compounds[a]

Company	Location	Annual capacity (10^3 metric tons)[b]
Kemiron Companies, Inc.	Kalama, Washington	
	Savannah, Georgia	
	Spokane, Washington	
Puerto Rico Alum Corporation	Penuelas, Puerto Rico	
Summit Research Labs	Huguenot, New York	
	Phoenix, Arizona	
	Somerset, New Jersey	
Aluminum fluoride		
Alcoa, Inc., Alcoa World Alumina	Point Comfort, Texas	60
CERAC, Inc.	Milwaukee, Wisconsin	Not applicable
ConocoPhillips	Billings, Montana	<1[f]
	Ponca City, Oklahoma	<1[f]
Ozark Fluorine Specialties, Inc.	Tulsa, Oklahoma	<2
Aluminum hydroxide		
Almatis, Inc.	Bauxite, Arkansas	
Franklin Industries, Inc., Franklin Industrial Minerals	Dalton, Georgia	
Gramercy Alumina LLC	Gramercy, Louisiana	
Huber Engineered Materials	Fairmount, Georgia	
	Kennesaw, Georgia	
	Quincy, Illinois	
IMERYS Pigments & Additives	Talking Rock, Georgia	
Sherwin Alumina Company	Corpus Christi, Texas	
Aluminum nitrate		
Blue Grass Chemical Specialties, LLC	New Albany, Indiana	
Mallinckrodt Baker, Inc.	Phillipsburg, New Jersey	
Mineral Research and Development	Harrisburg, North Carolina	
Thatcher Company	Salt Lake City, Utah	
Aluminum phosphate (aluminum orthophosphate)		
Innophos, Inc.	Chicago Heights, Illinois	
Johnson Matthey, Inc., Alfa Aesar	Ward Hill, Massachusetts	
PCS Phosphate Co., Inc.	Cincinnati, Ohio	
United-Erie, Inc.	Erie, Pennsylvania	
Aluminum phosphide[g]		
Bernardo Chemical, Ltd, Inc.		
Degesch America, Inc.		
Inventa Corporation		
Midland Fumigant, Inc.		
Pestcon Systems, Inc.		

Table 5-2. U.S. Producers of Selected Aluminum Compounds[a]

Company	Location	Annual capacity (10^3 metric tons)[b]
Aluminum potassium sulfate (Potash alum)		
Holland Company, Inc.	Adams, Massachusetts	
Aluminum sodium sulfate (Soda alum)		
General Chemical Corporation	East St. Louis, Illinois	
Aluminum sulfate (Alum, commercial)		
Alchem, Inc.	Rockwell, North Carolina	
Bay Chemical and Supply Company	Odem, Texas	
C & S Chemicals, Inc.	Austell, Georgia	
	Bartow, Florida	
	Joliet, Illinois	
	Randolph, Minnesota	
	Waycross, Georgia	
Delta Chemical Corporation	Ashtabula, Ohio	
	Baltimore, Maryland	
GAC Chemical Corporation	Searsport, Maine	
Gemini Industries, Inc.	Santa Ana, California	
General Chemical Corporation	Ashdown, Arkansas	
	Augusta, Georgia	
	Catawba, South Carolina	
	Cedar Springs, Georgia	
	Cleveland, Ohio	
	Covington, Virginia	
	Denver, Colorado	
	Detroit, Michigan	
	East Point, Georgia	
	East St. Louis, Illinois	
	Hopewell, Virginia	
	Indianapolis, Indiana	
	Jacksonville, Florida	
	Johnsonburg, Pennsylvania	
	Kalamazoo, Michigan	
	Macon, Georgia	
	Marrero, Louisiana	
	Menasha, Wisconsin	
	Middletown, Ohio	
	Pine Bluff, Arkansas	
	Pittsburg, California	
	Port St. Joe, Florida	
	Saukville, Wisconsin	
	Savannah, Georgia	

Table 5-2. U.S. Producers of Selected Aluminum Compounds[a]

Company	Location	Annual capacity (10^3 metric tons)[b]
	Springfield, Tennessee	
	Tacoma, Washington	
	Tampa, Florida	
	Toledo, Ohio	
	Vancouver, Washington	
	Wisconsin Rapids, Wisconsin	
GEO Specialty Chemicals, Inc., Aluminum Products Group	Bastrop, Louisiana	
	Chattanooga, Tennessee	
	Childersburg, Alabama	
	Counce, Tennessee	
	Demopolis, Alabama	
	De Ridder, Louisiana	
	Georgetown, South Carolina	
	Monticello, Mississippi	
	Pennington, Alabama	
	Plymouth, North Carolina	
	Savannah, Georgia	
W. R. Grace & Co., Grace Davison	Curtis Bay, Maryland	
	Lake Charles, Louisiana	
Holland Company, Inc.	Adams, Massachusetts	
Kemira Companies, Inc.	Antioch, California	
	Savannah, Georgia	
	Spokane, Washington	
Mallinckrodt Baker, Inc.	Paris, Kentucky	
Mallinckrodt, Inc., Pharmaceuticals Group	St. Louis, Missouri	
National Alum Corporation	Woodbine, Georgia	
Puerto Rico Alum Corporation	Penuelas, Puerto Rico	
Rhodia, Inc., Services & Specialties Division	Dominguez, California	
	Portland, Oregon	
Russ Chemical Company, Inc.	Odessa, Texas	
Southern Ionics, Inc.	Baton Rouge, Louisiana	
	Calhoun, Tennessee	
	Chickasaw, Alabama	
	Pasadena, Texas	
	Westlake, Louisiana	
	West Point, Mississippi	
Thatcher Company	Henderson, Nevada	
	Missoula, Montana	
	Salt Lake City, Utah	

Table 5-2. U.S. Producers of Selected Aluminum Compounds[a]

Company	Location	Annual capacity (10^3 metric tons)[b]
U.S. Aluminate Company, Inc.	Fairfield, Ohio	
	Michigan City, Indiana	
Sodium aluminosilicate		
Albemarle Corporation	Pasadena, Texas	
W.R. Grace & Co., Grace Division	Curtis Bay, Maryland	
	Lake Charles, Louisiana	
Huber Engineered Materials	Etowah, Tennessee	
	Havre de Grace, Maryland	
	Longview, Washington	
The PQ Corporation, Zeolyst and Catalyst Division	Kansas City, Kansas	
UOP, LLC	Chickasaw, Alabama	
Zeolyst International	Kansas City, Kansas	
Sodium aluminum phosphate		
ICL Performance Products L.P.	Carondelet, Missouri	
Innophos, Inc.	Chicago Heights, Illinois	
	Nashville, Tennessee	

[a]Derived from SRI 2007
[b]SRI Consulting estimates as of February 1, 2007; annual capacities were only reported for aluminum chloride (anhydrous), aluminum chloride (hydrous), and aluminum fluoride.
[d]Unit is currently idle.
[c]Capacities are on 100% $AlCl_3$ basis.
[e]Capacities, which are expressed as 100% $AlCl_3$, are nominal and easily expandable.
[f]Aluminum fluoride is reclaimed from refinery operations in small quantities.
[g]Manufacturers for aluminum phosphide were obtained from EPA 1998.

Aluminum oxide is produced during the recovery of bauxite, which is crushed, ground, and kiln dried, followed by leaching with sodium hydroxide, forming sodium aluminate, from which alumina trihydrate is precipitated and calcined (Bayer process). Aluminum sulfate obtained from coal mine waste waters can be reduced to aluminum oxide (HSDB 2007; Lewis 2001).

Aluminum phosphide can be manufactured in a high degree of purity, by heating aluminum and phosphorus. It can also be prepared from red phosphorus and aluminum powder, or from aluminum and zinc phosphide (HSDB 2007; O'Neil et al. 2001).

Aluminum sulfate is manufactured by reacting freshly precipitated pure aluminum hydroxide, bauxite, or kaolin, with an appropriate quantity of sulfuric acid. The resulting solution is evaporated and allowed to crystallize. Aluminum sulfate can also be produced by the treatment of pure kaolin or aluminum hydroxide or bauxite with sulfuric acid. The insoluble silic acid is removed by filtration and the sulfate is obtained by crystallization. It can be prepared similarly from waste coal mining shale and sulfuric acid (HSDB 2007; Lewis 2001).

Table 5-3 lists the facilities in each state that manufacture or process aluminum (fume or dust), the intended use, and the range of maximum amounts of aluminum that are stored on site. Table 5-4 lists the facilities in each state that manufacture or process aluminum oxide (fibrous form), the intended use, and the range of maximum amounts of aluminum oxide that are stored on site. The data listed in Tables 5-3 and 5-4 are derived from the Toxics Release Inventory (TRI05 2007). Only certain types of facilities were required to report (EPA 1995). Therefore, this is not an exhaustive list.

5.2 IMPORT/EXPORT

In 2006, nearly all of the 12.3 million metric tons of bauxite used in the United States was imported. Domestic mines have supplied <1% of the U.S. requirements for bauxite for many years. Import sources for bauxite (2002–2005) are Jamaica (31%), Guinea (30%), Brazil (17%), Guyana (12%), and other (10%). Import sources for alumina (2002–2005) are Australia (19%), Suriname (29%), Jamaica (9%), and other (12%). More than 90% of the bauxite consumed in the United States in 2006 was converted to alumina (USGS 2007a, 2007d).

Table 5-3. Facilities that Produce, Process, or Use Aluminum (Fume or Dust)

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	1	10,000	99,999	12
AL	37	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
AR	39	0	499,999,999	1, 3, 4, 5, 6, 7, 8, 11, 12, 13, 14
AZ	17	0	9,999,999	1, 3, 4, 5, 6, 7, 8, 11, 12, 13
CA	71	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	11	1,000	999,999	1, 2, 4, 5, 8, 11, 12
CT	20	0	9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
DE	4	1,000	9,999	2, 3, 4, 6, 7, 8, 11
FL	15	0	999,999	1, 5, 7, 8, 9, 11, 12
GA	21	0	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
IA	41	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
ID	7	10,000	999,999	1, 3, 4, 5, 7, 12, 13
IL	93	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	113	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	25	0	9,999,999	1, 2, 3, 5, 7, 8, 9, 10, 11, 12
KY	63	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
LA	16	0	9,999,999	1, 5, 6, 7, 8, 10, 11, 12, 13
MA	10	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11
MD	13	1,000	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9
ME	5	100	99,999	1, 3, 4, 5, 8, 9, 12
MI	80	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	28	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
MO	49	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MS	16	0	9,999,999	1, 3, 5, 7, 8, 10, 11, 12
NC	39	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ND	2	1,000	9,999	1, 5, 8
NE	5	1,000	99,999	1, 5, 6, 7, 8, 11, 12
NH	3	100	499,999,999	8
NJ	52	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13
NV	11	100	499,999,999	1, 2, 3, 5, 7, 8, 9, 10, 12, 13
NY	36	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12
OH	120	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	26	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
OR	29	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
PA	105	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PR	6	100	99,999	4, 8, 12
RI	3	1,000	999,999	7, 8, 9
SC	29	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12
TN	60	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13

Table 5-3. Facilities that Produce, Process, or Use Aluminum (Fume or Dust)

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
TX	64	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	18	0	9,999,999	1, 4, 5, 7, 8, 11, 12, 13
VA	27	0	999,999	1, 2, 3, 5, 7, 8, 11, 12
VT	3	0	999,999	8, 11, 12
WA	20	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13
WI	49	0	499,999,999	1, 2, 3, 5, 6, 7, 8, 9, 11, 12, 13, 14
WV	17	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12
WY	1	1,000	9,999	7

[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

Source: TRI05 2007 (Data are from 2005)

Table 5-4. Facilities that Produce, Process, or Use Aluminum Oxide (Fibrous Forms)

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	10,000	999,999	10
AL	56	1,000	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13
AR	41	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
AZ	16	1,000	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13
CA	96	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
CO	13	100	9,999,999	2, 5, 7, 8, 10, 11, 12, 13
CT	35	0	99,999,999	2, 3, 4, 7, 8, 10, 11, 12
DE	5	10,000	9,999,999	6, 7, 8, 10
FL	24	1,000	9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
GA	59	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
HI	3	10,000	999,999	10, 12
IA	21	100	49,999,999	1, 2, 3, 4, 5, 7, 8, 11, 12
IL	89	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	89	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
KS	25	100	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12
KY	55	100	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
LA	47	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MA	38	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MD	22	1,000	499,999,999	1, 2, 3, 4, 5, 6, 7, 10, 11, 12, 13
ME	7	1,000	999,999	6, 7, 8, 11, 12
MI	67	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MN	27	100	99,999,999	1, 2, 3, 5, 6, 7, 8, 10, 11, 12
MO	56	100	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MS	22	1,000	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
MT	11	0	499,999,999	2, 3, 6, 10, 11, 12
NC	50	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
ND	4	1,000	9,999,999	7, 10
NE	10	1,000	999,999	2, 4, 8, 10, 11, 12, 13
NH	12	1,000	499,999,999	1, 2, 3, 4, 7, 8, 9, 11, 12
NJ	45	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
NM	6	1,000	999,999	7, 8, 10, 11, 12
NV	3	100	999,999	1, 5, 6, 8, 9, 10
NY	78	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
OH	145	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
OK	41	1,000	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13
OR	14	100	99,999,999	2, 3, 4, 6, 8, 10, 11, 12
PA	115	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
PR	9	100	9,999,999	2, 3, 7, 8, 10, 11, 12

Table 5-4. Facilities that Produce, Process, or Use Aluminum Oxide (Fibrous Forms)

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
RI	2	10,000	99,999	2, 3, 7
SC	42	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12
SD	4	1,000	99,999	5, 8, 11
TN	70	100	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
TX	103	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
UT	19	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13
VA	30	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
VI	1	1,000,000	9,999,999	10
VT	6	1,000	99,999	8, 11, 12
WA	38	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
WI	43	100	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
WV	34	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
WY	5	10,000	999,999	6, 10, 11

[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

Source: TRI05 2007 (Data are from 2005)

5.3 USE

In 2006, transportation accounted for an estimated 40% of domestic consumption of aluminum, predominantly as automotive applications, with the remainder used in packaging, 28%; building, 13%; consumer durables, 7%; electrical, 5%; and other, 7% (USGS 2007c).

Aluminum chloride, anhydrous form, is used as an acid catalyst (especially in Friedel-Crafts-type reactions), as a chemical intermediate for other aluminum compounds, in the cracking of petroleum, in the manufacture of rubbers and lubricants, and as an antiperspirant. The hexahydrate form is used in preserving wood, disinfecting stables and slaughterhouses, in deodorants and antiperspirants, in cosmetics as a topical astringent, in refining crude oil, dyeing fabrics, and manufacturing parchment paper (O'Neil et al. 2001).

Aluminum chlorohydrate is an ingredient in commercial antiperspirant and deodorant preparations and is also used for water purification and treatment of sewage and plant effluent (Lewis 2001)

Aluminum hydroxide (alumina trihydrate) is used as an adsorbent, emulsifier, ion-exchanger, mordant in dyeing, and filtering medium. It is also used in the manufacturing of glass, paper, ceramics and pottery, printing inks, lubricating compositions, detergents, in the waterproofing of fabrics, in antiperspirants, dentifrices, and as a vaccine adjuvant (Baylor et al. 2002; Lewis 2001; O'Neil et al. 2001). Aluminum hydroxide is used as a flame retardant in the interiors of automobiles, commercial upholstered furniture, draperies, wall coverings, and carpets (Subcommittee on Flame-Retardant Chemicals 2000). Aluminum hydroxide is used as an antacid (O'Neil et al. 2001). Finely divided (0.1–0.6 microns) aluminum hydroxide is used for rubber reinforcing agent, paper coating, filler, and cosmetics (Lewis 2001). Aluminum hydroxide is also used pharmaceutically, as an antihyperphosphatemic, to lower the plasma phosphorus levels of patients with renal failure (O'Neil et al. 2001).

Aluminum nitrate is used in textiles (mordant), leather tanning, the manufacturing of incandescent filaments, catalysts in petroleum refining, nucleonics, anticorrosion agent, nitrating agent, and antiperspirants (Lewis 2001; O'Neil et al. 2001).

In 2006, 96% of the bauxite consumed in the United States was refined to alumina (aluminum oxide), with the remaining 4% consumed in nonmetallurgical uses, such as abrasives, chemicals, and refactories. Of the total alumina used in the United States in 2006, approximately 87% was used for primary

aluminum smelters and the remainder was used for nonmetallurgical uses, including abrasives, chemicals, refactories, and in specialty industries (USGS 2007a, 2007d). Other uses of aluminum oxide are in the manufacture of ceramics, electrical insulators, catalyst and catalyst supports, paper, spark plugs, crucibles and laboratory works, adsorbent for gases and water vapors, chromatographic analysis, fluxes, light bulbs, artificial gems, heat resistant fibers, food additive (dispersing agent), and in hollow-fiber membrane units used in water desalination, industrial ultrafiltration, and hemodialysis (HSDB 2007; Lewis 2001). Another application of aluminum oxide, which may have wide occupational use in the future, is as a dosimeter for measuring personnel radiation exposure (McKeever et al. 1995; Radiation Safety Guide 1999; Radiation Safety Newsletter 1998).

Aluminum phosphate is used in ceramics, dental cements, cosmetics, paints and varnishes, pharmaceuticals (antacid), and in paper and pulp industries (Lewis 2001; O'Neil et al. 2001). It is also used as a vaccine adjuvant (Baylor et al. 2002; Malakoff 2000). Aluminum phosphate, as basic sodium aluminum phosphate (SALP), is used as an emulsifying agent in pasteurized processed cheese, cheese food, and cheese spread. Acidic SALP is used as a leavening agent in cereal foods and related products, such as self-rising flour, prepared cake mixes, pancakes, waffles, and refrigerated or frozen dough or batter products (Chung 1992; Saiyed and Yokel 2005).

Aluminum phosphide is a fumigant used primarily for indoor fumigation of raw agricultural commodities, animal feeds, processed food commodities, and non-food commodities in sealed containers or structures to control insects, and for outdoor fumigation of burrows to control rodents and moles in nondomestic areas, noncropland, and agricultural areas. Aluminum phosphide reacts with the moisture in the atmosphere to produce phosphine gas, which is the substance that is active as a pesticide. Based on available pesticide survey usage information for 1987–1996, the estimated annual usage of aluminum phosphide is about 1.6 million pounds active ingredient. Major uses of aluminum phosphide include fumigation of wheat, peanuts, and stored corn. It was noted that usage estimates for aluminum phosphide are not precise due to scarcity of usage data sources for postharvest agriculture and non-agriculture uses/sites. All aluminum phosphide containing products have been classified as restricted use (EPA 1998). According to the National Pesticide Information Retrieval System, there are five active registrants for aluminum phosphide (NPIRS 2008).

Aluminum sulfate (alum) is used in leather tanning, sizing paper, as a mordent in dyeing, water purification, fireproofing and waterproofing of cloth, clarifying oils and fats, treating sewage, waterproofing concrete, deodorizing and decolorizing of petroleum, antiperspirants, and agricultural

pesticide. It is also used as a food additive, a foaming agent in fire foams, and in the manufacturing of aluminum salts (Lewis 2001; O'Neil et al. 2001). Aluminum sulfate, as sodium aluminum sulfate, is a component of household baking powder (Chung 1992). Alum is also used as a vaccine adjuvant (Baylor et al. 2002; Malakoff 2000). Aluminum potassium sulfate (potash alum) is used in dyeing (mordant), paper, matches, paints, tanning agents, waterproofing agents, aluminum salts, food additives, baking powder, water purification, astringent, and cement hardener (Lewis 2001). Aluminum ammonium sulfate (ammonium alum) is used in dyeing (mordant), water and sewage purification, sizing paper, retanning leather, clarifying agent, food additive, the manufacture of lakes and pigments, and fur treatment (Lewis 2001).

Other aluminum compounds that are used as food additives include aluminum silicates (anticaking agents) and aluminum color additives (lakes) (Saiyed and Yokel 2005; Soni et al. 2001).

5.4 DISPOSAL

Production of finished aluminum products by industrial facilities typically results in the generation of very large amounts of solid aluminum hydroxide anodizing residues (Saunders 1988). These aluminum-anodizing residues are currently classified as nonhazardous under the Federal Resource Conservation and Recovery Act (RCRA) regulations. These residues are typically dewatered to reduce the volume of waste prior to being landfilled. However, the heavy metal content of these solid waste residues can be of concern, especially in production processes using two-step anodizing systems that employ solutions containing elevated heavy metal concentrations. For these types of plants, Saunders (1988) has proposed implementation of a caustic-etch recovery system that will limit both the volume of aluminum-anodizing residue and the heavy metal content of the residue. Additional information on regulations and standards for aluminum and aluminum compounds is summarized in Chapter 8.

Approximately 24.7×10^6 and 1.15×10^5 pounds of aluminum (fume or dust) and aluminum oxide (fibrous forms) were reported for on-site disposal and other releases in 2004. On-site disposal or other releases include emissions to the air, discharges to bodies of water, disposal at the facility to land, and disposal in underground injection wells. Approximately 23.7×10^6 and 1.20×10^6 pounds of aluminum (fume or dust) and aluminum oxide (fibrous forms), respectively, were reported for off-site disposal and other releases in 2004. An off-site disposal or other release is a discharge of a toxic chemical to the environment that occurs as a result of a facility's transferring a waste containing a TRI chemical off-site for disposal or

other release (TRI04 2006). The TRI data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list.

In the United States, about 3 million metric tons of aluminum was recovered from purchased scrap in 2006, with 64% of this coming from new (manufacturing) scrap and 36% from old scrap (discarded aluminum products). Aluminum used beverage cans accounted for about 54% of the reported old scrap consumption in 2006. According to the Aluminum Association, Inc., the recycling rate for used aluminum beverage cans in 2004 was 51.6% (USGS 2007b, 2007c).

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

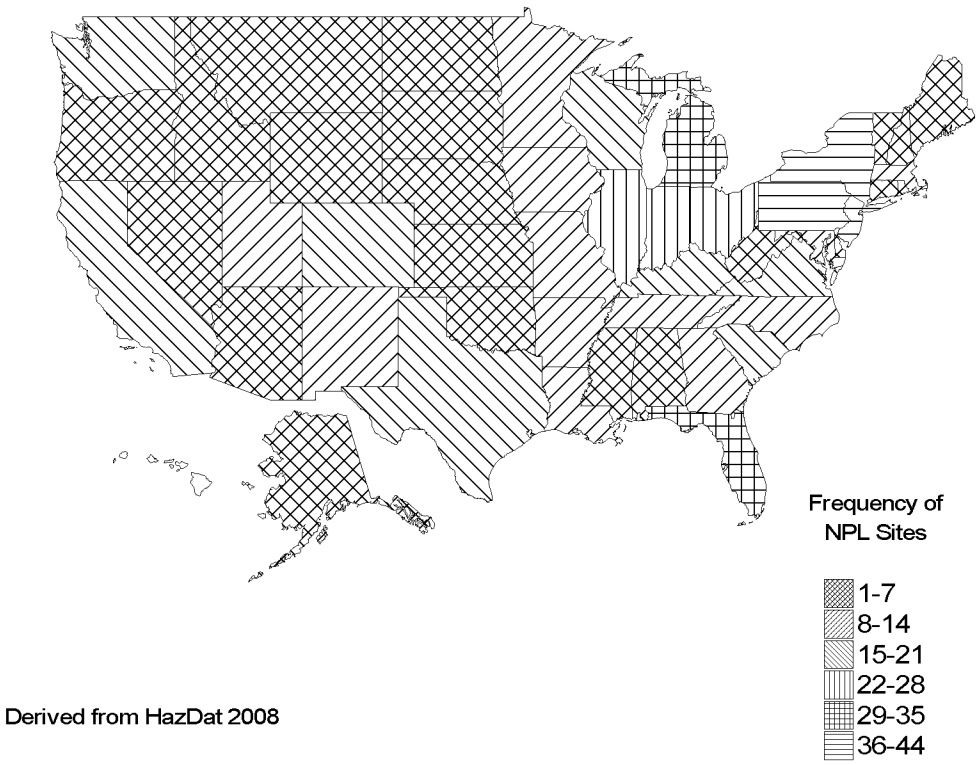
Aluminum has been identified in at least 596 of the 1,699 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2008). However, the number of sites evaluated for aluminum is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 590 are located within the United States, 2 are located in Guam, 3 are located in the Commonwealth of Puerto Rico, and 1 is located in the Virgin Islands (not shown).

Aluminum is the most abundant metal and the third most abundant element in the earth's crust, comprising about 8.8% by weight (88 g/kg). It is never found free in nature and is found in most rocks, particularly igneous rocks as aluminosilicate minerals (Lide 2005; Staley and Haupin 1992). Aluminum is also present in air, water, and many foods. Aluminum enters environmental media naturally through the weathering of rocks and minerals. Anthropogenic releases are in the form of air emissions, waste water effluents, and solid waste primarily associated with industrial processes, such as aluminum production. Because of its prominence as a major constituent of the earth's crust, natural weathering processes far exceed the contribution of releases to air, water, and land associated with human activities (Lantzy and MacKenzie 1979).

The behavior of aluminum in the environment depends upon its coordination chemistry and the characteristics of the local environment, especially pH. The major features of the biogeochemical cycle of aluminum include leaching of aluminum from geochemical formations and soil particulates to aqueous environments, adsorption onto soil or sediment particulates, and wet and dry deposition from the air to land and surface water.

Generally, aluminum is not bioaccumulated to a significant extent. However, certain plants can accumulate high concentrations of aluminum. For example, tea leaves may contain very high concentrations of aluminum, >5,000 mg/kg in old leaves (Dong et al. 1999). Other plants that may contain high levels of aluminum include Lycopodium (Lycopodiaceae), a few ferns, Symplocos (Symplocaceae), and Orites (Proteaceae) (Jansen et al. 2002). Aluminum does not appear to accumulate to any significant degree in cow's milk or beef tissue and is, therefore, not expected to undergo biomagnification in terrestrial food chains (DOE 1984). Similarly, because of its toxicity to many aquatic organisms, including fish, aluminum does not bioconcentrate in aquatic organisms to any significant degree (Rosseland et al. 1990).

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



Background concentrations of aluminum in rural air typically range from 0.005 to 0.18 μg/m^3 (Hoffman et al. 1969; Pötzl 1970; Sorenson et al. 1974), whereas concentrations in urban and industrial areas can be considerably higher, ranging from 0.4 to 8.0 μg/m^3 (Cooper et al. 1979; Dzubay 1980; Kowalczyk et al. 1982; Lewis and Macias 1980; Moyers et al. 1977; Ondov et al. 1982; Pillay and Thomas 1971; Sorenson et al. 1974; Stevens et al. 1978). Concentrations of aluminum are highly variable in drinking water, ranging from <0.001 to 1.029 mg/L (Schenk et al. 1989). The use of alum (aluminum sulfate) as a flocculent in water treatment facilities typically leads to high aluminum concentrations in finished waters (DOI 1970; Letterman and Driscoll 1988; Miller et al. 1984a). In a survey of 186 community water systems, the median aluminum concentration in finished water receiving coagulation treatment using alum was 0.112 mg/L, compared to 0.043 mg/L in finished water that received no coagulation treatment (Miller et al. 1984a). Dissolved aluminum concentrations in surface and groundwater vary with pH and the humic acid content of the water. High aluminum concentrations in natural water occur only when the pH is <5; therefore, concentrations in most surface water are very low.

Since aluminum is ubiquitous in the environment, the general population will be exposed to aluminum by the inhalation of ambient air and the ingestion of food and water. The consumption of foods containing aluminum-containing food additives are a major sources of aluminum in the diet (Saiyed and Yokel 2005; Soni et al. 2001). The use of other consumer items such as antiperspirants, cosmetics, internal analgesics (buffered aspirins), anti-ulcerative medications, antidiarrheals, and antacids that also contain aluminum compounds will result in exposure to aluminum. The intake of aluminum from food and drinking water is low, especially compared with that consumed by people taking aluminum-containing medicinal preparations. Daily intakes of aluminum from food range from 3.4 to 9 mg/day (Biego et al. 1998; MAFF 1999; Pennington and Schoen 1995), whereas aluminum-containing medications contain much higher levels of aluminum, for example 104–208 mg of aluminum per tablet/capsule/5 mL dose for many antacids (Zhou and Yokel 2005). While aluminum is naturally present in food and water, the greatest contribution to aluminum in food and water by far is the aluminum-containing additives used in water treatment and processing certain types of food such as grain-based products and processed cheese. Aluminum has no known physiological role in the human body (Nayak 2002).

The aluminum content of human breast milk generally ranged from 9.2 to 49 μg/L (Fernandez-Lorenzo et al. 1999; Hawkins et al. 1994; Koo et al. 1988; Simmer et al. 1990; Weintraub et al. 1986). Soy-based infant formulas contain higher concentrations of aluminum, as compared to milk-based infant formulas or breast milk. Recent reports provide average aluminum concentrations of 460–930 μg/L for soy-based

infant formulas and 58–150 µg/L for milk-based formulas (Fernandez-Lorenzo et al. 1999; Ikem et al. 2002; Navarro-Blasco and Alvarez-Galindo 2003).

Occupational exposures to aluminum occur during the mining and processing of aluminum ore into metal, recovery of scrap metal, production and use of aluminum compounds and products containing these compounds, and in aluminum welding. Individuals living in the vicinity of industrial emission sources and hazardous waste sites; individuals with chronic kidney failure requiring long-term dialysis or treatment with phosphate binders; patients requiring intravenous fluids; infants, especially premature infants fed soy-based formula containing high levels of aluminum; and individuals consuming large quantities of antacids, anti-ulcerative medications, antidiarrheal medications may also be exposed to high levels of aluminum.

According to the Toxic Chemical Release Inventory, in 2005, total releases of aluminum (fume or dust) to the environment (including air, water, and soil) from 329 large processing facilities were 45.6 million pounds (~2.07×10^4 metric tons) (TRI05 2007). In addition, in 2005, total releases of aluminum oxide (fibrous forms) to the environment (including air, water, and soil) from 59 large processing facilities were 2.59 million pounds (~1180 metric tons) (TRI05 2007). Tables 6-1 and 6-2 list amounts released from these facilities grouped by state. The TRI data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list.

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces,

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Aluminum (Fume or Dust)[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AK	1	0	0	0	0	1	0	0	0
AL	4	2,453	0	0	45,887	48,344	2,453	45,887	48,340
AR	3	0	0	0	0	3	0	750	750
AZ	4	7,167	0	0	230,729	237,900	7,217	230,679	237,896
CA	16	182,017	0	0	1,662,654	1,844,688	1,802,363	42,364	1,844,727
CO	1	1,500	0	0	53,058	54,559	1,500	53,058	54,558
CT	2	0	0	0	0	2	0	0	0
FL	5	1,624	0	0	23	1,652	1,624	23	1,647
GA	10	37,680	0	0	108,219	145,909	37,680	108,871	146,551
IA	8	11,570	0	0	43,052	54,630	11,570	43,052	54,622
ID	2	2,864	0	0	653,345	656,211	518,203	138,006	656,209
IL	16	62,008	0	0	520,607	582,631	62,008	525,882	587,890
IN	29	149,220	0	0	10,023,429	10,172,678	149,225	10,024,174	10,173,399
KS	3	0	0	0	0	3	0	0	0
KY	13	254,892	0	0	2,799,380	3,054,285	2,419,281	634,991	3,054,272
LA	4	1,184	0	0	13	1,201	1,197	0	1,197
MA	2	No data	No data	No data	No data	No data	No data	0	0
MD	2	0	0	0	0	2	0	0	0
MI	16	17,862	0	0	1,215,365	1,233,243	17,862	1,224,508	1,242,370
MN	6	58,268	0	0	157,233	215,507	58,268	157,277	215,545
MO	8	29,495	0	0	1,941,390	1,970,893	1,828,685	7,037,274	8,865,959
MS	1	0	0	0	550	551	0	550	550
NC	8	62,432	0	0	55,340	117,780	63,182	54,590	117,772
NE	2	0	0	0	31,105	31,107	21,263	9,842	31,105
NJ	6	4,413	0	0	5,222	9,641	4,413	5,222	9,635
NM	1	No data	No data	No data	No data	No data	No data	0	0
NV	4	259	0	0	330,084	330,347	330,343	0	330,343
NY	7	58,438	312	0	198,222	256,979	60,436	213,027	273,463
OH	33	50,159	2	0	2,170,512	2,220,706	253,161	2,237,892	2,491,053
OK	9	9,654	0	0	447,920	457,583	10,416	447,158	457,574
OR	4	646	0	0	1,295	1,945	646	1,295	1,941
PA	23	8,594	0	0	294,833	303,450	8,866	317,627	326,493
RI	1	No data	No data	No data	No data	No data	No data	0	0
SC	4	7,841	0	0	750	8,595	7,841	1,500	9,341
TN	21	93,021	0	0	887,911	980,953	185,281	795,651	980,932
TX	19	89,879	0	0	7,670,584	7,760,481	2,590,719	5,171,544	7,762,262

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Aluminum (Fume or Dust)[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
UT	6	187	0	0	372,634	372,827	147,182	225,639	372,821
VA	2	137	0	0	1,000	1,139	137	1,000	1,137
WA	4	846	0	0	128,819	129,669	846	129,421	130,267
WI	14	75,933	0	0	289,933	365,880	75,933	290,099	366,032
WV	5	3,112	0	0	4,732,012	4,735,129	3,112	4,732,012	4,735,124
Total	329	1,285,354	314	0	37,073,110	38,359,108	10,682,912	34,900,865	45,583,777

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI05 2007 (Data are from 2005)

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Aluminum Oxide (Fibrous Forms)[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	2	0	0	0	0	0	0	0	0
AR	1	0	0	0	0	0	0	0	0
CA	1	0	No data	0	0	0	0	0	0
CO	1	0	5	0	480	2,749	485	2,749	3,234
CT	1	0	0	0	0	0	0	0	0
GA	2	16	175	0	2,957	0	191	2,957	3,148
IA	2	0	0	0	40,320	0	0	40,320	40,320
IL	5	76	0	0	122,002	22,660	76	144,662	144,738
IN	3	901	250	0	5	10	1,156	10	1,166
KY	3	243	0	0	26,631	0	243	26,631	26,874
LA	2	0	0	0	0	0	0	0	0
MI	2	0	0	0	375,000	0	0	375,000	375,000
MO	1	250	0	0	750	0	1,000	0	1,000
NC	4	56	10	0	60,797	4,342	61	65,144	65,205
NE	1	2	0	0	20	0	22	0	22
NM	1	0	0	0	0	0	0	0	0
NY	2	250	0	0	0	29,808	250	29,808	30,058
OH	2	980	0	0	110,958	0	980	110,958	111,938
OK	1	0	No data	0	0	0	0	0	0
PA	6	247	0	0	178,893	6,781	247	185,674	185,920
SC	2	14	0	7	23,556	424	14	23,987	24,001
TN	4	3	0	0	0	0	3	0	3
TX	4	11	0	0	431,166	0	11	431,166	431,177
VA	2	500	0	0	37,159	0	37,409	250	37,659
WI	3	260	0	0	1,059,128	0	1,059,138	250	1,059,388

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Aluminum Oxide (Fibrous Forms)[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
WV	1	0	0	0	48,000	0	48,000	0	48,000
Total	59	3,810	440	7	2,517,822	66,774	1,149,287	1,439,565	2,588,852

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI05 2007 (Data are from 2005)

imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

6.2.1 Air

Estimated releases of 1.29 million pounds (~586 metric tons) of aluminum (fume or dust) to the atmosphere from 329 domestic manufacturing and processing facilities in 2005, accounted for about 2.8% of the estimated total environmental releases from facilities required to report to the TRI (TRI05 2007). Estimated releases of 3,810 pounds (~1.73 metric tons) of aluminum oxide (fibrous forms) to the atmosphere from 59 domestic manufacturing and processing facilities in 2005, accounted for about 1.5% of the estimated total environmental releases from facilities required to report to the TRI (TRI05 2007). These releases are summarized in Tables 6-1 and 6-2.

Aluminum is released to the environment by both natural processes and anthropogenic sources. Because of its prominence as a major constituent of the earth's crust, natural processes far exceed the contribution of anthropogenic releases to the environmental distribution of aluminum (Lantzy and MacKenzie 1979). Anthropogenic releases are primarily to the atmosphere. The largest source of airborne aluminum-containing particulates is the flux of dust from soil and the weathering of rocks (Lee and Von Lehmden 1973; Sorenson et al. 1974). In addition, aluminum-containing dust is generated by volcanic activity (Varrica et al. 2000). Human activities, such as mining and agriculture, contribute to this wind-blown dust (Eisenreich 1980; Filipek et al. 1987). About 13% of atmospheric aluminum is attributed to anthropogenic emissions (Lantzy and MacKenzie 1979). The major anthropogenic sources of aluminum-containing particulate matter include coal combustion, aluminum production, and other industrial activities, such as smelting, that process crustal minerals (Lee and Von Lehmden 1973). Aluminum concentrations in air particulate emissions from iron and steel foundries and brass and bronze refineries range from about 100 to 1,000 ppm (Lee and Von Lehmden 1973). Que Hee et al. (1982) also found that aluminum was one of the most abundant elements quantified in coal stack emissions from power plants located in both the eastern and western United States. In addition, in U.S. cities, motor vehicle emissions contribute an estimated 0.9–9% of the observed elemental concentration of aluminum in these atmospheres (Ondov et al. 1982).

Aluminum has been identified in air samples collected at 14 of the 596 NPL hazardous waste sites where it has been detected in some environmental media (HazDat 2008).

6.2.2 Water

Estimated releases of 314 pounds (~0.14 metric tons) of aluminum (fume or dust) to surface water from 329 domestic manufacturing and processing facilities in 2005, accounted for about 0.0007% of the estimated total environmental releases from facilities required to report to the TRI (TRI05 2007). Estimated releases of 440 pounds (~0.20 metric tons) of aluminum oxide (fibrous forms) to surface water from 59 domestic manufacturing and processing facilities in 2005, accounted for about 0.017% of the estimated total environmental releases from facilities required to report to the TRI (TRI05 2007). These releases are summarized in Tables 6-1 and 6-2.

Aluminum occurs ubiquitously in natural waters as a result of the weathering of aluminum-containing rocks and minerals. Of the known geochemical responses to environmental acidification, the best documented is the mobilization of aluminum from terrestrial to aquatic environments (Campbell et al. 1992). This mobilization of aluminum is often episodic in nature and is associated with pH depressions (acidification) occurring during the spring snowmelt or associated with erosion from specific storm events (Campbell et al. 1992; Nelson and Campbell 1991; Rosseland et al. 1990).

Aluminum concentrations in surface waters can be increased directly or indirectly by human activity through industrial and municipal discharges, surface run-off, tributary inflow, groundwater seepage, and wet and dry atmospheric deposition (Eisenreich 1980). For example, aluminum is released to surface waters in the effluent from bauxite processing and aluminum manufacturing facilities at concentrations that can be toxic to aquatic life (His et al. 1996; Trieff et al. 1995). However, the effluents of these facilities typically contain not only aluminum, but also a complex mixture of heavy metals such as iron, chromium, and mercury, as well as minerals, silica, and other compounds, and synergistic effects of these metals and compounds cannot be ruled out. The use of aluminum sulfate and other aluminum compounds as coagulating agents in the treatment of raw drinking water supplies can significantly increase the total aluminum content in finished water (Cech and Montera 2000; Henshaw et al. 1993; Miller et al. 1984a; Qureshi and Malmberg 1985; USGS 1984b). Weathering of sulfide ores exposed to the atmosphere in inactive mines and tailings dumps releases large quantities of sulfuric acid and metals such as aluminum (Filipek et al. 1987). Increasingly, acid environments caused by such acid mine drainage or by acid rain will subsequently cause an increase in the dissolved aluminum content of the surrounding waters (Brusewitz 1984; Filipek et al. 1987). In addition, atmospheric deposition is a source of aluminum input to surface water. The atmospheric loading of aluminum to Lake Michigan was estimated to be 5 million

kg/year, of which 74% was to the southern basin where the influence of agricultural and industrial activity (e.g., steel manufacturing and cement production) was greatest (Eisenreich 1980).

Aluminum has been identified in surface water and groundwater samples collected at 251 and 391 of the 596 NPL hazardous waste sites, respectively, where it has been detected in some environmental media (HazDat 2008).

6.2.3 Soil

Estimated releases of 37.1 million pounds (~$1.68x10^4$ metric tons) of aluminum (fume or dust) to soils from 329 domestic manufacturing and processing facilities in 2005, accounted for about 81% of the estimated total environmental releases from facilities required to report to the TRI (TRI05 2007). Estimated releases of 2.52 million pounds (~1,140 metric tons) of aluminum oxide (fibrous forms) to soils from 59 domestic manufacturing and processing facilities in 2005, accounted for about 97% of the estimated total environmental releases from facilities required to report to the TRI (TRI05 2007). An additional 7 pounds (3 kilograms) of aluminum oxide (fibrous forms) were released via underground injection (TRI05 2007). These releases are summarized in Tables 6-1 and 6-2.

Aluminum is the most abundant metal and the third most abundant element in the earth's crust, comprising about 8.8% by weight (88 g/kg) (Staley and Haupin 1992). Aluminum can be released naturally by the weathering of aluminum-containing rocks. Aluminum is also released to soil as a major constituent of many mining wastes and is also contained in solid wastes from coal combustion and aluminum reduction and other metal processing operations (DOI 1983, 1984). Wilson et al. (2002) estimated that several hundred thousand pounds of aluminum containing chaff have been release to the Chesapeake Bay during research and training operations by the Naval Research Laboratory-Chesapeake Bay Detachment over the past 25 years.

Aluminum has been identified in soil and sediment samples collected at 253 and 190 of the 596 NPL hazardous waste sites, respectively, where it has been detected in some environmental media (HazDat 2008).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Aluminum is the most abundant metal in the earth's crust, but is never found in its elemental state in nature. In compounds, aluminum occurs in its only oxidation state (+3) (Lide 2005). Aluminum occurs widely in nature with silicates, such as mica and feldspar, as the hydroxo oxide (bauxite), and as cryolite (Na_3AlF_6) (Cotton et al. 1999). Aluminum's behavior in the environment is strongly influenced by its coordination chemistry. Aluminum partitions between solid and liquid phases by reacting and complexing with water molecules and anions such as chloride, fluoride, sulfate, nitrate, phosphate, and negatively charged functional groups on humic materials and clay.

The transport and partitioning of aluminum in the environment is determined by its chemical properties, as well as the characteristics of the environmental matrix that affect its solubility. At a pH >5.5, naturally occurring aluminum compounds exist predominantly in an undissolved form such as gibbsite, $Al(OH)_3$, or as aluminosilicates except in the presence of high amounts of dissolved organic material or fulvic acid, which binds with aluminum and can cause increased dissolved aluminum concentrations in streams and lakes (Brusewitz 1984). Organic acids have been found to be important weathering agents for dissolving and transporting aluminum in an alpine soil environment (Litaor 1987). The ability of these organic acids to complex aluminum in sub-alpine soil solutions was found to increase as the pH rose from 3.8 to 5 (Dahlgren and Ugolini 1989). In this study, dissolved aluminum was found primarily as organic complexes when organic carbon/metal ratios were >50 (Dahlgren and Ugolini 1989).

In general, decreasing pH (acidification) results in an increase in mobility for monomeric forms of aluminum (Goenaga and Williams 1988), which is of concern with respect to the occurrence of acid rain and the release of acid mine drainage. Aluminum in soil solutions and surface waters in a mining region rich in metallic sulfides was in a labile form, as Al-SO_4 and Al^{3+} species. Acidic conditions are created by the microbial oxidation of sulfides in tailing piles, resulting in sulfuric acid. In contrast, in areas not affected by acidification, aluminum in solution was partitioned between labile and non-labile forms, the latter being predominantly bound to fluorine (Alvarez et al. 1993). In soils, the most soluble form of aluminum under acidic conditions is nonsilicaceous, organically-bound aluminum (Mulder et al. 1989).

In groundwater or surface water systems, an equilibrium with a solid phase form is established that largely controls the extent of aluminum dissolution which can occur. In acid sulfate waters resulting from mine drainage, gibbsite and kaolinite are not stable, and the solubility of the minerals jurbanite

($Al(SO_4)(OH)\cdot H_2O$) or alunite ($KAl_3(SO_4)_2(OH)_6$) may control aluminum levels (Filipek et al. 1987). In a Colorado alpine watershed soil, the chemical equilibria of aluminum in interstitial water at a pH range of 4.4–7.2 were controlled by amorphous aluminosilicate rather than gibbsite (Litaor 1987).

In addition to the effect of pH on mobility, the type of acid entering environmental systems may also be important. Nitric acid was found to leach more aluminum from soil columns representative of high-elevation forest floor soils than did sulfuric acid (James and Riha 1989). However, in mineral horizons below the forest floor, the study found that concentrations of aluminum leached by these acids did not differ from concentrations of aluminum leached by distilled, deionized water at a pH of 5.7. The authors concluded that soluble constituents from the forest floor affected the aluminum solubility in the underlying mineral horizons under the leaching conditions that they used. These constituents may have included natural buffering agents which resist changes in pH and, therefore, negate or mediate the effect of the acid.

The ability of mineralized soil to control the migration of aluminum was observed in another study. Acidic leachate from coal waste containing aluminum was percolated through soil containing varying amounts of calcium carbonate (Wangen and Jones 1984). Soluble aluminum was found to decrease dramatically as the pH of the percolating leachate increased and aluminum oxide precipitates formed; at pH 6, no dissolved aluminum was measured. The authors concluded that alkalinized carbonaceous soils provide the best control material for acidic leachates from coal mineral wastes.

The adsorption of aluminum onto clay surfaces can be a significant factor in controlling aluminum mobility in the environment, and these adsorption reactions, measured in one study at pH 3.0–4.1, have been observed to be very rapid (Walker et al. 1988). However, clays may act either as a sink or a source for soluble aluminum depending on the degree of aluminum saturation on the clay surface (Walker et al. 1988).

The presence of high levels of suspended solids in stream surface water during storm episodes resulted in higher concentrations of adsorbed aluminum than in the absence of suspended solids (Goenaga and Williams 1988). The increased adsorption was not strictly linear, with higher concentrations of suspended solids due to variations in the particle size distribution and the nature of the particles.

Within the pH range of 5–6, aluminum complexes with phosphate and is removed from solution. Because phosphate is a necessary nutrient in ecological systems, this immobilization of both aluminum

and phosphate may result in depleted nutrient states in surface water (Brusewitz 1984). Conversely, aluminum has been added to a nutrient-rich lake in Sweden with some success in an effort to arrest the "aging process" caused by an overabundance of phosphate (Jernelov 1971).

Aluminum salt coagulants are used in the treatment of potable drinking water, and unretained aluminum (approximately 11% of the added aluminum) was found to be transported through a water distribution system (Driscoll and Letterman 1988).

Aluminum, as a constituent of soil, weathered rock, and solid waste from industrial processes, is transported through the atmosphere as windblown particulate matter and is deposited onto land and water by wet and dry deposition. Atmospheric loading rates of aluminum to Lake Michigan were estimated at 5 million kg/year (Eisenreich 1980). In this study, most of the aluminum was generally associated with large particles that were deposited near their source. In a study, the wet and dry deposition of aluminum was measured biweekly for 1 year at two sites on Massachusetts Bay, Turro and Nahant. The average total deposition rate was 0.1 g/m^2-year, of which 29% was in rain (wet deposition) (Golomb et al. 1997).

Plant species and cultivars of the same species differ considerably in their ability to take up and translocate aluminum to above-ground parts (Kabata-Pendias and Pendias 1984). Tea leaves may contain very high concentrations of aluminum, >5,000 mg/kg in old leaves (Dong et al. 1999). Other plants that may contain high levels of aluminum include Lycopodium (Lycopodiaceae), a few ferns, Symplocos (Symplocaceae), and Orites (Proteaceae) (Jansen et al. 2002). Aluminum is often taken up and concentrated in root tissue (Kabata-Pendias and Pendias 1984). In sub-alpine ecosystems, the large root biomass of the Douglas fir, *Abies amabilis*, takes up aluminum and immobilizes it, preventing large accumulation in above-ground tissue (Vogt et al. 1987). It is unclear to what extent aluminum is taken up into root food crops and leafy vegetables. An uptake factor (concentration of aluminum in the plant/concentration of aluminum in soil) of 0.004 for leafy vegetables and 0.00065 for fruits and tubers has been reported (DOE 1984), but the pH and plant species from which these uptake factors were derived are unclear. Based upon these values, however, it is clear that aluminum is not taken up in plants from soil, but is instead biodiluted.

Transfer coefficients of 0.0002 $(kg/day)^{-1}$ for uptake into milk and 0.0015 $(kg/day)^{-1}$ for uptake into beef tissue have been reported (DOE 1984). The transfer coefficients represent the fraction of daily aluminum intake in feed that is transferred to a kilogram of milk or beef muscle. Based upon the above values,

aluminum is not transferred to beef muscle or milk from feed to any appreciable extent and therefore would not be expected to bioaccumulate in terrestrial food chains.

The potential for accumulation of aluminum has been studied in several aquatic species including fish (Buckler et al. 1995; Cleveland et al. 1991; Hamdy 1993; McDonald et al. 1991; Wilkinson and Campbell 1993), amphibians (Freda and McDonald 1990), crustaceans (Madigosky et al. 1991), snails (Brooks et al. 1992), aquatic insects (Frick and Herrmann 1990; Guerold et al. 1995; Krantzberg and Stokes 1990), and aquatic plants (Albers and Camardese 1993; Vuori et al. 1990). Bioconcentration of aluminum in fish is a function of the water quality (e.g., pH and total organic carbon) (Cleveland et al. 1989).

Brook trout have been shown to accumulate slightly more aluminum (measured as whole-body residues) at pH 5.6–5.7 than at pH 6.5–6.6 (Cleveland et al. 1989). Cleveland et al. (1991) reported that the estimated steady-state bioconcentration factors (BCF) for aluminum in brook trout were 215, 123, and 36 at pH 5.3, 6.1, and 7.2, respectively. When transferred to water of the same pH without added aluminum, brook trout eliminated aluminum from tissues more rapidly at pH 5.3 than at pH 6.1 and 7.2. In tissues of smallmouth bass, aluminum concentrations were higher and more variable in gill tissue than in other tissues (Brumbaugh and Kane 1985). Aluminum concentrations in rainbow trout from an alum-treated lake, an untreated lake, and a hatchery were highest in gill tissue and lowest in muscle (Buergel and Soltero 1983). Aluminum residue analyses in brook trout have shown that whole-body aluminum content decreases as the fish advance from larvae to juveniles (Cleveland et al. 1989). These results imply that the aging larvae begin to decrease their rate of aluminum uptake, to eliminate aluminum at a rate that exceeds uptake, or to maintain approximately the same amount of aluminum while the body mass increases. The decline in whole-body aluminum residues in juvenile brook trout may be related to growth and dilution by edible muscle tissue that accumulated less aluminum than did the other tissues (Cleveland et al. 1989). Wilkinson and Campbell (1993) studied aluminum uptake in Atlantic salmon at a pH of 4.5 under conditions simulating spring snowmelt. These authors reported that gill uptake was slow, approaching a steady state only after 3 days of exposure. The greatest fraction of the gill-associated aluminum was not sorbed to the gill tissue, but to the gill mucus. The authors believe that the mucus appears to retard aluminum transport from solution to the membrane surface, thus delaying the acute biological response of the fish. Buckler et al. (1995) reported concentrations of aluminum in whole-body tissue of the Atlantic salmon exposed to high concentrations of aluminum ranging from 3 μg/g (for fish exposed to 33 μg/L) to 96 μg/g (for fish exposed to 264 μg/L) at pH 5.5. After 60 days of exposure, BCFs ranged from 76 to 190 and were directly related to the aluminum exposure concentration. In acidic waters (pH 4.6–5.3) with low concentrations of calcium (0.5–1.5 mg Ca/L), labile aluminum between

25 and 75 µg/L is toxic (Rosseland et al. 1990). Because aluminum is toxic to many aquatic species, it is not bioaccumulated to a significant degree (BCF <300) in most fish and shellfish; therefore, consumption of contaminated fish does not appear to be a significant source of aluminum exposure in humans.

Aluminum uptake for the leopard frog (*Rana pipiens*) was positively correlated to exposure time and pH; however, no BCF values were reported because the authors felt that the body aluminum accumulation was too variable for useful prediction of the exposure history or physiological status of the frogs (Freda and McDonald 1990).

Bioconcentration of aluminum has also been reported for several aquatic invertebrate species. BCF values ranging from 0.13 to 0.5 in the whole-body were reported for the snail, *Helix aspersa*, fed a single 24-hour meal containing aluminum in a barley-flour pellet (Brooks et al. 1992). Madigosky et al. (1991) reported high tissue residues of aluminum in the red swamp crayfish (*Procambarus clarkii*) collected from roadside drainage ditches in Louisiana. Mean aluminum concentrations as µg/g dry weight in crayfish from roadside ditches ranged from 1.75 to 6.39 in abdominal muscle, 3.1–22.74 in the hepatopancreas, 309.4–981.50 in the alimentary tract, 10.85–77.45 in the exoskeleton, and 30–140 in the blood. These values were significantly elevated above those of control crayfish where the concentrations (µg Al/g dry weight) were 1.22 in abdominal muscle, 1.42 in the hepatopancreas, 26.97 in the alimentary tract, 4.28 in the exoskeleton, and 37.9 in the blood.

Bioconcentration of aluminum has also been reported for aquatic insects. Frick and Herrmann (1990) reported aluminum accumulation in mayfly nymphs (*Heptagenia sulphurea*) at low pH (4.5). The nymphs were exposed at two concentrations (0.2 and 2 mg Al/L) and for two exposure times (2 and 4 weeks), the longer time period including a molting phase. When nymphs were exposed to the higher concentration of aluminum for two instar periods, with a molt in between, the aluminum content (2.34 mg Al/g dry weight) nearly doubled compared with that of a one-instar treatment (1.24 mg Al/g dry weight). The major part of the aluminum was deposited in the exuviae of the nymphs, as the aluminum determination in the nymphs showed a 70% decrease in aluminum content after molting. These authors speculate that internally accumulated aluminum in the nymphs may be transferred to terrestrial predators (e.g., birds). They also hypothesized that externally deposited aluminum may be transferred to terrestrial food chains by aquatic invertebrates that leave the water in their last instar to molt on shore. An important contribution to the idea of biomagnification of aluminum was made by Nyholm (1981). Using semi-quantitative multi-element microanalysis, he related impaired breeding of pied flycatchers (*Ficedula hypoleuca*) in Sweden to the occurrence of aluminum in the bone marrow of the birds. A diet of

stoneflies was suspected of forming a link between the lake and the terrestrial predators. Although the matter is far from clear, Nyholm (1981) seems to imply that the insects (stoneflies) were adults and that these could contain significant amounts of aluminum even after having left the exuviae behind (Frick and Herrmann 1990).

Vuori et al. (1990) sampled tufts of the aquatic moss, *Fontinalis dalecarlica*, from the River Lestijoki in Western Finland. The concentrations of aluminum in the water were low (87–196 µg/L, pH 6.5–7.0) relative to the concentrations in the young terminal shoots of *F. dalecarlica* appeared to be quite high (303–1,852 µg/g dry weight). The authors concluded that there was an effective accumulation of aluminum in the moss tissue. Albers and Camardese (1993) compared concentrations of aluminum and other metals in aquatic species of three acidified (pH≈5) and three nonacidified (pH≈6.5) constructed wetlands. They found that the metal content of *Sparganium americanum* (bur-reed) was only slightly affected by acidification.

6.3.2 Transformation and Degradation

As an element, aluminum cannot be degraded in the environment, but may undergo various precipitation or ligand exchange reactions. Aluminum in compounds has only one oxidation state (+3), and would not undergo oxidation-reduction reactions under environmental conditions. Aluminum can be complexed by various ligands present in the environment (e.g., fulvic and humic acids). The solubility of aluminum in the environment will depend on the ligands present and the pH.

6.3.2.1 Air

Aluminum-containing particulate matter in the atmosphere is mainly derived from soil and industrial processes where crustal materials (e.g., minerals) are processed. Aluminum is found as silicates, oxides, and hydroxides in these particles (Eisenreich 1980). Aluminum compounds cannot be oxidized and atmospheric transformations would not be expected to occur during transport. If aluminum metal particulates were released to air during metal processing, they would be rapidly oxidized.

6.3.2.2 Water

The trivalent aluminum ion is surrounded by six water molecules in solution (Cotton et al. 1999). The hydrated aluminum ion, $[Al(H_2O)_6]^{3+}$, undergoes hydrolysis, in which a stepwise deprotonation of the coordinated water ligands forms bound hydroxide ligands (e.g., $[Al(H_2O)_5(OH)]^{2+}$, $[Al(H_2O)_4(OH)_2]^{+}$)

(Snoeyink and Jenkins 1980). The speciation of aluminum in water is pH dependent. The hydrated trivalent aluminum ion is the predominant form at pH levels below 4. Between pH 5 and 6, the predominant hydrolysis products are $Al(OH)^{2+}$ and $Al(OH)_2^{+}$, while the solid $Al(OH)_3$ is most prevalent between pH 5.2 and 8.8. The soluble species $Al(OH)_4^{-}$ is the predominant species above pH 9, and is the only species present above pH 10 (Martell and Motekaitis 1989). Polymeric aluminum hydroxides appear between pH 4.7 and 10.5, and increase in size until they are transformed into colloidal particles of amorphous $Al(OH)_3$, which crystalize to gibbsite in acid waters (Brusewitz 1984). Polymerization is affected by the presence of dissolved silica; when enough silica is present, aluminum is precipitated as poorly crystallized clay mineral species (Bodek et al. 1988).

Hydroxyaluminum compounds are considered amphoteric (e.g., they can act as both acids and bases in solution) (Cotton et al. 1999). Because of this property, aluminum hydroxides can act as buffers and resist pH changes within the narrow pH range of 4–5 (Brusewitz 1984).

Monomeric aluminum compounds, typified by aluminum fluoride, chloride, and sulfate, are considered reactive or labile compounds, whereas polymeric aluminum species react much more slowly in the environment (USGS 1984a). Aluminum has a stronger attraction for fluoride in an acidic environment compared to other inorganic ligands (Brusewitz 1984). Fulvic acid is also an important ligand for aluminum under acidic conditions, and it has been observed that as the temperature is lowered, the rate of complexation of aluminum with fluoride is considerably slowed, while the rate of complexation between aluminum and fulvic acid is only slightly decreased in rate (Plankey and Patterson 1987). This suggests that during snow-melt conditions, when aluminum and hydrogen ion concentrations increase, complexation with fulvic acid could preferentially occur over complexation with fluoride.

6.3.2.3 Sediment and Soil

Aluminum is present in many primary minerals. The weathering of these primary minerals over time results in the deposition of sedimentary clay minerals, such as the aluminosilicates kaolinite and montmorillonite. The weathering of soil results in the more rapid release of silicon, and aluminum precipitates as hydrated aluminum oxides such as gibbsite and boehmite, which are constituents of bauxites and laterites (Bodek et al. 1988). Aluminum is found in the soil complexed with other anions, such as fluoride, sulfate, and phosphate.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to aluminum depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of aluminum in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on aluminum levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring aluminum in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

There are varying levels of aluminum in the atmosphere, depending on the location of the sampling site, meteorologic conditions, and the level of industrial activity or traffic in the area. Aluminum levels are expected to be low in areas influenced by the ocean and high in areas with wind-blown soil. Background concentrations of aluminum in the atmosphere generally range from 0.005 to 0.18 μg/m^3 (Hoffman et al. 1969; Pötzl 1970; Sorenson et al. 1974). In rural areas of Hawaii, aluminum concentrations have been measured at a range of 0.005–0.032 μg/m^3 (Hoffman et al. 1969), whereas a concentration range of 0.27–0.39 μg/m^3 has been reported in Manitoba National Park in Canada (AEC 1971). Atmospheric aluminum concentrations in U.S. cities and industrial areas are considerably higher, ranging from about 0.4 to 8.0 μg/m^3 (Cooper et al. 1979; Dzubay 1980; Kowalczyk et al. 1982; Lewis and Macias 1980; Moyers et al. 1977; Ondov et al. 1982; Pillay and Thomas 1971; Sorenson et al. 1974; Stevens et al. 1978). The range of the concentration of aluminum in fine (<1–2.5 μm) and course (2.5–10 μm) particles from two industrial areas, Southeast Chicago, Illinois and East St. Louis, Illinois were 22–539 ng/m^3 (125 ng/m^3 mean) and 24–1,370 ng/m^3 (153 ng/m^3 mean), respectively, for fine particles and 8.2–1760 ng/m^3 (390 ng/m^3 mean) and 17–2,120 ng/m^3 (442 ng/m^3 mean), respectively, for coarse particles. At a rural site (Bondville, Illinois), the aluminum concentrations in fine and coarse particles ranged from 32 to 293 ng/m^3 (95 ng/m^3 mean) and from 32 to 3,120 ng/m^3 (338 ng/m^3 mean), respectively which was not much different than the aluminum concentration from the industrial sites (Sweet et al. 1993). A mean aluminum concentration of 474.6 ng/m^3 (range 38.4–2,619.6 ng/m^3) was reported in particulate matter collected in air from downtown Rio de Janeiro, Brazil; samples were collected during the period from September 2001 to August 2002 (Quiterio et al. 2004). Mean aluminum concentrations in winter and summer indoor air sampled in 1999 were 41 and 39 ng/m^3 in the homes of 46 high school students from West Central Harlem, New York City who participated in the Toxic Exposure Assessment a Columbia/Harvard (TEACH) study (Kinney et al. 2002). Aluminum concentrations can also vary with

seasonal meteorological conditions. For example, in Mackinac Island, Michigan, summer concentrations averaged about 0.25 μg/m^3, while winter concentrations were only about 0.18 μg/m^3 (AEC 1971).

6.4.2 Water

The concentrations of dissolved aluminum in water vary with pH and the humic-derived acid content of the water (Brusewitz 1984). Aluminum is only sparingly soluble in water between pH 6 and 8. Because the pH of about 95% of naturally-occurring water is between 6 and 9 and since high aluminum concentrations occur in surface water bodies only when the pH is <5, the aluminum concentration in most natural waters is extremely low (Filipek et al. 1987; Snoeyink and Jenkins 1980; Sorenson et al. 1974). In general, aluminum concentrations in surface waters at pH levels above 5.5 will be <0.1 mg/L (Brusewitz 1984; Miller et al. 1984a; Sorenson et al. 1974; Taylor and Symons 1984). However, even at neutral pH levels, higher aluminum concentrations have been found in lakes with a high humic acid content (Brusewitz 1984). Aluminum concentrations in marinewaters tend to be much lower (i.e., <0.001 mg/L) than those found in freshwater lakes and streams (Brusewitz 1984), probably because of increased alkalinity in marinewater compared to fresh water.

At lower pH levels, the aluminum content significantly increases because of increased solubility of aluminum oxide and salts in acidic solutions. For example, aluminum has been found at concentrations of up to 90 mg/L in tributaries that drain mines containing massive sulfide deposits (Filipek et al. 1987). In heavily contaminated surface waters in a mining region rich in sulfides, the water was highly acidic (pH <3.5) and the levels of soluble aluminum were >2 mmol/L (50 mg/L) (Alvarez et al. 1993). Similarly, surface water samples contaminated with acidic mine drainage collected at seven different locations in the vicinity of abandoned coal mines in west-central Indiana had aluminum concentrations of 6.0–269 mg/L (Allen et al. 1996). The pH ranged from 2.1 to 3.4 at these sites.

Aluminum was detected at dissolved aluminum concentrations ranging from 0.001 to 2.760 mg/L with a mean concentration of 0.074 mg/L in 456 of 1,577 raw surface water samples collected during a 5-year survey at various locations across the United States (DOI 1970). Dissolved aluminum concentrations were detected in about 48% of the 380 finished drinking waters sampled and ranged from 0.003 to 1.6 mg/L with a mean of 0.179 mg/L (DOI 1970). In another survey of 186 community water systems, median aluminum concentrations for all finished drinking water samples ranged from 0.026 to 0.161 mg/L (Miller et al. 1984a). These authors further reported that the median aluminum concentration in finished water that received no coagulation treatment was 0.043 mg/L (range, 0.016–1.167 mg/L)

compared to the median of 0.112 mg/L (range, 0.014–2.670 mg/L) in finished water receiving alum (aluminum sulfate) coagulation treatment. In the supplies in which no coagulant was used during treatment, 29% of supplies using surface water as their source had aluminum concentrations exceeding 0.05 mg/L, whereas only 4% of supplies using groundwater sources exceeded this level. When aluminum coagulants were used, 69% of all supplies had residual aluminum concentrations >0.05 mg/L (Miller et al. 1984a). In another study, the aluminum content in treated water at facilities using alum coagulation treatment of raw waters ranged from about 0.01 to 1.3 mg/L with a mean of about 0.157 mg/L (Letterman and Driscoll 1988). Tap water samples were collected in 1998 in the service area of East Houston, Texas water purification plant; 44% of these samples had aluminum concentrations >0.2 mg/L. Aluminum concentrations as high as 0.53 mg/L were observed in samples collected near the treatment plant that used an alum coagulant. An average decrease of 7 μg/L/km was observed along the distribution system (Cech and Montera 2000).

Schenk et al. (1989) measured aluminum concentrations in drinking water collected primarily in the western and central parts of the United States from outlets from which water was consumed rather than from the original water treatment plant. Aluminum concentrations in drinking water in various regions of the United States are listed in Table 6-3. Although aluminum concentrations in drinking water may range from undetectable to 1.029 mg/L, aluminum concentrations in most drinking water in the United States were generally <0.1 mg/L (Schenk et al. 1989). While several water sources in the west coast states (California, Oregon, and Washington) were found to contain undetectable concentrations of aluminum (<0.001 mg/L), several cities in other geographic areas of the United States had high aluminum concentrations (>0.4 mg/L). These included Peoria, Illinois (0.467 mg/L); Coos Bay, Oregon (0.483 mg/L); Watertown, South Dakota (0.502 mg/L); Waco, Texas (0.520 mg/L); Yellowstone National Park, Wyoming (0.608 mg/L); Philadelphia, Pennsylvania (0.688 mg/L); and Charleston, South Carolina (1.029 mg/L).

Henshaw et al. (1993) studied concentrations of various components, including aluminum, in drinking water derived from the Great Lakes in six communities in the United States and Ontario, Canada. Alum was used as a coagulant in all six communities. It was found that aluminum concentrations were generally higher in treated waters as compared to raw water. Between 1986 and 1990, mean aluminum concentrations in raw water were 0.020–0.053, 0.058–0.070, 0.012–0.023, 0.020–0.037, and 0.058–0.476 mg/L in Milwaukee, Wisconsin; Rochester, New York; Thunder Bay, Ontario; Toronto, Ontario; and Windsor, Ontario, respectively. Between 1986 and 1990, mean aluminum concentrations in treated water were 0.085–0.200, 0.070–0.115, 0.027–0.032, 0.080–0.139, and 0.113–0.727 mg/L in Gary,

Table 6-3. Aluminum Concentrations Detected in Drinking Water in Various Regions of the United States

U.S. States	Aluminum concentration (µg/L)[a]
California	0–274
Colorado	42–166
Hawaii	12–124
Idaho	28–63
Illinois	3–467
Indiana	1–137
Kansas	12–245
Kentucky	9–400
Louisiana	12–210
Michigan	6–123
Minnesota	24–93
Missouri	2–368
Montana	11–98
New York[b]	254–299
Nevada	5–126
Ohio	2–245
Oregon	0–483
Pennsylvania[c]	688
South Carolina	2–1,029
South Dakota	2–502
Tennessee[d]	45
Texas	1–520
Utah	19–51
Washington	0–118
Wisconsin	12–118
Wyoming	16–608

[a]Range in values reported for each state
[b]Water sampled in New York City only
[c]Water sampled in Philadelphia only (one sample)
[d]Water sampled in Memphis only (one sample)

Source: Schenk et al. 1989

Indiana; Rochester, New York; Thunder Bay, Ontario; Toronto, Ontario; and Windsor, Ontario, respectively. Data for raw water in Gary, Indiana and treated water in Milwaukee, Wisconsin were not provided (Henshaw et al. 1993). Aluminum concentrations in 172 samples of bottled water sold in Canada ranged from <0.010 to 0.568 μg/g (<0.010–0.567 mg/L), with a mean of 0.027 μg/g (0.027 mg/L) (Dabeka et al. 1992). Drinking water from 35 cities and villages in Galicia, northwest Spain were analyzed for dissolved aluminum during 1997 to 2003; an average aluminum concentration of 0.126 mg/L was reported, with concentrations ranging from 0.008 to 0.650 mg/L (Rubinos et al. 2007).

Aluminum has been measured in atmospheric precipitation (i.e., rain and snow) in the United States at concentrations up to 1.2 mg/L (Dantzman and Breland 1970; DOI 1971; Fisher et al. 1968; USGS 1964). Aluminum has been measured in rainwater samples collected during the Global Change Expedition in the North Atlantic Ocean (Lim and Jickells 1990). These authors reported that comparisons between acid-leachable and total (dissolved plus particulate) trace aluminum concentrations suggest that the acid-leachable fraction of aluminum can significantly underestimate total concentrations of aluminum in rainwater. Acid-leached mean concentrations of aluminum in rainwater collected during three rainfall events in the North Atlantic were 33.7, 12.2, and 1.99 μg/L. Overall, the acid-leached concentrations of aluminum in rainwater for seven rainfall events ranged from 1.14 to 35.2 μg/L. These values were compared with acid-leachable aluminum concentrations in precipitation from remote areas which ranged from 2.1 to 15.44 μg/L. Total (dissolved plus particulate) aluminum concentrations in North Atlantic precipitation samples collected in 1988 ranged from 6.1 to 827 μg/L (Lim and Jickells 1990).

Aluminum concentrations in groundwater wells at neutral pH generally fall below 0.1 mg/L (Brusewitz 1984). In areas receiving acid precipitation, aluminum concentrations in groundwater may be >10 times the concentrations found in areas with neutral pH levels in the water (Brusewitz 1984), possibly due to precipitation of aluminum compounds in the more alkaline medium, or the reaction of aluminum with available silicates. In another study, Miller et al. (1984a) reported that the median concentration of aluminum in finished water obtained from groundwater was 0.031 mg/L (range, 0.014–0.290 mg/L) as compared to the median concentration in surface water of 0.043 mg/L (range, 0.016–1.167 mg/L). These authors also reported that, while 55% of the raw surface waters sampled contained aluminum concentrations >0.05 mg/L, only 4% of the raw groundwater samples contained aluminum concentrations >0.05 mg/L.

6.4.3 Sediment and Soil

Aluminum is the most abundant metal and the third most abundant element in the earth's crust, comprising about 8.8% by weight (88 g/kg) (Staley and Haupin 1992). Its concentration in soils varies widely, ranging from about 0.07% by weight (0.7 g/kg) to over 10% by weight (100 g/kg) (Sorenson et al. 1974; USGS 1984c). Varying concentrations are found in different soil samples taken from the same area and in areas with different vegetation types (Brusewitz 1984; Sorenson et al. 1974). In Hawaii, aluminum contents were much higher with concentrations ranging from 79 to 317 g/kg (Moomaw et al. 1959). Soils in Florida and parts of Georgia, Texas, Oklahoma, and Michigan contain <20 g/kg of soil, whereas soils from portions of the Pacific Northwest, New England, Colorado, and Nevada have concentrations >80 g/kg (Sparling and Lowe 1996). Mean aluminum concentrations in cultivated and uncultivated soil samples collected during a number of field studies were 33 g/kg (range 7–>100 g/kg) for subsurface soils in the eastern United States, 54 g/kg (range 5–>100 g/kg) in subsurface soils in the western United States, and 57 g/kg (range 13–76 g/kg) in surface soils collected in Colorado (Connor and Shacklette 1975). Ma et al. (1997) reported a mean aluminum concentration of 0.730 g/kg (range 0.01–4.300 g/kg) in 40 surface soil samples from Florida. Aluminum concentrations in 1,903 soils samples collected from the United States, as well as the Virgin Islands, Guam, and Puerto Rico, were reported to range from 0.5 to 142 g/kg, with a median value of 46 g/kg (Burt et al. 2003). A median aluminum concentration of 1.8 mg/kg was reported in soils collected form 25 playgrounds located in urban Uppsala, Sweden's fourth largest city (Ljung et al. 2006).

Aluminum concentrations in soil also vary with different vegetation types. For example, aluminum concentrations in the soils of coniferous forests are often higher than in soils of beech forests since coniferous forests tend to have more acid soils (Brusewitz 1984). Alternate views of the data are that the acidic soil produced by conifers can preferentially mobilize aluminum from deeper layers toward surface soil, or that conifers over beech preferentially grow in soils rich in aluminum and it is their metabolic processes which produce more acidic soil.

Concentrations of various elements in 541 streambed-sediment samples collected from 20 study areas in the conterminous United States (1992–1996) were analyzed as part of the National Water-Quality Assessment Program of the U.S. Geological Survey. Aluminum was present in all samples; concentrations ranged from 1.4 to 14% by weight (14–140 g/kg), with a median of 6.4% by weight (64 g/kg) (Rice 1999). Mean aluminum concentrations in sediments collected in 1993 and 1994 from Lake Erie, Lake Ontario, and the Niagara River ranged from 1.339 to 13.823 g/kg dry weight (Lowe and

Day 2002). Mean aluminum concentrations in sediments collected from three lakes in central Texas near a coal-fired power plant were 5.32, 8.16, and 8.64% in the Gibbons Creek Reservoir, Hall Lake, and Yarboro Lake, respectively (Menounou and Presley 2003). A mean aluminum concentration of 56.1 g/kg was reported in sediments form Terra Nova Bay, Antarctica (Giordano et al. 1999).

6.4.4 Other Environmental Media

Aluminum occurs naturally in many edible plants and is added to many processed foods. The concentrations in foods and beverages vary widely, depending upon the food product, the type of processing used, and the geographical areas in which food crops are grown (Brusewitz 1984; Sorenson et al. 1974). In general, the foods highest in aluminum are those that contain aluminum additives (e.g., processed cheese, grain products, and grain-based desserts) (Greger 1992; Pennington 1987; Saiyed and Yokel 2005). Because of the variability of reported concentrations of aluminum in foods, the many new manufactured food products on the market, and the increasing use of aluminum as a packaging material, a wide range of beverages and foods have been analyzed. The aluminum concentrations in a number of beverages, foods, and food products are listed in Table 6-4. Most unprocessed foods, (with the exception of some herbs and tea leaves) typically contain <5 mg/kg aluminum (Greger 1992; MAFF 1999; Pennington 1987; Schenk et al. 1989). Concentrations of aluminum in foods generally ranged from <0.15 mg/kg in eggs, apples, raw cabbage, corn, and potatoes to 695 mg/kg in American cheese (Greger 1992; MAFF 1999; Pennington 1987; Schenk et al. 1989). López et al. (2000) measured aluminum concentrations in 17 different spices and aromatic herbs widely consumed in Spain and in the Mediterranean diet; concentrations ranged from 3.74 to 56.50 mg/kg dry weight in cinnamon and oregano, respectively.

The high aluminum concentrations seen in some processed foods (e.g., processed cheeses, baked goods, and nondairy cream substitutes) are likely to have been introduced into the foods as additives, such as the anti-caking agent, sodium aluminosilicate, which is present in salt, nondairy creamers, and many other powdered materials (Table 6-4) (Saiyed and Yokel 2005; Schenk et al. 1989). The most commonly used food additives containing aluminum are: acidic sodium aluminum phosphate (leavening agent in baked goods); basic sodium aluminum phosphate (emulsifying agent in processed cheese); aluminum sulfates (acidifying agents); bentonite (materials-handling aid); aluminum color additives (lakes) from various food dyes; and aluminum silicates (anti-caking agents) (Greger 1992; Saiyed and Yokel 2005).

Table 6-4. Estimated Aluminum Concentrations of Selected Foods

Foods	Aluminum concentration	Reference
Beverages (mg/L)		
Fruit juices (e.g., orange, reconstituted lemon, peach)	0.043–4.130	Schenk et al. 1989
Soft drinks (e.g., ginger ale, diet cola)	0.103–2.084	Schenk et al. 1989
Alcoholic beverages (e.g., beer, wine, wine coolers, champagne)	0.067–3.20	Schenk et al. 1989
Spirits (e.g., brandy, vodka, whiskey)	0.148–0.635	Schenk et al. 1989
Tea, steeped from tea bags	0.424–2.931	Schenk et al. 1989
Teas (1% extract)	0.378–3.55	Schenk et al. 1989
Herbal teas (1% extract)	0.14–1.065	Schenk et al. 1989
Instant coffee (1% solution)	0.02–0.581	Schenk et al. 1989
Whole coffee (3% extract)	0.235–1.163	Schenk et al. 1989
Beverages	1.3[a]	MAFF 1999
Animal products (mg/kg)		
Beef, cooked[a]	0.2	Greger et al. 1985
Cheese (e.g., Swiss, cheddar, bleu)	3.83–14.1	Schenk et al. 1989
Cheese, (e.g., cottage, cheddar, Swiss)	0.12–19	Pennington 1987
Cheese, American	411–695	Pennington 1987
Cheese, processed	297	Greger et al. 1985
Chicken, with skin, cooked[a]	0.7	Greger et al. 1985
Egg, chicken	0.107	Schenk et al. 1989
Eggs, scrambled	2.865	Schenk et al. 1989
Eggs, cooked[a]	0.1	Greger et al. 1985
Eggs	0.14	MAFF 1999
Fish (cod), cooked[a]	0.4	Greger et al. 1985
Fish, salmon	5.44	Schenk et al. 1989
Fish, herring	0.127	Schenk et al. 1989
Fish	6.1	MAFF 1999
Ham, cooked[a]	1.2	Greger et al. 1985
Meat products	1.9	MAFF 1999
Milk, whole	0.06–2	Pennington 1987
Milk (skim, whole, and powdered)	0.028–7.9	Schenk et al. 1989
Milk	0.07	MAFF 1999
Poultry	0.3	MAFF 1999
Salami	1.12	Pennington 1987
Yoghurt, plain low-fat	1.12	Pennington 1987
Yoghurt, strawberry, sweetened	0.63	Pennington 1987
Fruits (mg/kg)		
Apple, fresh	0.14	Pennington 1987

Table 6-4. Estimated Aluminum Concentrations of Selected Foods

Foods	Aluminum concentration	Reference
Banana, fresh	0.05	Pennington 1987
Grapes, fresh	1.81	Pennington 1987
Peaches, fresh	0.51	Pennington 1987
Raisins, dried	3.08	Pennington 1987
Strawberries, fresh	2.25	Pennington 1987
Fresh fruit	0.29	MAFF 1999
Fruit products	0.82	MAFF 1999
Grains (mg/kg)		
Biscuits, baking powder, refrigerated type	16.3	Pennington 1987
Bread, white	0.351	Schenk et al. 1989
Bread, white	2.33	Pennington 1987
Bread, whole wheat	2.91	Pennington 1987
Bread, pumpernickel	13.2	Schenk et al. 1989
Bread	6.6	MAFF 1999
Cereal (e.g., Post Raisin Bran®, Malt-o-Meal Wheat Cereal®)	0.040–29.33	Schenk et al. 1989
Miscellaneous cereals	5.2	MAFF 1999
Corn chips	1.23	Pennington 1987
Cornbread, homemade	400	Pennington 1987
Muffin, blueberry	128	Pennington 1987
Oatmeal, cooked	0.68	Pennington 1987
Oats	2.21–4.18	Schenk et al. 1989
Rice, cooked[a]	1.7	Greger et al. 1985
Rice, yellow, Rice-a-Roni®	1.97	Schenk et al. 1989
Spaghetti, cooked[a]	0.4	Greger et al. 1985
Vegetables and legumes (mg/kg)		
Asparagus	4.4	Greger et al. 1985
Beans, green, cooked[a]	3.4	Greger et al. 1985
Beans, navy, boiled	2.06	Pennington 1987
Cabbage, raw	0.1	Greger et al. 1985
Cauliflower, cooked[a]	0.2	Greger et al. 1985
Corn, boiled	0.1	Pennington 1987
Cucumber, fresh, pared	0.11	Pennington 1987
Green vegetables	3.1	MAFF 1999
Lettuce	0.6	Greger et al. 1985
Lettuce	0.08	Schenk et al. 1989
Peanut butter	2.0	Greger et al. 1985
Peanut butter, natural	6.29	Schenk et al. 1989
Peas, cooked[a]	1.9	Greger et al. 1985

Table 6-4. Estimated Aluminum Concentrations of Selected Foods

Foods	Aluminum concentration	Reference
Potatoes, unpeeled, boiled[a]	0.1	Greger et al. 1985
Potatoes, unpeeled, baked	2.4	Greger et al. 1985
Potato, red	3.63	Schenk et al. 1989
Potato, sweet	1.01	Schenk et al. 1989
Potatoes	0.9	MAFF 1999
Spinach, cooked[a]	25.2	Greger et al. 1985
Tomatoes, cooked[a]	0.1	Greger et al. 1985
Other vegetables	2.7	MAFF 1999
Canned vegetables	0.97	MAFF 1999
Herbs and spices (mg/kg dry weight)		
Basil	24.80–27.30	López et al. 2000
Cinnamon	18.54–56.50	López et al. 2000
Garlic	13.60–15.25	López et al. 2000
Mustard	30.40–38.56	López et al. 2000
Nutmeg	22.81–24.80	López et al. 2000
Oregano	3.74–40.41	López et al. 2000
Pepper, black	5.79–24.41	López et al. 2000
Thyme	6.35–7.90	López et al. 2000
Other food products (mg/kg)		
Baking powder, commercial (Na Al sulfate containing)	20,000–26,000	Sorenson et al. 1974
Candy, milk chocolate	6.84	Pennington 1987
Chocolate cookie, Oreo®	12.7	Schenk et al. 1989
Cocoa	45	Greger et al. 1985
Nondairy creamer	25.7–94.3	Schenk et al. 1989
Nuts	4.0	MAFF 1999
Oils and fats	1.1	MAFF 1999
Pickles with aluminum additives	39.2[b]	Greger et al. 1985
Pickles	0.126–9.97	Schenk et al. 1989
Salad dressing, Kraft Miracle Whip®	3.7	Schenk et al. 1989
Salt with aluminum additives	164	Greger et al. 1985
Salt	31.3–36.6	Schenk et al. 1989
Soup	0.032–3.6	Schenk et al. 1989
Sugars and preserves	2.7	MAFF 1999

[a]Food not cooked or stored in aluminum pans, trays, or foil.

Commercially available teas contain high concentrations of aluminum; 30–45% of this aluminum may be dissolved into an infusion of tea (Dong et al. 1999). Aluminum concentrations ranging from 0.2 to 9.5 mg/L have been reported in tea (Baxter et al. 1989; Flaten and Odegard 1988; Koch et al. 1989; Schenk et al. 1989; Müller et al. 1998; Pennington 1987; Pennington and Jones 1989; Kralj et al. 2005; Mehra et al. 2007). Fairweather-Tait et al. (1987) reported that approximately one-third of the aluminum in commercially available tea leaves was extracted into the tea (1.0 g tea/100 mL water); aluminum concentrations ranged from 2.7 to 4.9 mg/L in the tea after 5 minutes. Fimreite et al. (1997) reported aluminum concentrations of 4–5 mg/L in tea after 10 minutes. Schenk et al. (1989) reported that herbal teas contain lower concentrations of aluminum than ordinary tea (0.140–1.065 mg/L). Total aluminum concentrations in black, green, and red tea infusions ranging from 0.5 to 4.0 mg/L, with 10–35% of the total aluminum from an anion-exchange column as aluminum citrate. The remaining aluminum, which was strongly retained by the column, likely corresponds to aluminum species bound to penolic compounds. Addition of lemon or milk was found to change the distribution of the aluminum species in the tea infusions (Kralj et al. 2005).

Brewed coffee (3% extract) and instant coffee (1% solution) contain aluminum concentrations of 0.235–1.163 and 0.02–0.581 mg/L, respectively (Schenk et al. 1989). Aluminum concentrations ranging from 0.1 to 0.34 mg/L have been reported in coffee (Koch et al. 1989; Müller et al. 1998). Another report provided aluminum concentration in coffee beans ranging from 11 to 21 mg/kg (Koch et al. 1989). The aluminum content of ground coffee beans has been measured at 51.8 mg/kg (Lione et al. 1984). López et al. (2000) reported aluminum concentrations in coffee ranging from 25.60 to 29.08 mg/kg dry weight. Müller et al. (1998) reported an aluminum concentration of 19 mg/kg dry weight in ground coffee. Lione et al. (1984) estimated that brewing coffee in a new aluminum pot can add from 0.88 mg (immediately after brewing) to 1.18 mg aluminum (after 12-hour storage in the pot and subsequent reheating) to each cup.

Aluminum concentrations in wines and spirits were 0.388–3.2 and 0.148–0.635 mg/L, respectively (Schenk et al. 1989). Lopez et al. (1998) reported mean aluminum concentrations in alcoholic beverages consumed in Spain; concentrations were 94.8–1,682.6, 36.5–795.2, and 15.7–739.6 µg/L in wine, beer, and other alcoholic beverages (cider, brandy, rum, whisky, gin, anisette, and liquor), respectively.

In fiscal years 1985/1986, the FDA conducted a survey of elements in fresh clams and oysters collected from U.S. coastal areas in use for shellfish production (Capar and Yess 1996). The average concentration (wet weight basis) of aluminum found in the four shellfish categories surveyed were: clams (hardshell),

23±23 mg/kg (n=74); clams (softshell), 115±110 mg/kg (n=59); Eastern oyster, 33±26 mg/kg (n=104); and Pacific oyster, 30±28 mg/kg (n=46). Cod and bluefin tuna from the Northwest Atlantic Ocean contained an average of 1 and 0.4 mg/kg of aluminum, respectively, in muscle tissue (Hellou et al. 1992a, 1992b).

Cooking foods in aluminum pots and pans or storing foods in aluminum foil or cans may increase the aluminum content in some foods since aluminum may dissolve when in contact with a salty, acidic, or alkaline food (Abercrombie and Fowler 1997; Greger et al. 1985; King et al. 1981; Muller et al. 1993b; Nagy and Nikdel 1986). Aluminum concentrations in precooked foods (e.g., applesauce, green beans, beef, eggs, ham, pudding, rice, and tomato sauce) ranged from <0.1 to 21.6 mg/kg, while concentrations in the foods after cooking in conditioned aluminum pans and stainless steel pans ranged from 0.24 to 125 mg/kg and from <0.1 to 3.4 mg/kg, respectively (Greger et al. 1985). Acidic foods, such as tomatoes, tomato sauce, and applesauce, especially when cooked for >15 minutes, tended to accumulate more aluminum than other foods (Greger et al. 1985). Greger et al. (1985) also reported that foods cooked in new aluminum cookware had higher aluminum concentrations than foods cooked in old aluminum cookware or aluminum cookware that had been treated to simulate use. In addition, the aluminum concentrations in the foods prepared in any aluminum cookware (old, new, or treated to simulate use) had higher aluminum concentrations than the same foods cooked in stainless steel cookware. A study by Lin et al. (1997) noted that cooking with aluminum utensils may be an important aluminum exposure source for patients with chronic renal disease.

Abercrombie and Fowler (1997) reported in a small sampling of canned drinks stored at 15–20 °C, the aluminum content ranged from <0.1 to 74 mg/kg depending on the product and storage time. This study concluded that there appeared to be little basis for concern about the ingestion of aluminum when the internal protective coating of cans remains intact, the cans are stored properly, and the contents are consumed in a reasonable period of time. Fairweather-Tait et al. (1987) reported mean aluminum concentrations in Coca-Cola® and Pepsi-Cola® of 0.09 and 0.05 µg/g, respectively. Average aluminum concentrations in various beverages purchased in Australia, New Zealand, and Thailand were 0.90 and 0.15 in non-cola soft drinks in aluminum cans and glass bottles, respectively, and 0.66 and 0.24 in cola drinks in aluminum cans and glass bottles, respectively. Aluminum concentrations averaged 0.16 mg/L in beer in either aluminum cans or glass bottles (Duggan et al. 1992). Muller et al. (1993b) reported migration of aluminum from aluminum cans (unlacquered) into Coca-Cola® (pH 2.5) and diet Coca-Cola® (pH 3.0), and that the concentration of aluminum increased as the storage period increased. Concentrations of aluminum ranged from 46 to 170 µg/L in Coca-Cola® (storage for 40–101 days) and

from 14 to 250 µg/L in diet Coca-Cola® (storage for 44–173 days), respectively. Vela et al. (1998) examined the change in aluminum concentration in beer packaged in aluminum cans over time. Two brands of beer stored at 5 °C showed little change in aluminum concentration over 5 months. However, when stored at 23 °C, the concentrations increased from 50.0 to 546.5 µg/L and from 108.0 to 414.0 µg/L for the two brands of beer after 5 months. Joshi et al. (2003) studied the potential for the migration of aluminum into commercial sauces packaged in aluminum pouches. The results of this study indicated that after 45 days at 22 and 50 °C samples showed only minor changes in aluminum content as compared to fresh samples.

Aluminum concentrations of 0.6–3.7 and 0.1–0.4 mg/g were reported in four different types of tobacco and two samples of cannabis, respectively (Exley et al. 2006). Various elements were determined in tobacco used in the manufacture of 12 brands of cigarettes in the United States; aluminum concentrations ranged from 0.699 to 1.2 mg/g (Iskander et al. 1986).

Aluminum compounds are also used extensively in the manufacture of cosmetics (e.g., aluminum hexahydrate in deodorants) and in medical treatments (e.g., aluminum hydroxide in antacids to control gastric hyperacidity or aluminum oxide in dental ceramic implants) (Brusewitz 1984; FDA 2002; NIH 2004; NRC 1982). Many antacids contain 300–600 mg aluminum hydroxide (approximately 104–208 mg of aluminum) per tablet/capsule/5 mL dose (Zhou and Yokel 2005). Lione (1985a) reported aluminum content/dose (single tablet or 5 mL liquid) for antacids, internal analgesics (buffered aspirins), antidiarrheals, and anti-ulcerative drugs. The aluminum content per dose (single tablet or 5 mL liquid) ranged from 35 to 208 mg for antacids, 9–52 mg for buffered aspirins, 36–1,450 mg for antidiarrheal drugs, and 207 mg for an anti-ulcerative drug. Potential daily aluminum dosage ranged from 126 to 5,000 mg for these medications (Lione 1985a). Aluminum hydroxide (1–5%) is found in car polishes and paints and aluminum chlorohydrate (>1–20%) is found in antiperspirants and deodorants (NIH 2004).

Fernandez-Lorenzo et al. (1999) reported mean aluminum concentrations of 225.9 (8–1,149), 69.0 (20–204), and 152.5 (104–201) µg/L in infant formulas, whole cow's milk, and soy milk, respectively, in a study in Spain. Ikem et al. (2002) reported mean aluminum concentrations of 58, 92, and 150 µg/L in milk-based powdered formulas from Nigeria, the United Kingdom, and the United States, respectively. Mean aluminum concentrations of 101 and 460 µg/L were reported for milk-based liquid formulas from the United Kingdom and soy-based powder formulas from the United States, respectively. Daily intakes of aluminum for infants in the United States were estimated to be 97, 573, and 361 µg/day for milk-based powder formulas, soy-based powder formulas, and hypoallergenic powder formulas from the United

States (Ikem et al. 2002). Navarro-Blasco and Alvarez-Galindo (2003) reported aluminum concentrations in soy-based infant formulas from Spain that ranged from 313 to 3,479 µg/L, with a mean of 930 µg/L. Mean aluminum concentrations in other types of Spanish infant formula were 499, 237, 252, 292, 574, 687, and 453 µg/L for preterm formula, non-adapted starter formula, adapted starter formula, follow-up formula, lactose-free formula, hypoallergenic formula, and inform error diet formula, respectively. Aluminum concentrations were determined in infant formulas and food in Turkey (Sipahi et al. 2006). Aluminum concentrations in cereal-, milk-, cereal plus milk-based baby food were reported to be 6.43, 8.02, and 7.43, 3.33 and 13.15 µg/g, respectively. Aluminum concentrations in starches and rice flours, traditionally used in baby foods, were also reported as 3.33 and 13.15 µg/g, respectively (Sipahi et al. 2006).

Older reports on aluminum concentrations in infant formulas are also available; however, it is not known if these values would be necessarily representative of aluminum levels in infant formulas currently on the market and available to consumers. Aluminum concentrations in cow's milk-based infant formulas generally ranged from 4 to 700 µg/L and from 5 to 2,500 µg/L in soy-based infant formulas (Baxter et al. 1989, 1990, 1991; Bloodworth et al. 1991; Simmer et al. 1990). Average aluminum concentrations in infant formula from Canada were 0.129, 0.217, and 0.717 µg/g in ready-to-use, concentrated, and powder milk-based infant formulas, respectively. Aluminum concentrations in Canadian soy-based formulas were 1.98, 1.41, and 9.44 µg/g in ready-to-use, concentrated, and powder milk-based infant formulas, respectively (Dabeka and McKenzie 1990).

The median aluminum level in breast milk collected from 12 Canadian women was reported to be 14 µg/L (range <5–45 µg/L) (Koo et al. 1988). In an Australian study, Weintraub et al. (1986) reported human breast milk concentrations of 30 µg/L. Simmer et al. (1990) reported a mean aluminum concentration of 49 µg/L in breast milk collected from Australian women. Hawkins et al. (1994) reported a mean breast milk aluminum concentrations of 9.2 µg/L collected from 15 nursing mothers in the United Kingdom. In a study of Croatia women, an average aluminum concentration in breast milk was 380 µg/L, with a range of 4 to 2,670 µg/L (Mandić et al. 1995). Fernandez-Lorenzo et al. (1999) reported mean aluminum concentrations of 23.9 µg/L (range 7–42 µg/L) in human milk in a study in Spain. Baxter et al. (1991) reported a mean aluminum concentration of 27 µg/L (range 3–79 µg/L) in a study in the United Kingdom.

Concentrations of aluminum in whole blood and plasma have been reported to range from 0.14 to 6.24 mg/L and from 0.13 to 0.16 mg/L, respectively (Sorenson et al. 1974). Aluminum concentrations in

serum have been reported as 1.46 and 0.24 mg/L, using neutron activation and atomic absorption analysis, respectively (Berlyne et al. 1970). An aluminum concentration in serum of 0.037 mg/L was reported using flameless atomic absorption analysis (Fuchs et al. 1974). Versieck and Cornelis (1980) discussed the possibility of aluminum contamination in blood and plasma samples from some of these early studies. This may question the reliability of aluminum levels reported in some older reports. House (1992) reported a geometric mean aluminum concentration of 0.0267 mg/L in serum and plasma for 71 office employees who were not occupationally exposed to aluminum. Mean plasma or serum aluminum concentrations were reported from various studies ranging from 0.0016 to 0.035 mg/L (House 1992). Drablos et al. (1992) analyzed aluminum serum concentrations in 230 nonexposed workers (controls) and reported a mean aluminum serum concentration of 0.005 mg/L. Nieboer et al. (1995) reviewed 34 studies on aluminum concentrations in serum or plasma, and also reported that aluminum serum concentrations in the general population were typically <0.01 mg/L. In an investigation of workers at an open bauxite mine in Surinam, serum aluminum concentrations of 24 men working in the mine for an average of 24 years were low and not statistically different from controls (de Kom et al. 1997). Razniewska and Trzcinka-Ochocka (2003) reported mean aluminum concentrations of 0.99 and 9.75 μg/L in serum and urine, respectively, in 18 healthy subjects not using medications containing aluminum.

A mean aluminum concentration of 23.21 μg/L (range 5.98–206.93 μg/L) was reported in serum samples collected form 533 female children (6–8 years old) living in Riyadh City, Saudi Arabia (Al-Saleh and Shinwari 1996). Hawkins et al. (1994) reported plasma aluminum concentrations in infants fed various formulas and breast milk. A mean plasma aluminum concentration of 8.6 μg/L was reported in breast fed infants; mean aluminum concentrations in plasma of infants fed various formulas ranged from 9.2 to 15.2 μg/L. Mean aluminum plasma concentrations of 9.9, 8.4, and 13.4 μg/L in breastfed infants at birth, 1 month, and 3 months of age, respectively. Infants on soy-based infant formulas, containing 1,600–1,700 μg/L of aluminum, were reported to have mean aluminum plasma concentrations of 8.2–12.4, 7.6–8.5, and 10.8–12.4 μg/L at birth, 1 month, and 3 months of age, respectively (Litov et al. 1989).

Aluminum concentrations in the urine can serve as an indicator of increased exposure to aluminum because a large proportion of ingested aluminum passes quickly through the body. Drablos et al. (1992) analyzed aluminum urine concentrations in 230 nonexposed workers (controls) and reported a mean aluminum urine level of 0.005 mg/L (range, 0.001–0.037 mg/L). Nieboer et al. (1995) reviewed eight studies on aluminum concentrations in urine and reported that aluminum urine concentrations in healthy individuals typically ranged from 0.0027 to 0.0081 mg/L. In a Finnish study of aluminum in urine from 3,212 occupationally exposed workers, mostly aluminum welders, between 1993 and 1996, the average

annual urinary aluminum level was 1.4 µmol/L (0.038 mg/L) and the range was 1.08–2.04 µmol/L (0.029–0.055 mg/L) (Valkonen and Aitio 1997). The samples, collected as part of a routine occupational health program, were collected after the weekend as a morning specimen. The mean urinary aluminum concentration in 44 nonexposed persons, who did not use antacid preparations, was 0.33 µmol/L (0.0089 mg/L), and the range and standard deviation were 0.07–0.82 µmol/L (0.002–0.022 mg/L) and 0.18 µmol/L (0.0022 mg/L), respectively. The mean serum aluminum concentration of 21 of these nonexposed individuals was 0.06 µmol/L (0.0016 mg/L), and the range and standard deviation were 0.02–0.13 µmol/L (0.0005–0.0035 mg/L) and 0.03 µmol/L (0.0008 mg/L), respectively. Drablos et al. (1992) studied aluminum concentrations in workers at an aluminum fluoride plant. Mean aluminum concentrations in urine were 0.011 mg/L (range, 0.002–0.046 mg/L) for 15 plant workers, 0.032 mg/L (range, 0.006–0.136 mg/L) for 7 foundry workers, and 0.054 mg/L (range, 0.005–0.492 mg/L) for 12 potroom workers as compared to 0.005 mg/L (range, 0.001–0.037 mg/L) for 230 unexposed controls. Mean aluminum concentrations were 5.06 and 3.74 µg/L in blood, and 6.56 and 6.35 µg/L in urine of 103 workers in the optoelectronic industry and 67 controls, respectively (Liao et al. 2004). Pre- and postshift average aluminum concentrations in urine ranging from 0.13 to 0.153 mg/L were reported in welders from the construction industry (Buchta et al. 2005). Aluminum concentrations in human breast tissue and breast tissue fat of 4–437 nmol/g (0.1–12 µg/g) dry weight and 3–192 nmol/g oil (0.08–5.18 µg/g oil), respectively, have been reported (Exley et al. 2007).

Nieboer et al. (1995) reported background concentrations of aluminum in bone of 1–3 µg/g dry weight. Background aluminum concentrations in brain tissues (primarily grey matter) of healthy individuals typically ranges from 1 to 3 µg/g dry weight or <0.5 µg/g wet weight (Nieboer et al. 1995). Markesbery et al. (1984) determined trace element concentrations in various human brain regions in infants through adults. Aluminum concentrations were shown to increase with increasing age. Mean aluminum concentrations in adults were 0.467 µg/g wet weight, as compared to 0.298 µg/g wet weight in infants. Overall aluminum concentrations ranged from ≤0.050 to 3.05 µg/g, with the highest mean aluminum concentrations in the globus pallius (0.893 µg/g) and the lowest in the superior parietal lobule (0.282 µg/g).

Metal concentrations were determined in spermatozoa and seminal plasma from men working in two industrial companies, a refinery and a polyolefin factory, 40 km east of Helsinki, Finland, and from sperm bank donor candidates from Helsinki, Finland in 1994. Aluminum concentrations in the factory employees were 0.93 and 0.54 mg/kg in spermatozoa and seminal plasma, respectively, and were 2.52 and 0.87 mg/kg in spermatozoa and seminal plasma, respectively, in the donor candidates. The

authors attributed the lower concentrations in the factory workers to good quality of occupational protection in the factories. In addition, the factory employees lived in the countryside as compared to the donor candidates, who lived in a more urban area (Hovatta et al. 1998). Mean aluminum concentrations in seminal plasma of 2,200, 1,530, and 270 µg/L were reported in samples collected from men working in smelter, refinery, and chemical industries respectively. A mean concentration of 460 µg/L was reported in hospital workers (control group) (Dawson et al. 2000). Mean aluminum concentrations ranged from 18.0 to 101.0 µg/L in seminal plasma collected from 64 apparently healthy men (21–35 years of age) recruited from the University of Texas (Dawson et al. 1998). A mean aluminum concentration of 15.0 µg/L was reported in sweat collected from the arms of 15 normal, healthy subjects while exercising (Omokhodion and Howard 1994). Sighinolfi et al. (1989) reported aluminum concentration ranging from 25 to 102 µg/L in human saliva.

Aluminum concentrations in hair ranging from 0.1 to 36 µg/g have been reported (Alder et al. 1976; Caroli et al. 1994). Imahori et al. (1979) measured various elements in 202 human hair samples collected from a local population in the Tokyo metropolitan area. Aluminum was detected in 95 and 99 of the male and female hair samples, respectively. Mean aluminum concentrations were 13.7 mg/kg (range <0.24–65.0 mg/kg) and 13.6 mg/kg (<1.93–67.1 mg/kg) in male and female hair samples, respectively. Kobayashi et al. (1989) reported mean hair aluminum concentrations of 3.9 and 6.2 µg/g in patients with senile dementia of Alzheimer type and a control group, respectively. Shore and Wyatt (1983) reported aluminum concentrations of 7.5 and 6.2 ppm (µg/g) in hair from patients with Alzheimer's disease and age-matched (nondemented) controls, respectively. Elemental concentrations were determined in hair from children (6–15 years old) living in environmentally degraded districts of the East Aral Sea region (Kazakhstan and Uzbekistan). Mean aluminum concentrations were 89.5 and 113.6 mg/kg in samples collected from two regions, Kazalinsk and Zhanakorgan, respectively (Chiba et al. 2004). Wilhelm et al. (1989) reported that use of hair analysis as an indicator of systematically incorporated metals may not be reliable, since endogenous metal concentrations in hair may be masked by the uptake of metals, including aluminum, from exogenous sources.

Human albumin solutions and other biological products intended for human use may contain aluminum because aluminum compounds are used in their manufacture or as a result of contamination. In albumin products, aluminum is generally introduced as a contaminant from filters, filter aides, buffer solutions, and anticoagulants, as well as the container itself. The aluminum level in a 5% pooled human albumin solution was 0.507 µg/mL (Progar et al. 1996).

Metal concentrations were measured in two lichen species (*Parmelic conspersa* and *Xanthoria calcicola*) from the island of Vulcano and around Mt. Etna, Sicily. Aluminum concentrations were 14,619 and 17,964 mg/kg dry weight in lichens collected near Mt. Etna and Vulcano, respectively (Varrica et al. 2000).

Mean aluminum concentrations in the soft tissues of zebra mussels (*Dreissena polymorpha*) collected in 1993 and 1994 from Lake Erie, Lake Ontario, and the Niagara River ranged from 232 to 5,030 mg/kg dry weight (Lowe and Day 2002). Whole fish composites were analyzed for various metals as part of a survey of 167 lakes in the northeastern United States as part of the Environmental Monitoring and Assessment Program (1992–1994); a mean aluminum concentration of 8.26 mg/kg wet weight (range 0.26–114.5 mg/kg wet weight) was reported (Yeardley et al. 1998). Aluminum concentrations ranged from 2 to 4 mg/kg dry weight in the livers of various seabirds collected from the northern Pacific Ocean in 1992 (Elliott 2005). Mean aluminum concentrations in the feathers of nestling black-crowned night-herons in the Chesapeake and Delaware Bays ranged from 9.18 to 78.85 mg/kg dry weight (Golden et al. 2003).

An aluminum concentration of 25,948 mg/kg was reported in house dust from residences in Ottawa, Canada (Butte and Heinzow 2002).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Since aluminum is ubiquitous in the environment, the general population will be exposed to aluminum by inhalation of ambient air and the ingestion of food and water. Pennington and Schoen (1995) reported average daily intakes of 8–9 and 7 mg/day for adult men and woman, respectively, based on an FDA Total Diet Study. According to the 1997 total diet study conducted by the Food Standards Agency, the average U.K. population dietary exposure to aluminum was estimated to be 3.4 mg/day (MAFF 1999). Greger (1992) estimated that most adults consume 1–10 mg aluminum per day from natural sources. Biego et al. (1998) reported a daily average intake for aluminum of 4.2 mg in a study in France. Food additives containing aluminum, including preservatives, coloring agents, anticaking agents, and leavening agents are major dietary sources of aluminum in the United States (Saiyed and Yokel 2005; Soni et al. 2001).

In a report on FDA's Total Diet Study, the foods highest in aluminum were those suspected of containing aluminum additives (e.g., processed cheese, grain products, and grain-based desserts) (Pennington 1987).

Measured daily dietary intakes of aluminum were reported to range from 2 to 14 mg/day. The major contributors to aluminum in the diet are grain products (24–49%), dairy products (17–36%), desserts (9–26%), and beverages (5–10%) (Pennington 1987). FDA revised their Total Diet Study in 1991 to reflect current food consumption patterns and to include additional sex-age groups (Pennington and Schoen 1995). Dietary intakes ranged from 0.7 mg/day for infants to 11.5 mg/day for 14–16-year-old males. The aluminum intake of adult males ranged from 8 to 9 mg/day and that for adult females was about 7 mg/day. Dietary intakes for 2-, 6-, and 10-year-old children were 4.6, 6.5, and 6.8 mg/day, respectively. Aluminum intakes per kilogram of body weight were 0.10 mg/kg for infants, 0.35 mg/kg for 2-year-old children, and 0.30 mg/kg for 10-year-old children. The other sex age groups had aluminum intakes of 0.10–0.15 mg/kg, except for 14–16-year-old males who had an aluminum intake of 0.18 mg/kg. Principal sources for aluminum were milk and diary products (36%), fish and crustaceans (29%), cereals (16%), and vegetables (8%).

Saiyed and Yokel (2005) reported the aluminum content in various foods in the United States with aluminum food additives. Cheese from a frozen pizza was reported to contain up to 14 mg of aluminum from basic sodium aluminum phosphate. An equivalent amount of cheese from a ready-to-eat restaurant pizza contained 0.03–0.09 mg of aluminum. Up to 1.5 mg of aluminum were found in single serving packets of nondairy creamer containing sodium aluminosilicate. Products such as baking powder, pancake and waffle mixes, and ready-to-eat pancakes contained up to 180 mg of aluminum per serving (Saiyed and Yokel 2005).

Cooking in aluminum containers often results in statistically significant, but not biologically important, increases in the aluminum content of some foods. In one study, increases in the aluminum content of foods after contact with aluminum utensils were <1 mg/kg for 47% of the food examined and <10 mg/kg for 85% of the food examined (Pennington and Schoen 1995). The migration of aluminum from cookware into food will increase with the acidity of the food and the duration of exposure. For example, red current juice was prepared by boiling berries for 3 hours in either an aluminum or stainless steel pot. The aluminum concentrations of the juice prepared in the aluminum pot was 89.1 mg/L, whereas the juice prepared in the stainless steel pot was 1.83 mg/L (Valkonen and Aitio 1997). Aluminum was also shown to migrate into fish baked on aluminum foil. Increases in aluminum concentration ranged from a factor of 2 for saithe fillets baked on aluminum foil without added ingredients (0.10–0.21 mg/kg) to a factor of about 70 for mackerel fillets grilled on aluminum foil with onion rings and mixed spices (0.07–5.04 mg/kg). The migration of aluminum into foods appeared to be dependent on factors such as temperature, duration of cooking, the composition and pH of the food, and the presence of other

substances (e.g., organic acids and salt) (Ranau et al. 2001). A study by Lin et al. (1997) noted that cooking with aluminum utensils may be an important aluminum exposure source for patients with chronic renal disease.

The intake of aluminum in foods is low compared with the amount of aluminum consumed when taking aluminum-containing medication, such as antacids, buffered aspirins, antidiarrheal agents, and certain anti-ulcer drugs at their recommended dosages (Lione 1983, 1985a; Pennington and Schoen 1995; Soni et al. 2001; Zhou and Yokel 2005). Antacids and buffered aspirin, which are often taken in multiple daily doses for prolonged periods, contain 4–562 mg/kg of aluminum (Lione 1983; Schenk et al. 1989; Shore and Wyatt 1983). For example, according to Pennington and Schoen (1995), buffered aspirin may contain 10–20 mg of aluminum per tablet. Many antacids contain 300–600 mg aluminum hydroxide (approximately 104–208 mg of aluminum) per tablet/capsule/5 mL dose (Zhou and Yokel 2005). Other exposures to aluminum can occur through the use of cosmetics and other consumer products containing aluminum compounds (Lewis 2001; NIH 2004; O'Neil et al. 2001).

Pennington and Schoen (1995) reported average daily intakes of 8–9 and 7 mg/day for adult men and woman, respectively, based on an FDA Total Diet Study. According to the 1997 total diet study conducted by the Food Standards Agency, the average U.K. population dietary exposure to aluminum was estimated to be 3.4 mg/day (MAFF 1999). Biego et al. (1998) reported a daily average intake for aluminum of 4.2 mg in a study in France.

Lione (1985a) estimated that 126–728 and 840–5,000 mg were possible daily doses of aluminum consumed in buffered aspirins and antacids products, respectively. These doses are from 6 to almost 40 times and 42–250 times greater, respectively, than aluminum doses obtained from consumption of food. When large oral loads of aluminum (1,000–4,000 mg/day) in the form of antacids are ingested, some of this excess aluminum is absorbed, usually <1% of the intake amount in healthy individuals (Gorsky et al. 1979; Kaehny et al. 1977; Reiber et al. 1995).

Median concentrations of aluminum in drinking water not receiving coagulation treatment and that receiving coagulation treatment have been reported as 0.043 and 0.112 mg/L, respectively (Miller et al. 1984a). If the total dose of aluminum obtained from water is calculated based on an estimated consumption of 1.4 L/day, the amount of aluminum ingested would respectively be 0.06 and 0.16 mg/day or roughly 1% of the 7–9 mg/day for adults from dietary sources.

While the intake of aluminum is mainly through the ingestion of food and drinking water, inhalation of ambient air represents a small contribution to an individual's exposure to aluminum (Browning 1969). Background concentrations of aluminum in the atmosphere generally range from 0.005 to 0.18 μg/m^3 in the United States (Hoffman et al. 1969; Sorenson et al. 1974). If the inhalation rate is taken to be 20 m^3/day, then the total amount of aluminum obtained from inhalation of 0.18 μg/m^3 would be 3.6 μg/day, suggesting that ambient air is not normally a major exposure pathway for aluminum. This is negligible compared with the estimated dietary intake for adults of 7–9 mg/day. However, the aluminum content of air in urban and industrial areas has been reported to be considerable higher, ranging from 0.4 to 8.0 μg/m^3 (Cooper et al. 1979; Dzubay 1980; Kowalczyk et al. 1982; Lewis and Macias 1980; Moyers et al. 1977; Ondov et al. 1982; Pillay and Thomas 1971; Sorenson et al. 1974; Stevens et al. 1978). If the inhalation rate is taken to be 20 m^3/day, then the total amount of aluminum inhaled would range from 8 to 160 μg/day, which is still negligible compared with the aluminum intake from dietary sources. Dusts arising from soil, especially in industrial or agricultural areas (Eisenreich 1980), and from the metal surfaces of air conditioners can contain large amounts of aluminum (Crapper McLachlan 1989), resulting in high localized concentrations and, subsequently, in higher exposures. Typically, however, for the general population, inhalation is likely to be less important as an exposure pathway than is dietary exposure to aluminum, but may represent a source of greater exposure in some urban environments.

Occupational exposure to aluminum occurs not only in the refining of the primary metal, but also in secondary industries that use aluminum products (e.g., aircraft, automotive, and metal products), and aluminum welding (Nieboer et al. 1995). Three major steps are involved in primary aluminum production. Aluminum is first extracted with caustic soda from bauxite ore, precipitated as aluminum hydroxide, and subsequently converted to aluminum oxide in a calcination process. In the second step, the oxide is dissolved in molten cryolite (Na_3AlF_6) and electrolyzed to yield the pure molten metal. The electrolytic cells are called pots and the work area is called the potroom. Casting is the final step in the process where molten aluminum is poured into ingots in the foundry. Exposure is primarily to aluminum hydroxide and oxide in the initial extraction and purification process, to aluminum oxide and aluminum fluoride in the potroom (as well as to tar-pitch volatiles including PAHs), and to partially oxidized aluminum metal fumes in the foundry (Drablos et al. 1992; IARC 1984; Nieboer et al. 1995).

Most of the studies of occupational exposure (aluminum refining and metal industry workers) to aluminum have dealt with inhalation of aluminum-containing dust particles. Rarely is a worker exposed solely to aluminum-containing dust; exposure to mixtures of aluminum with fine respirable particles or other toxic chemicals is more prevalent. For example, it had been observed that the incidence of bladder

cancer was unusually high among aluminum reduction workers. An epidemiological study showed that volatile PAHs in coal tar pitch, however, were the actual causative agents (Theriault et al. 1984a). Synergism among metal dusts, fine particles, toxic chemicals including PAHs, and cigarette smoke is a highly plausible cause of skin irritation and cancers appearing in workers for many industrial processes involving aluminum.

According to the National Occupational Exposure Study (NOES) conducted by NIOSH from 1981 to 1983, the industries with the largest numbers of workers potentially exposed to aluminum and aluminum compounds include: plumbing, heating, and air conditioning; masonry and other stonework; electrical work; machinery except electrical; certified air transportation equipment; electrical components; fabricated wire products; general medical and surgical hospitals; industrial buildings and warehouses; and special dies, tools, jigs, and fixtures (NIOSH 1991).

A group of 44 aluminum welders in the train body and truck trailer construction industry were monitored for aluminum exposure (Buchta et al. 2005). Median aluminum concentrations of 5.6 mg/m^3 (range: 0–31.5 mg/m^3) and 4.5 mg/m^3 (range: 1.3–15.6 mg/m^3) in respirable dust in air were reported in welding fumes in 1999 and 2001, respectively. Median aluminum concentrations in aluminum welders were 152.7 µg/L (range: 2.9–656.3 µg/L) and 145.5 µg/L (range: 5.0–656.3 µg/L) in urine in pre- and post-shift samples in 2001, respectively. Median aluminum concentrations in aluminum welders were 10.6 µg/L (range: 3.3–40.3 µg/L) and 14.3 µg/L (range: 3.8–51.0 µg/L) in plasma in pre- and post-shift samples in 2001, respectively (Buchta et al. 2005).

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).

As with adults, exposures of children to aluminum from breathing air, drinking water, and eating food is generally low. As aluminum is part of the natural environment and found widely in soils, rocks, and foods, exposure to low levels of aluminum is unavoidable. Children are likely to ingest dirt from their unwashed hands or when playing with soils and may be exposed to aluminum in this manner. Children living in proximity to hazardous waste sites or industries that release aluminum to the environment may be exposed to higher levels of aluminum than are found in the natural environment via ingestion of aluminum contained in soil, or via inhalation of aluminum from soil that is entrained in air. While aluminum contained in dirt may be in many forms, some of these forms may be embedded in minerals not bioavailable even in the acid environment of the stomach.

When FDA revised their Total Diet Study in 1991, several sex-age groups relating to children were included (Pennington and Schoen 1995). Average dietary intakes of aluminum in children are shown in Table 6-5. Dietary intakes of aluminum for children ranged from 0.7 mg/day for infants to 11.5 mg/day for 14–16-year-old males. Aluminum intakes per kilogram of body weight for children ranged from 0.10 mg/kg for infants to 0.35 mg/kg for 2-year-old children. The major sources of aluminum in food by age-sex group are shown in Table 6-6. Processed foods containing aluminum additives such as processed cheese and grain-based products constitute the foods with the largest quantities of aluminum and the largest components of the dietary intake of children. Soy-based formula may contain high quantities of aluminum and infants on such formula would have much higher dietary intakes of aluminum than other infants. Pennington and Schoen (1995) reported that soy-based infant formula was a major contributor to aluminum for infants, contributing 0.161 mg/day.

As with adults, aluminum intake from aluminum-containing medication, such as antacids, buffered aspirins, and antidiarrheal agents would overwhelm ordinary dietary intakes (Pennington and Schoen 1995). Children may be exposed to aluminum from aluminum-containing medications, vaccinations, parenteral feeding, dialysis fluids, and treatment for hyperphosphatemia (Advenier et al. 2003; Andreoli et al. 1984; Baylor et al. 2002; Bougle et al. 1991; Bozynski et al. 1989; Chedid et al. 1991; Goyens and Brasseur 1990; Griswold et al. 1983; Klein et al. 1989; Koo et al. 1986, 1992; Malakoff 2000; Milliner et al. 1987; Moreno et al. 1994; Naylor et al. 1999; Offit and Jew 2003; Randall 1983; Robinson et al. 1987; Salusky et al. 1990; von Stockhausen et al. 1990; Warady et al. 1986). Advenier et al. (2003) reported a mean aluminum concentration of 1.6 μmol/L (0.043 mg/L) in parenteral nutrition solutions, resulting

Table 6-5. Dietary Intakes of Aluminum in Children

	Aluminum intake	
Age-sex group	(mg/day)	(mg/kg)
6–11-Months	0.7	0.10
2-Years	4.6	0.35
6-Years	6.5	0.30
10-Years	6.8	0.11
14–16-Years (females)	7.7	0.15
14–16-Years (males)	11.5	0.18

Source: Pennington and Schoen 1995

Table 6-6. Major Sources of Aluminum in Food by Age-Sex Group

	Aluminum/day	
Foods by age-sex group (Al/day)	mg	Percent of total intake
6–11-month-old infants (0.7 mg)		
Soy-based formula	0.161	23.0
American processed cheese	0.122	17.4
Yellow cake with icing	0.088	12.6
Green beans, strained	0.038	5.4
Pancakes	0.029	4.1
Total	**0.438**	**62.6**
2-year-old children (4.6 mg)		
Cornbread	1.580	34.3
American processed cheese	1.037	22.5
Yellow cake with icing	0.384	8.3
Fish sticks	0.173	5.4
Pancakes	0.113	2.5
Tortillas	0.093	2.0
Muffins	0.093	2.0
Fruit drink from powder	0.079	1.7
Taco/tostada	0.071	1.5
Tea	0.061	1.3
Total	**3.684**	**80.1**
6-year-old children (6.5 mg)		
American processed cheese	1.382	21.3
Yellow cake with icing	1.091	16.8
Pancakes	0.752	11.6
Fish sticks	0.529	8.1
Cornbread	0.450	6.9
Tortillas	0.297	4.6
Taco/tostada	0.209	3.2
Muffins	0.202	3.1
Hamburger	0.104	1.6
Fruit drink from powder	0.105	1.6
Total	**5.121**	**78.8**
10-year-old children (6.8 mg)		
American processed cheese	1.498	22.0
Cornbread	1.105	16.3
Pancakes	0.858	12.6
Tortillas	0.344	5.1
Yellow cake with icing	0.350	5.1
Fish sticks	0.280	4.1
Taco/tostada	0.259	3.8

Table 6-6. Major Sources of Aluminum in Food by Age-Sex Group

	Aluminum/day	
Foods by age-sex group (Al/day)	mg	Percent of total intake
Muffins	0.207	3.0
Chocolate cake with icing	0.141	2.1
Chocolate snack cake	0.144	2.1
Total	**5.186**	**76.3**
14–16-year-old females (7.7 mg)		
American processed cheese	2.139	27.8
Yellow cake with icing	0.906	11.8
Cornbread	0.781	10.1
Taco/tostada	0.682	8.9
Pancakes	0.668	8.7
Tortillas	0.325	4.2
Muffins	0.219	2.8
Cheeseburger	0.183	2.4
Tea	0.159	2.1
Fish sticks	0.125	1.6
Total	**6.187**	**80.4**
14–16-year-old males (11.5 mg)		
Cornbread	4.209	36.6
American processed cheese	1.978	17.2
Pancakes	1.038	9.0
Yellow cake with icing	0.925	8.0
Taco/tostada	0.398	3.5
Tortillas	0.398	3.5
Cheeseburger	0.310	2.7
Tea	0.225	2.0
Hamburger	0.211	1.8
Fish sticks	0.170	1.5
Total	**9.862**	**85.8**

Source: Pennington and Schoen 1995

in a mean aluminum daily intake of 0.08 μmol/kg/day (0.002 mg/kg/day). An upper limit of 0.90 μg/L for aluminum in all large-volume parenteral solutions used in total parenteral nutrition therapy was set by the FDA (Advenier et al. 2003). Aluminum compounds such as aluminum hydroxide, aluminum phosphate, or aluminum sulfate (alum) are commonly used as an adjuvant in many vaccines licensed by the FDA; the amount of aluminum in vaccines is limited to no more than 0.85 mg/dose (Baylor et al. 2002).

Elevated levels of aluminum may be found in the tissues and fluids of children undergoing treatments, such as parenteral feeding or dialysis, or if they are receiving aluminum-containing medications (Advenier et al. 2003; Andreoli 1990; Andreoli et al. 1984; Bougle et al. 1991; Bozynski et al. 1989; Chedid et al. 1991; Goyens and Brasseur 1990; Griswold et al. 1983; Klein et al. 1989; Koo et al. 1986, 1992; Milliner et al. 1987; Moreno et al. 1994; Naylor et al. 1999; Robinson et al. 1987; Roodhooft et al. 1987; Salusky et al. 1986, 1990; von Stockhausen et al. 1990); however, these levels are atypical of the general population.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to individuals who are occupationally exposed to aluminum (see Section 6.5), there are several groups within the general population that have potentially higher exposures (higher than background) than the general population. These populations include members of the general population living in the vicinity of industrial emission sources and hazardous waste sites, individuals with chronic kidney failure requiring long-term hemodialysis treatment, infants fed a formula diet containing high levels of aluminum, and individuals consuming large quantities of antacid formulations for gastric disorders, anti-ulcerative medications, buffered analgesics for arthritis, or antidiarrheal medications. Furthermore, the elderly are at risk because of multiple chronic diseases including ulcers and other gastrointestinal diseases, rheumatoid arthritis, and renal disorders. Aluminum has been detected in virtually all food products (especially plant-derived and processed foods), ambient air, drinking water, and soils. Substantially higher concentrations of aluminum have been detected in localized areas around some industrial and hazardous waste disposal sites.

Individuals living or working in proximity to aluminum production facilities may be exposed to higher concentrations of aluminum in the ambient air than members of the general population. In addition, individuals living in proximity to hazardous waste sites may be exposed to aluminum via ingestion of aluminum contained in soil from their unwashed hands when working or playing with contaminated soils

and sediments. Children in particular are likely to ingest dirt from their unwashed hands, or inhale resuspended dust during near-ground activities. If residential wells are the primary source of drinking water, this may also pose a risk to human health via consumption of contaminated drinking water.

Individuals with chronic renal failure requiring long-term hemodialysis treatment are another group within the general population that may be exposed to greater than background levels of aluminum (Alfrey 1987; Chappuis et al. 1988, 1989; Chedid et al. 1991; Fernández-Martin et al. 1998; Griswold et al. 1983; Lione 1985a; Marumo et al. 1984; Muller et al. 1993b; Salusky et al. 1990; Winterberg et al. 1987). Elevated levels of aluminum may be found in the tissues and fluids of individuals undergoing treatments, such as hemodialysis, or if they are receiving aluminum-containing medications (Chappuis et al. 1988, 1989; Chedid et al. 1991; Griswold et al. 1983; Marumo et al. 1984; Salusky et al. 1990; Tsukamoto et al. 1979; Winterberg et al. 1987); however, these levels are atypical of the general population. Aluminum levels in virtually every body tissue are significantly higher in this group of patients if aluminum is present in the dialysate (Alfrey et al. 1980; Cooke and Gould 1991). In addition, Main and Ward (1992) reported a 10-fold increased serum aluminum concentration in a hemodialysis patient after she was prescribed effervescent analgesic tablets containing citrate. This patient was already taking aluminum hydroxide capsules. Once the effervescent analgesic tablets were discontinued, the patient's serum aluminum levels fell to acceptable levels within 3 weeks. Since citrate appeared to enhanced aluminum absorption, these authors stated that patients with renal failure taking aluminum compounds should not be prescribed citrate-containing preparations. In a study by Fernández-Martin et al. (1998), a decrease in serum aluminum concentrations in patients on hemodialysis over the past 10 years was observed, from 61.8 μg/L in 1988 to 25.7 μg/L in 1996. These reductions have been achieved due to the restriction of the use of oral aluminum hydroxide, as well as to the use of adequate water treatment systems.

The oral intake of aluminum tends to be higher for children than for adults (Greger 1992). Calculations based on the FDA's Total Diet Study suggest that 2-year-old children (13 kg body weight) consumed almost 3 times as much aluminum per kg body weight as adult males (75 kg body weight) or adult females (60 kg body weight), respectively (0.48 versus 0.18 and 0.15 mg aluminum/kg body weight, respectively) (Greger 1992). Infants fed milk-based or soy-based infant formulas can be exposed to higher concentrations of aluminum than infants fed breast milk or cows' milk (see Section 6.4.4). Within this group, the infants believed to be most at risk would be preterm infants with impaired renal function because they would be less able to excrete the absorbed aluminum (Bishop 1992; Greger 1992; Koo et al. 1988, 1992; Weintraub et al. 1986).

As discussed in Section 6.4.4, individuals consuming large quantities of antacid formulations, anti-ulcerative medications, buffered analgesics, or antidiarrheal medications are exposed to higher than background doses of aluminum in their diet. Lione (1985a) estimated that 126–728 and 840–5,000 mg were possible daily doses of aluminum consumed in buffered aspirins for rheumatoid arthritis and antacid products, respectively. These doses are 6–40 and 42–250 times greater, respectively, than aluminum doses obtained from consumption of foods (3.4–9 mg/day) (Biego et al. 1998; MAFF 1999; Pennington and Schoen 1995).

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 aluminum is available. Where adequate information is not available, ATSDR, in conjunction with 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 aluminum.

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 and chemical properties of aluminum and various aluminum-containing compounds are sufficiently well defined to allow an assessment of the environmental fate of these compounds (HSDB 2008; Lewis 2001; Lide 2005; O'Neil et al. 2001). No additional data are needed at this time.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2005, became available in May of 2007. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Because aluminum compounds occur naturally (Browning 1969; Dinman 1983; IARC 1984; NRC 1982) and are widely used in industry, in the manufacture of household products, and in processing, packaging, and preserving food (Browning 1969; Lewis 2001; O'Neil et al. 2001; Stokinger 1981; Venugopal and Luckey 1978), the potential for human exposure to these compounds through ingestion of food and water and inhalation of airborne particulates is substantial. Recent data on production, import/export, and use are available (Lewis 2001; O'Neil et al. 2001; USGS 2007a, 2007c). Information on disposal of aluminum compounds is limited. In the United States, about 3 million metric tons of aluminum was recovered from purchased scrap in 2005 (USGS 2007b, 2007c). TRI data are available for releases of aluminum, as fume or dust and as aluminum oxide (fibrous forms) (TRI05 2007). Additional information on disposal would be useful in assessing the potential for the release of and exposure to aluminum compounds.

Environmental Fate. Aluminum partitions to air, water, soil, and plant material. As an element, aluminum cannot be degraded in the environment; it can undergo various precipitation or ligand exchange reactions in the environment. Its partitioning to various media is determined by the physical and chemical properties of the aluminum compound and the characteristics of the environmental matrix that affects its solubility (Brusewitz 1984; Dahlgren and Ugolini 1989; Filipek et al. 1987; Goenaga and Williams 1988; James and Riha 1989; Litaor 1987; Mulder et al. 1989; Wangen and Jones 1984). Aluminum is transported through the atmosphere primarily as a constituent of soil and other particulate matter (Eisenreich 1980). Transformations are not expected to occur during transport of aluminum through the atmosphere. Aluminum partitions between solid and liquid phases by reacting and complexing with water molecules, anions, and negatively charged functional groups on humic materials and clay (Bodek et al. 1988). Information on the environmental fate of aluminum is sufficient to permit a general understanding of transport and transformation in all environmental media. No additional information is needed at this time.

Bioavailability from Environmental Media. Aluminum compounds are deposited in the lungs following inhalation (Christie et al. 1963; Steinhagen et al. 1978; Stone et al. 1979; Thomson et al. 1986) and are poorly absorbed following ingestion (Hohl et al. 1994; Priest et al. 1998; Stauber et al. 1999; Steinhausen et al. 2004). A fractional absorption of 1.5–2% was estimated based on the relationship between urinary aluminum excretion and the airborne soluble aluminum to which workers were exposed (Yokel and McNamara 2001). Very limited information is available regarding absorption following dermal contact; however, this pathway of exposure is not expected to be significant. Additional

information on absorption following ingestion of soils contaminated with aluminum compounds and dermal contact would be useful in assessing bioavailability following exposure via these routes, particularly at hazardous waste sites.

Food Chain Bioaccumulation. Little information is available on the uptake of aluminum into food crops. Uptake into root crops is of particular importance, since many plant species concentrate aluminum in their roots (DOE 1984; Kabata-Pendias and Pendias 1984; Vogt et al. 1987). The limited information available on bioconcentration in animals appears to indicate that aluminum is not significantly taken up by livestock (DOE 1984). The fact that in studies dealing with aluminum in food, aluminum is generally present in low concentrations in fruit, vegetables, and meat products that do not contain aluminum additives or have other contact with aluminum (e.g., cooked in aluminum pots) (Greger et al. 1985; MAFF 1999; Pennington 1987; Pennington and Schoen 1995; Schenk et al. 1989; Sorenson et al. 1974), would support a conclusion that aluminum does not bioaccumulate in the food chain. Because of its toxicity to many aquatic species, aluminum does not bioconcentrate appreciably in fish and shellfish and therefore, it would not be a significant component of the diet of animals that feed upon them (Rosseland et al. 1990). Further studies on the uptake of aluminum by plants, especially those grown on acid soils, would be useful in expanding a limited database and characterizing the importance of food chain bioaccumulation of aluminum as a source of exposure for particular population groups.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of aluminum in contaminated media at hazardous waste sites are needed so that the information obtained on levels of aluminum in the environment can be used in combination with the known body burden of aluminum to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Estimates of human exposure to aluminum from food (Biego et al. 1998; Greger 1992; MAFF 1999; Pennington 1987; Pennington and Schoen 1995; Saiyed and Yokel 2005; Schenk et al. 1989; Sorenson et al. 1974), drinking water (Cech and Montera 2000; DOI 1970; Letterman and Driscoll 1988; Miller et al. 1984a; Schenk et al. 1989), and air (Browning 1969; Crapper McLachlan 1989; Sorenson et al. 1974) are available, as are estimates from exposure from antacids, buffered analgesics, antidiarrheal and anti-ulcerative compounds (Lione 1983, 1985a; Schenk et al. 1989; Shore and Wyatt 1983; Zhou and Yokel 2005). Information on the intake of aluminum from vitamins and other dietary supplements is lacking and would be useful in estimating human exposure. Additional information on the occurrence of

aluminum in the atmosphere, surface water, groundwater, and soils surrounding hazardous waste sites would be helpful in updating estimates of human intake.

Exposure Levels in Humans. Measurements of the aluminum content in human tissues, especially in blood (Berlyne et al. 1970; de Kom et al. 1997; Drablos et al. 1992; Fuchs et al. 1974; House 1992; Liao et al. 2004; Nieboer et al. 1995; Razniewska and Trzcinka-Ochocka 2003; Sorenson et al. 1974), urine (Buchta et al. 2005; Drablos et al. 1992; Liao et al. 2004; Nieboer et al. 1995; Razniewska and Trzcinka-Ochocka 2003; Valkonen and Aitio 1997), and breast milk (Baxter et al. 1991; Fernandez-Lorenzo et al. 1999; Hawkins et al. 1994; Koo et al. 1988; Mandić et al. 1995; Simmer et al. 1990; Weintraub et al. 1986), are available. However, Versieck and Cornelis (1980) discussed the possibility of aluminum contamination in blood and plasma samples from some of early studies. This may question the reliability of aluminum levels reported in some older reports.

Measurements of aluminum in other human tissues and fluids, such as bone, brain, saliva, spermatozoa, and seminal fluid are also available (Dawson et al. 1998, 2000; Hovatta et al. 1998; Markesbery et al. 1984; Nieboer et al. 1995; Sighinolfi et al. 1989). However, recent biological monitoring data, particularly for aluminum in blood and urine, are limited. More recent information would be useful in assessing current exposure levels. Additional biological monitoring data for populations surrounding hazardous waste sites would be useful in helping to better characterize human exposure levels.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Measurements of the aluminum content in tissues, blood, and urine of children who have been exposed to aluminum, as well as unexposed children, are limited. Chiba et al. (2004) reported aluminum concentrations in hair of children. Al-Saleh and Shinwari (1996) reported aluminum concentrations in serum samples of girls aged 6–8 years. Hawkins et al. (1994) and Litov et al. (1989) reported plasma aluminum concentrations in infants fed various formulas and breast milk. Studies measuring aluminum concentrations in tissues, blood, and urine of specialized groups of children (e.g., infants with renal failure or on parenteral nutrition) have also been reported (Advenier et al. 2003; Andreoli 1990; Andreoli et al. 1984; Bougle et al. 1991; Bozynski et al. 1989; Chedid et al. 1991; Goyens and Brasseur 1990; Griswold et al. 1983; Klein et al. 1989; Koo et al. 1986, 1992; Milliner et al. 1987; Moreno et al. 1994; Naylor et al. 1999; Robinson et al. 1987; Roodhooft et al. 1987; Salusky et al. 1986, 1990; von Stockhausen et al. 1990).

Additional information monitoring aluminum concentrations in children would be useful in assessing both the normal aluminum content of children and the effect of exposure on aluminum concentrations in children. This information would also be useful in assessing differences in the effect of aluminum exposure on children to that of adults. While the largest source of aluminum exposure in adults is from aluminum-containing medications and cosmetics, we do not know the amount of such products that may be given to children. Additional information on the intake of available aluminum from soil during childhood activities, or the placental transfer to fetal blood, especially among pregnant women taking antacids as a result of abdominal upsets, would be useful in assessing exposure levels in children.

Data are available on the intake of aluminum in food eaten by children and from their diet (Dabeka and McKenzie 1990; Koo et al. 1988; Pennington and Schoen 1995; Pennington 1987; Simmer et al. 1990; Weintraub et al. 1986). Aluminum concentrations in human breast milk, infant formula, and cow's milk have been reported. The aluminum content of human breast milk generally ranged from 9.2 to 49 μg/L, lower than that reported in infant formulas (Fernandez-Lorenzo et al. 1999; Hawkins et al. 1994; Koo et al. 1988; Simmer et al. 1990; Weintraub et al. 1986). Soy-based infant formulas contain higher concentrations of aluminum, as compared to milk-based infant formulas or breast milk. Recent reports provide average aluminum concentrations ranging from 460 to 930 μg/L for soy-based infant formulas and from 58 to 150 μg/L for milk-based formulas (Fernandez-Lorenzo et al. 1999; Ikem et al. 2002; Navarro-Blasco and Alvarez-Galindo 2003). Infant formulas are much higher in aluminum than human breast milk. Daily intakes of aluminum for infants in the United States were estimated to be 97, 573, and 361 μg/day from milk-based powder formulas, soy-based powder formulas, and hypoallergenic powder formulas, respectively (Ikem et al. 2002).

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 aluminum were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries 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 exposure to this substance.

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2006) 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. These studies are summarized in Table 6-7.

Table 6-7. Ongoing Studies on Aluminum

Investigator	Affiliation	Research description	Sponsor
Longnecker, M	Not provided	This research proposes to study elemental concentrations in toenails, which may provide a good measure of exposure for various elements, including aluminum.	NIH
Yokel, RA	University of Kentucky, Lexington, Kentucky	The overall objective of the proposed research is to test the null hypothesis that the bioavailability of aluminum is comparable from foods and from drinking water.	NIH

NIH = National Institutes of Health

Source: FEDRIP 2006

This page is intentionally blank.

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring aluminum, its metabolites, and other biomarkers of exposure and effect to aluminum. 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.

7.1 BIOLOGICAL MATERIALS

Because of the ubiquitous nature of aluminum, contamination is a major problem encountered in the analysis of aluminum by all methods except accelerator mass spectroscopy (AMS) using radioactive ^{26}Al. When using the other methods, all items used during collection, preparation, and assay should be checked for aluminum contribution to the procedure. Only by taking these stringent precautions will one be able to produce accurate results. A variety of analytical methods have been used to measure aluminum levels in biological materials, including AMS, graphite furnace atomic absorption spectrometry (GFAAS), flame atomic absorption spectrometry (FAAS), eletrothermal atomic absorption spectrometry (ETAAS), neutron activation analysis (NAA), inductively coupled plasma-atomic emission spectrometry (ICP-AES), inductively coupled plasma-mass spectrometry (ICP-MS), and laser microprobe mass spectrometry (LAMMA) (Roggli et al. 1999; Maitani et al. 1994; Owen et al. 1994; Razniewska and Trzcinka-Ochocka 2003; Van Landeghem et al. 1994) (see Table 7-1). Front-end separation techniques such as chromatography are frequently coupled with analytical methods.

AMS is a technique that can now be used to accurately determine the atomic content in as little as a few milligrams of biological material. AMS has been used in the past for measuring long-lived radionuclides that occur naturally in our environment, but it is suitable for analyzing the ratio of the concentrations of radioactive ^{26}Al to stable ^{27}Al in biological samples. AMS combines a particle accelerator with ion sources, large magnets, and detectors, and is capable of a detection limit of one atom in 10^{15} (1 part per quadrillion [ppq]). This method has biomedical applications regarding the uptake and distribution of aluminum in the body, but is dependent upon the availability of the radioactive ^{26}Al tracer, which is

Table 7-1. Analytical Methods for Determining Aluminum in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Serum	Direct injection into atomizer	GFAAS	Low µg/L levels	No data	King et al. 1981
Serum	Dilution with water; addition of EDTA	GFAAS	2 µg/L	No data	Alderman and Gitelman 1980
Serum	Centrifugation and injection of supernatant	GFAAS	14.3 µg/L	97–102%	Bettinelli et al. 1985
Serum (Al-organic acid species)	Addition of sodium bicarbonate; direct injection into chromatography column	HPLC/ICP-AES	No data	No data	Maitani et al. 1994
Serum (Al-organic acid species)	Dilution with mobile phase; fractions collected for ETAAS analysis	HPLC/ETAAS	No data	98–100% in spiked and synthetic serum	Wrobel et al. 1995
Serum (Al-organic acid species)	Addition of citrate buffer; direct injection into chromatography column	HPLC/ETAAS	0.12 µg/L	99.2±12.4%	Van Landeghem et al. 1994
Plasma	Dilution	GFAAS	3–39 µg/L	97–105%	Wawschinek et al. 1982
Whole blood, plasma, or serum	Dilution with water	GFAAS	24 µg/L	No data	Gardiner et al. 1981
Whole blood	Addition of sodium citrate; centrifugation; injection of supernatant	GFAAS	Low µg/L levels	No data	Gorsky and Dietz 1978
Whole blood	Dilution with Triton X-100	GFAAS	1.9 µg/L (serum); 1.8 µg/L (plasma); 2.3 µg/L (whole blood)	No data	Van der Voet et al. 1985
Urine	Digestion; ion-exchange clean-up	NAA	50 µg/L	No data	Blotcky et al. 1976
Urine and blood	Dilution with water	GFAAS or ICP-AES	Low µg/L levels	No data	Sanz-Medel et al. 1987
Urine and serum	Dilution with 0.2% nitric acid and water	ETAAS	0.6 µg/L (serum and urine)	No data	Razniewska and Trzcinka-Ochocka (2003)
Urine	Direct injection	GFAAS	Low µg/L levels	No data	Gorsky and Dietz 1978
Urine	Direct injection	GFAAS	Low µg/L levels	No data	Gorsky and Dietz 1978

Table 7-1. Analytical Methods for Determining Aluminum in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine and blood	Dilution with water	ICP-AES	1 µg/L (urine); 4 µg/L (blood)	No data	Allain and Mauras 1979
Biological tissues	Homogenization with EDTA	GFAAS	0.002–10.057 µg/g	95–106%	LeGendre and Alfrey 1976
Biological tissues	Freeze-drying; grinding for homogenization	NAA	8 µg/g	No recovery; RSD <10%	Wood et al. 1990
Biological tissues	Drying; nitric acid digestion; dilution with water	GFAAS	0.5 µg/g	80–117%	Bouman et al. 1986
Biological tissues	Mounting of paraffin sections of formalin fixed tissue on carbon discs; deparaffin sample	SEM/EDXA	0.1% by weight in a detected particle	NA	Abraham and Burnett 1985
Kidney, liver, urine	Acid digestion; dilution with water	ICP-AES	No data	98.8±8.6% in liver	Maitani et al. 1994
Kidney, liver, femur	Microwave nitric acid digestion; addition of internal standard, dilution with eluent	SEC/ICP-MS	0.04 µg/g	100±14% of spiked Al in reference material	Owen et al. 1994
Brain	Freeze drying; acid digestion; dilution with potassium dichromate matrix modifier	GFAAS	0.03 µ/g	No data	Xu et al. 1992a
Brain	Fixing and embedding in polymer matrix; sectioning and staining to visualize Al deposits; laser vaporization of selected sample surface into mass spectrometer	LAMMA	Low µg/g range	No data	Lovell et al. 1993
Hair	Isopropanol wash; nitric acid digestion; dilution with water	GFAAS	0.65 µg/g	84–105%	Chappuis et al. 1988
Human blood, urine, serum, feces	Acid digestion, Parr bomb technique, microwave, or hot plate method	ICP-AES	1 µg/L	>75%	Que Hee and Boyle 1988
Human milk/infant formula	Homogenization; microwave digestion with boiling nitric acid/hydrogen peroxide	ICP-MS	4.8–11 ng/g	No data	de la Flor St. Remy et al. 2004

Table 7-1. Analytical Methods for Determining Aluminum in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human milk/cow milk/infant formula	Dilution with ultrapure water	ICP-MS	3 µg/L	No data	Martino et al. 2000
All	None	AMS	1 ppq	NA	Flarend and Elmore 1997

AMS = accelerated mass spectroscopy; EDTA = ethylene diamine tetra acetic acid; EDXA = dispersive x-ray analysis; ETAAS = electrothermal atomic absorption spectrometry; GFAAS = graphite furnace atomic absorption spectrometry; HLPC/ICP-AES = high-performance liquid chromatography/ICP-AES; ICP-AES = inductively coupled plasma - atomic emission spectroscopy; ICP-MS = inductively coupled plasma-mass spectrometry; LAMMA = laser ablution microprobe mass spectrometry; NA = not applicable; NAA = neutron activation analysis; ppq = parts per quadrillion; SEC/ICP-MS = size-exclusion chromatography/ICP-AES/mass spectrometry; SEM = scanning electron microscopy

produced using a cyclotron. The first step in the analysis process is the chemical extraction of aluminum (both stable and radioactive) from the biological sample using a method which is free of aluminum contamination. The extractant is loaded into a holder and inserted through a vacuum lock into the ion source, which then employs ion bombardment to ionize the sample atoms. These are removed from the sample using magnets, and are separated by mass and charge by accelerators, bending magnets, and electron stripper screens. An electrostatic analyzer selects particles based on their energy, and a gas ionization detector counts the ions one at a time using a rate of energy loss assessment that distinguishes between any competing isobars. The amount of ^{26}Al can be calculated from the measured ratio of ^{26}Al to ^{27}Al and the amount of carrier added during the chemical preparation of the sample (Elmore and Phillips 1987; Flarend and Elmore 1997).

GFAAS is the most common technique used for the determination of low-ppb (μg/L) levels of aluminum in serum, plasma, whole blood, urine, and biological tissues (Alder et al. 1977; Alderman and Gitelman 1980; Bettinelli et al. 1985; Bouman et al. 1986; Chappuis et al. 1988; Couri et al. 1980; Gardiner and Stoeppler 1987; Gorsky and Dietz 1978; Guillard et al. 1984; Keirsse et al. 1987; Rahman et al. 1985; Savory and Wills 1986; CEC 1984; van der Voet et al. 1985; Wrobel et al. 1995; Xu et al. 1992a). This is because GFAAS offers the best combination of sensitivity, simplicity, and low cost. When used as a detector for high-performance liquid chromatography (HPLC), GFAAS can analyze for species of complexed or bound aluminum which have been separated into fractions on the chromatography column (Van Landeghem et al. 1994).

NAA has been used to determine low levels of aluminum in biological tissues and urine (Blotcky et al. 1976; Savory and Wills 1986; Wood et al. 1990; Yukawa et al. 1980). NAA involves the bombardment of a sample with neutrons, which transforms some of the stable ^{27}Al atoms into several radioactive aluminum isotopes beginning with ^{28}Al, and measurement of the induced radioactivity. Advantages of NAA include good sensitivity and relative independence from matrix (or media) effects and interferences. Moreover, this technique can be used to detect almost all elements of environmental concern in the same sample (Sheldon et al. 1986). One major problem with using NAA with aluminum is the need to correct for interfering reactions with phosphorus and silicon, which produce the same radioisotope (^{28}Al) of aluminum. Other disadvantages of this technique include its high cost, the limited availability of nuclear reactors for NAA analysis, the short 2.25-minute half-life of ^{28}Al that requires prompt analysis of the sample following bombardment with neutrons, and disposal problems of radioactive waste.

The ICP-AES technique, also referred to as ICP-optical emission spectroscopy (ICP-OES), has been reported for the measurement of aluminum in biological materials and is an excellent alternative to

GFAAS for those laboratories possessing the appropriate instrumentation (Allain and Mauras 1979; Lichte et al. 1980; Maitani et al. 1994; Que Hee and Boyle 1988; Que Hee et al. 1988; Sanz-Medel et al. 1987). ICP-AES is a multi-elemental technique that is relatively free of chemical interferences. The matrix problems that can exist in atomic absorption spectrometry (AAS) are minimized in ICP-AES due to the very high excitation temperature of the sample (Savory and Wills 1986). The limits of detection for the ICP-AES method have been reported to be about 1 and 4 μg aluminum/L of urine and blood, respectively (Allain and Mauras 1979). A major problem with using the ICP-AES technique is the intense and broad emission of calcium, which increases the aluminum background and can raise the detection limit for this element (Allain and Mauras 1979; Que Hee and Boyle 1988; Savory and Wills 1986). Titanium also interferes with aluminum analysis (Que Hee and Boyle 1988). Also, the relatively high cost and complexity of this technique can limit its routine use in many laboratories. However, ICP-AES, especially ICP-MS, technologies have advanced recently largely through the efforts of the Department of Energy, and the cost of analysis has declined considerably.

Inductively coupled plasma-mass spectrometry (ICP-MS) is a powerful technique that uses an inductively coupled plasma as an ion source and a mass spectrometer as an ion analyzer. It can measure the presence of >75 elements in a single scan, and can achieve detection limits down to parts per trillion (ppt) levels for many elements—levels that are two or three orders of magnitude lower than those obtained by ICP-AES (Keeler 1991). It is more expensive than ICP-AES and requires more highly skilled technical operation. Aluminum levels in urine and saliva were detected down to 0.02 μg/mL and in blood serum to 0.001 μg/mL using ICP-MS (Ward 1989). Speciation studies have employed ICP-MS as a detector for aluminum in tissue fractions separated by size-exclusion chromatography (SEC) with detection limits of 0.04 μg/g in femur, kidney, and brain (Owen et al. 1994). ICP-MS has been used to determine metal concentrations, including aluminum, in human milk, cow milk, and infant formulas (de la Flor St. Remy et al. 2004; Martino et al. 2000).

LAMMA has been utilized for the analysis of aluminum in brain tissue affected with Alzheimer's disease (Lovell et al. 1993). This analytical technique of nuclear microscopy can simultaneously image and analyze features in unstained and untreated tissue sections, and therefore avoids contamination problems associated with tissue prepared using conventional chemical techniques. Lovell et al. (1993) reported aluminum concentrations in neurofibrillary tangle (NFT)-bearing neurons and in NFT-free neurons in brain tissue from seven autopsy-confirmed Alzheimer's disease patients. LAMMA was also used in a study that did not detect aluminum in pyramidal neurons in brain tissue from Alzheimer's disease patients (Makjanic et al. 1998). However, in tissue that had been subject to conventional procedures such as

fixation and osmication, aluminum was observed in both neurons and surrounding tissue. The method, however, requires rigorous histological sectioning and preparation prior to analysis, specialized analytical equipment, and highly trained personnel.

Secondary ion mass spectrometry (SIMS) is an analytical method that can be used for the imaging of aluminum and other metals in a variety of materials or biological specimins (Goldsmith et al. 1999; Linton and Goldsmith 1992). This technique uses a primary ion beam to generate secondary ions from the specimen, which are analyzed by mass spectrometry. Spatial resolution is reported to be comparable to that attainable with electron microscopy.

Adequate digestion methods are important in the determination of all metals, including aluminum. Que Hee and Boyle (1988) showed that Parr bomb digestions were always superior to hot plate digestions for many elements, including aluminum, in feces, liver, and testes. Microwaving in closed vessels produced lower aluminum recoveries in liver than Parr bomb digestions. The Parr bomb values for citrus leaves were within 5% of the NBS certified values.

Abraham and Burnett (1983) described a method for quantitative analysis of inorganic particulate burden *in situ* in tissue sections using scanning election microscopy (SEM) with backscattered election (BSE) imaging and energy dispersive x-ray analysis (EDXA). This method can compliment bulk tissue analysis since the analyst can observe the association of certain elements within a particle and the particle size. This information can be correlated to cellular or tissue changes with the types, locations, and concentrations of particles within the tissue. In addition, small samples (<1 µg) can be analyzed. EDXA, which is used to identify the chemical composition of the mineral, allows for separation of particulates into two major classes, endogenous and exogenous. Endogenous particles contain calcium or iron in combination with phosphorus as major constituents along with smaller amounts of sodium, magnesium, and potassium. The remaining particles are considered exogenous, and are divided into three major classes: silica, silicates, and metals. This method has been used to identify aluminum particulates in various human tissues, including lung, kidney, brain, and bone (Baxter et al. 1985; Hull and Abraham 2002; Jederlinic et al. 1990; Perl and Brody 1980; Perl et al. 1982).

Razniewska and Trzcinka-Ochocka (2003) reported a method for the determination of aluminum concentrations in blood serum and urine using ETAAS. Serum and urine samples were analyzed directly following dilution with 0.2% nitric acid and water. The detection limit was reported to be 0.6 µg/L for

serum and urine, with a quantification limit of 1.2 µg/L. This method provided reliable aluminum levels at concentrations observed among non-exposed, healthy individuals.

7.2 ENVIRONMENTAL SAMPLES

A number of analytical techniques have been used for measuring aluminum concentrations in environmental samples. These include GFAAS, FAAS, NAA, ICP-AES, ICP-MS, spectrophotometry using absorbance and fluorescence detection, phosphorimetry, chromatography, and gas chromatography equipped with an electron capture detector (GC/ECD) (Andersen 1987, 1988; AOAC 1990; APHA 1998a, 1998b, 1998c, 1998d; Dean 1989; Fernandez de la Campa et al. 1988; EPA 1983a, 1983b, 1994a, 1994b, 1994c, 2000; Fleming and Lindstrom 1987; Gardiner et al. 1987; NIOSH 1994, 2003a, 2003b, 2003c; OSHA 2001, 2002; USGS 1996). They are summarized in Table 7-2.

There are three NIOSH methods (7300, 7301, and 7303) that analyze elements, including aluminum, in air by ICP-AES; these methods differ only in the digestion method. NIOSH method 7013 analyzes aluminum in air using FAAS. In all of these NIOSH methods, particulate from the air is collected over a filter, either a 0.8-µm cellulose ester membrane or a 5.0-µm polyvinyl chloride membrane. The applicable working ranges are 0.5–10 mg/m^3 for a 100-L air sample by Method 7013, 0.005–2.0 mg/m^3 for a 500-L air sample by Methods 7300 and 7301, and up to 100 mg/m^3 in a 500-L sample for Method 7303. The digestion procedures in Method 7013 (nitric acid) will not dissolve alumina (Al_2O_3); lithium borate fusion is needed. The digestion procedure in Method 7300 (nitric/perchloric acid) may not completely solubilize some species of aluminum; alternative producers are cited in the method (NIOSH 1994, 2003a, 2003b, 2003c).

Method ID-121 (OSHA 2002) can be used to determine the amount of aluminum particulates in the workplace atmosphere. Airborne particulates are collected on filters using calibrated sampling pumps and the samples are analyzed using flame atomic absorption or emission spectrometry. This method can also determine aluminum contained in wipe and bulk samples. Method ID-109-SG (OSHA 2001) determines aluminum oxide in workplace atmospheres. In this method sample filters are fused with a flux containing lithium borate, ammonium nitrate, and sodium bromide in platinum crucibles in order to solubilize the aluminum oxide.

Method 990.08 (AOAC 1990) determines metals, including aluminum, in solid wastes (coal fly ash, industrial and electroplating sludges, mine tailings, river sediment, and soils).

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collect sample on MCE filter, followed by digestion by HNO_3	Method 7013 (FAAS)	2 µg/sample	No data	NIOSH 1994
Air	Collect sample on MCE or PVC filter, followed by nitric/perchloric acid ashing	Method 7300 (ICP-AES)	0.115 µg/filter	101.5–105.4% (MCE) 77.4–92.9% (PVC)	NIOSH 2003a
Air	Collect sample on MCE filter, followed by hot block/HCl/HNO_3 digestion	Method 7303 (ICP-AES)	0.111 µg/mL	No data	NIOSH 2003b
Air	Collect sample on MCE or PVC filter, followed by aqua regia ashing	Method 7301 (ICP-AES)	0.115 µg/filter	99.6–208.1% (MCE) -1.9–112.1% (PVC)	NIOSH 2003c
Air	Collect sample on MCE or PVC filter, followed by HNO_3 digestion or extraction with deionized water	Method ID-121 (FAAS or AES)	0.02 µg/mL	94.5% (average)	OSHA 2002
Air (Al_2O_3)	Collect sample on LAPVC filter, followed by fusion with $LiBO_2/NH_4NO_3$/NaBr	Method ID-109-SG (FAAS)	0.5 µg/mL	96% (average)	OSHA 2001
Water	Filter and acidify filtrate with HNO_3 and analyze	Method 3113 B (GFAAS)	3 µg/L	No data	APHA 1998a
Water	Digest sample with HNO_3/HCl and analyze	Method 3120 B (ICP-AES)	40 µg/L	No data	APHA 1998b
Water	Filter and acidify filtrate with HNO_3 and analyze	Method 3125 (ICP-MS)	0.03 µg/L	98.42% (mean)	APHA 1998c
Water	Acidify with H_2SO_4, add ascorbic acid, buffer and dye (Erichrome cyanine R); measure absorbance at 535 nm	Method 3500-Al B (Spectro-photo-meter)	6 µg/L	No data	APHA 1998d
Water, waste water, and solid wastes	For dissolved constituents: filter, acidify filtrate, and analyze; for samples containing solids: digestion with HNO_3/HCl prior to analysis	Method 200.7 (ICP-AES)	45 µg/L	88–113%	EPA 1994a

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water, waste water, sludges, and soils	For dissolved constituents: filter, acidify filtrate, and analyze; for samples containing solids: digestion with HNO_3/HCl prior to analysis	Method 200.8(ICP-MS)	1.0 µg/L (aqueous) 0.4 mg/kg (solids)	100.4% (average)	EPA 1994b
Water, waste water, sludges, and soils	For dissolved constituents: filter, acidify filtrate, and analyze; for samples containing solids: digestion with HNO_3/HCl prior to analysis	Method 200.9 (GFAAS)	7.8 µg/L	97.1–111.7%	EPA 1994c
Water	For dissolved constituents: filter, acidify filtrate, and analyze; for samples containing solids: digestion with HNO_3/HCl prior to analysis	Method 6010C (ICP-AES)	30 µg/L	No data	EPA 2000
Water	Filter, acidify filtrate, and analyze	Method I-1472-95 (ICP-AES)	5 µg/L	86.1–99.9%	USGS 1996
Water and waste water	For dissolved constituents, filter, acidify filtrate, and analyze; for suspended metals digest with HNO_3 and analyze	Method 202.1 (FAAS)	100 µg/L	No data	EPA 1983a
Water and waste water	For dissolved constituents, filter, acidify filtrate, and analyze; for suspended metals digest with HNO_3 and analyze	Method 202.2 (GFAAS)	3 µg/L	No data	EPA 1983b
Solid wastes	Digest sample in HNO_3/H_2O_2 /HCl, dilute with water; remove particulate matter	Method 990.08 (ICP-AES)	45 µg/L	No data	AOAC 1990
Soil	Filter sample and clean-up on chromatography column	GFAAS	No data	No data	Gardiner et al. 1987
Fly ash	Dry sample in vacuum and irradiate	NAA	No data	Not applicable	Fleming and Lindstrom 1987
Plants	Digest sample with nitric acid and analyze	Spectro-photo-meter	7 µg/L	Not applicable	Dean 1989

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Rock, magma, soil, paint, citrus leaves	Acid digest sample using Parr bomb or microwave	ICP-AES	0.001 µg/L	90%	Que Hee and Boyle 1988
Dialysis fluids	Dilute sample with acidic Triton X-100	Phosphor-imetry	3 µg/L	No data	Andersen 1987
Dialysis fluids	Add Ferron and cetyl-trimethylammonium bromide solution to sample and measure phosphorescence at 586 nm	Phosphor-imetry	5.4 µg/L	No data	Fernandez de la Campa et al. 1988
Rock, soil	Digest with acid	AMS	10^{-15} g/g sample	Not applicable	Flarend and Elmore 1997

AMS = accelerated mass spectroscopy; FAAS = flame atomic absorption spectrometry; GC/ED = gas chromatography/electron capture detector; GFAAS : graphite furnace atomic absorption spectrometry; ICP-AES = inductively couples plasma-atomic absorption spectrometry; ICP-MS = inductively couples plasma-mass spectrometry LAPVC = Low Ash Polyvinyl Chloride; MCE = mixed cellulose ester; NAA = neutron activation analysis; PVC = polyvinyl chloride

Method 200.7 (EPA 1994a) provides procedures for determination of metals, including aluminum, in solution in water, wastewater, and solid wastes. Method 200.8 (EPA 1994b) provides procedures for determination of dissolved elements, including aluminum in groundwater, surface water, and drinking water, as well as determination of total recoverable element concentrations in these waters as well as waste waters, sludges and soils samples. Method 200.9 (EPA 1994c) provides procedures for the determination of dissolved and total recoverable elements, including aluminum, by graphite furnace atomic absorption (GFAA) in groundwater, surface water, drinking water, storm runoff, industrial and domestic wastewater, as well as determination of total recoverable elements in sediment, sludges, and soil.

GFAAS and FAAS are the techniques (Methods 202.1 and 202.2) recommended by EPA for measuring low levels of aluminum in water and waste water. Detection limits of 100 and 3 µg of aluminum/L of sample were obtained using the FAAS and GFAAS techniques, respectively (EPA 1983a, 1983b). Spectrophotometry and GC/ECD have also been employed to measure low-ppb (µg/L) levels of aluminum in water (Dean 1989; Ermolenko and Dedkov 1988; Gosink 1975). Flow-injection systems using absorbance (Benson et al. 1990) and fluorescence detection (Carrillo et al. 1992) have been used to monitor aqueous aluminum levels in the field and in the laboratory setting, with detection limits as low as 0.3 µg/L. Ion chromatography using spectrophoto-metric detection and on-line preconcentration gives an effective detection limit <1 µg/L in aqueous samples. GFAAS is the method of choice for measuring low-ppb levels of aluminum in dialysis fluids (Andersen 1987, 1988; Woolfson and Gracey 1988).

The GFAAS and NAA techniques have been employed for measuring aluminum levels in soil and fly ash, respectively (Fleming and Lindstrom 1987; Gardiner et al. 1987). Que Hee and Boyle (1988) employed ICP/AES to measure aluminum in rocks, soils, volcano magma, and print. Aluminum silicate matrices require disruption by hydrofluoric acid/nitric acid digestion in Parr bombs to achieve >90% recoveries of aluminum and other elements in preparation for ICP-AES analysis using wet ashing (Que Hee and Boyle 1988). Aluminum in air particulates and filters has been determined by pressurized digestion and ICP-AES detection (Dreetz and Lund 1992). Microwave digestions in closed polypropylene bottles gave the same concentrations of aluminum for rocks and soils.

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 aluminum is available. Where adequate information is not available, ATSDR, in conjunction with 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 aluminum.

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. GFAAS is the method of choice for measuring low-ppb levels of aluminum in whole blood, serum, plasma, urine, and various biological tissues (Alder et al. 1977; Alderman and Gitelman 1980; Bettinelli et al. 1985; Bouman et al. 1986; Chappuis et al. 1988; Couri et al. 1980; Gardiner and Stoeppler 1987; Gorsky and Dietz 1978; Guillard et al. 1984; Keirsse et al. 1987; Rahman et al. 1985; Savory and Wills 1986; CEC 1984; van der Voet et al. 1985). Chromatographic techniques coupled with GFAAS detection have been used to separate various metal species and determine aluminum content in serum (Maitani et al. 1994; Van Landeghem et al. 1994). The NAA and ICP-AES methods have also been used to measure ppb levels of aluminum in biological tissues and fluids (Blotcky et al. 1976; Savory and Wills 1986; Yukawa et al. 1980). ICP-MS has the requisite sensitivity to detect low-ppb levels of aluminum (Ward 1989) in biological and environmental media though it is more expensive than GFAAS. However, the cost of ICP-MS, as well as ICP-AES, analyses has decreased significantly over the last few years. LAMMA can detect aluminum deposits in specific structures of the brain and might be used to correlate the effects of aluminum accumulation (Lovell et al. 1993).

SEM/EDXA allows for quantitative analysis of inorganic particulate burden *in situ* in tissue sections. This method can compliment bulk tissue analysis since the analyst can observe the association of certain elements within a particle and the particle size. This information can be correlated to cellular or tissue

changes with the types, locations, and concentrations of particles within the tissue (Abraham and Burnett 1983).

Although sensitive analytical methods are available for measuring the presence of aluminum in biological tissues and fluids, it is not known whether data collected using these techniques have been used to correlate the levels of aluminum in biological materials to exposure and effect levels. The problem of contamination during tissue preparation (Makjanic et al. 1998) makes this task more challenging.

Razniewska and Trzcinka-Ochocka (2003) noted that there was a need for a simple and sensitive method for the routine measurement of aluminum concentrations in serum and urine. These authors reported a method measuring aluminum concentrations in serum and urine using ETAAS. This method provided reliable results at concentrations observed among non-exposed, healthy individuals. There is a need for additional methods that can measure aluminum concentrations in blood and urine at low concentrations, approximately 1–10 µg/L.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. FAAS and ICP-AES have been used to measure aluminum in air (Dreetz and Lund 1992; NIOSH 1994, 2003a, 2003b, 2003c; OSHA 2001, 2002). For measuring aluminum in water and waste water, spectrophotometry (Benson et al. 1990; Carrillo et al. 1992; Ermolenko and Dedkov 1988), GC/ECD (Gosink 1975), and FAAS and GFAAS (EPA 1983a, 1983b) have been employed. GFAAS has been used to analyze aluminum in the soil (Gardiner et al. 1987), and GFAAS (Andersen 1987) as well as phosphorimetry (Fernandez de la Campa et al. 1988) have been useful in determining aluminum levels in dialysis fluids. The method used to measure aluminum levels in flyash is NAA (Fleming and Lindstrom 1987). The media of most concern for potential exposure to aluminum are water and dialysis fluids. GFAAS technique is sensitive for measuring background levels of aluminum in water (EPA 1983b) and dialysis fluids (Andersen 1987; Woolfson and Gracey 1988) and levels of aluminum at which health effects might begin to occur. GFAAS and FAAS are the techniques (Methods 202.1 and 202.2) recommended by EPA for detecting aluminum levels in water and waste water (EPA 1983a, 1983b). GFAAS is the method of choice for measuring low-ppb levels of aluminum in dialysis fluids (Andersen 1987; Woolfson and Gracey 1988). ICP-AES has been utilized to detect aluminum in biological media (leaves, feces, serum, blood, liver, spleen, kidney, urine, and testes) and environmental matrices (rocks, soils, water, volcano magma, paint) in addition to other elements (Que Hee and Boyle 1988) and, more recently, ICP-MS has been shown to be useful for even more sensitive analyses of such media. No additional methods for detecting elemental aluminum in environmental media appear to be necessary at

this time. A need exists for developing a range of NIST analytical standards for calibrating instruments and assessing the accuracy and precision of the various analytical methods.

7.3.2 Ongoing Studies

The information in Table 7-3 was found as a result of a search of the Federal Research in Progress database (FEDRIP 2006).

Table 7-3. Ongoing Studies on Aluminum

Investigator	Affiliation	Research description	Sponsor
Mutti, A.	University of Parma, Parma, Italy	The present research project is aimed at applying the most sensitive, selective and specific reference analytical techniques to the study of the composition of exhaled breath condensate in chronic obstructive pulmonary disease patients using ETAAS and ICP-MS.	NIH
Progar, J	Not provided	The goal of the research program is directed toward the development of analytical methodology to determine the quantitative, qualitative, and/or structural identification of inorganic chemical constituents and impurities in drug and biological products through spectrometric means, including FAAS, GFAAS, FES, ICP-AES, and ICP-MS.	NIH
May, JC	Not provided	The research goal is to ensure the safety, purity and potency of vaccines and other biological products through research relating to the development of new or improved accurate, validated, qualitative and/or quantitative methods for the determination and/or characterization of the chemical preservatives, stabilizers, inactivators, adjuvants, residual moisture, protein and other chemical constituents of vaccines and biological products.	NIH

ETAAS = Electro-thermal atomic absorption spectroscopy; FAAS = flame atomic absorption spectrometry; FES = flame emission spectrometry; GFAAS = graphite furnace atomic absorption spectrometry; ; ICP-AES = inductively coupled argon plasma-emission spectrometry ICP-MS = Inductively coupled plasma - mass spectrometry; NIH = National Institutes of Health

Source: FEDRIP 2006

8. REGULATIONS AND ADVISORIES

The international and national regulations and guidelines regarding aluminum and aluminum compounds in air, water, and other media are summarized in Table 8-1.

ATSDR has derived an intermediate-duration oral minimal risk level (MRL) of 1 mg Al/kg/day for aluminum. This MRL is based on a NOAEL of 26 mg Al/kg/day and a LOAEL of 130 mg Al/kg/day for neurodevelopmental effects in the offspring of mice exposed to aluminum lactate in the diet on gestation day 1 through lactation day 21 followed by pup exposure until postnatal day 35 (Golub and Germann 2001). The MRL was derived by dividing the NOAEL by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) and a modifying factor of 0.3 to account for the higher bioavailability of the aluminum lactate used in the principal study, as compared to the bioavailability of aluminum in the human diet and drinking water.

ATSDR has derived a chronic-duration oral MRL of 1 mg Al/kg/day for aluminum. This MRL is based on a LOAEL of 100 mg Al/kg/day for neurological effects in mice exposed to aluminum lactate in the diet during gestation, lactation, and postnatally until 2 years of age (Golub et al. 2000). The MRL was derived by dividing the LOAEL by an uncertainty factor of 300 (3 for the use of a minimal LOAEL, 10 for animal to human extrapolation, and 10 for human variability) and a modifying factor of 0.3 to account for the higher bioavailability of the aluminum lactate used in the principal study, as compared to the bioavailability of aluminum in the human diet and drinking water.

EPA has not derived a reference dose (RfD) or reference concentration (RfC) for aluminum, but has derived an RfD for aluminum phosphide of $4x10^{-4}$ mg/kg/day based on a NOAEL of 0.51 mg/kg of food or 0.025 mg/kg/day (phosphine) converted to 0.043 mg/kg/day of aluminum phosphide for body weight and clinical parameters observed in a rats during a chronic oral study (IRIS 2008).

Table 8-1. Regulations and Guidelines Applicable to Aluminum and Compounds

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification for aluminum production	Group 1[a]	IARC 1987
WHO	Air quality guidelines	No data	WHO 2000
	Drinking water quality guidelines for aluminum[b]	≤0.1 mg/L in large water treatment facilities	WHO 2004
		≤0.2 mg/L in small water treatment facilities	
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA) for aluminum and compounds (as Al)		ACGIH 2005
	Metal dust	10 mg/m^3	
	Pyro powders	5 mg/m^3	
	Soluble salts	2 mg/m^3	
	Alkyls (NOS)	2 mg/m^3	
	TLV (8-hour TWA) for aluminum oxide[c]	10 mg/m^3	
EPA	AEGL-1 for aluminum phosphide[d]	Not recommended due to insufficient data	EPA 2006a
	AEGL-2 for aluminum phosphide[d]		
	10 minutes	4.0 ppm	
	30 minutes	4.0 ppm	
	60 minutes	2.0 ppm	
	4 hours	0.50 ppm	
	8 hours	0.25 ppm	
	AEGL-3 for aluminum phosphide[d]		
	10 minutes	7.2 ppm	
	30 minutes	7.2 ppm	
	60 minutes	3.6 ppm	
	4 hours	0.90 ppm	
	8 hours	0.45 ppm	
	Hazardous air pollutant	No data	EPA 2006c 42 USC 7412

Table 8-1. Regulations and Guidelines Applicable to Aluminum and Compounds

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
NIOSH	REL (10-hour TWA)		NIOSH 2005
	Aluminum	10 mg/m^3 (total dust) 5 mg/m^3 (respirable fraction)	
	Aluminum oxide	15 mg/m^3 (total dust) 5 mg/m^3 (respirable fraction)	
OSHA	PEL (8-hour TWA) for general industry for aluminum metal (as Al) and aluminum oxide	15 mg/m^3 (total dust) 5 mg/m^3 (respirable fraction)	OSHA 2007b 29 CFR 1910.1000
	PEL (8-hour TWA) for shipyard industry for aluminum metal (as Al) and aluminum oxide	15 mg/m^3 (total dust) 5 mg/m^3 (respirable fraction)	OSHA 2007a 29 CFR 1915.1000
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act for aluminum sulfate	Yes	EPA 2006b 40 CFR 116.4
	Drinking water standards and health advisories	0.05–0.2 mg/L	EPA 2006f
	National primary drinking water standards	No data	EPA 2003
	National secondary drinking water standards for aluminum	0.05–0.2 mg/L	EPA 2008 40 CFR 143.3
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act for aluminum sulfate	5,000 pounds	EPA 2006h 40 CFR 117.3
	Water quality criteria for human health for aluminum		EPA 2006e
	Freshwater CMC	750 µg/L	
	Freshwater CCC	87 µg/L	
c. Food			
FDA	Bottled drinking water for aluminum	0.2 mg/L	FDA 2005 21 CFR 165.110
d. Other			
ACGIH	Carcinogenicity classification for aluminum oxide	A4[e]	ACGIH 2005
EPA	Carcinogenicity classification for aluminum phosphide	No data	IRIS 2008
	RfC for aluminum phosphide	No data	
	RfD for aluminum phosphide	$4x10^{-4}$ mg/kg/day	

Table 8-1. Regulations and Guidelines Applicable to Aluminum and Compounds

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Identification and listing of hazardous substances; hazardous waste number for aluminum phosphide	P006	EPA 2006d 40 CFR 261, Appendix VIII
	Pesticide classified as restricted use for aluminum phophide	Yes[f]	EPA 2006g 40 CFR 152.175
	Pesticide exemptions from the requirement of a tolerance		EPA 2006l 40 CFR 180.910
	Aluminum hydroxide (for use as a diluent and carrier)	Yes[g]	
	Aluminum oxide (for use as a diluent)	Yes[g]	
	Aluminum sulfate (for use as a safener adjuvant)	Yes[g]	EPA 2006m 40 CFR 180.920
	Superfund, emergency planning, and community right-to-know		EPA 2006i 40 CFR 302.4
	Designated CERCLA hazardous substance	Yes	
	Reportable quantity		
	Aluminum phosphide	100 pounds	
	Aluminum sulfate	5,000 pounds	
	Effective date of toxic chemical release reporting		EPA 2006k 40 CFR 372.65
	Aluminum (fume or dust)	01/01/87	
	Aluminum oxide (fibrous forms)	01/01/87	
	Aluminum phosphide	01/01/95	
	Extremely hazardous substances and their threshold planning quantities for aluminum phosphide	500 pounds	EPA 2006j 40 CFR 355, Appendix A

Table 8-1. Regulations and Guidelines Applicable to Aluminum and Compounds

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
NTP	Carcinogenicity classification	No data	NTP 2004

[a]Group 1: carcinogenic to humans
[b]Reason for not establishing a guideline value: owing to limitations in the animal data as a model for humans and the uncertainty surrounding the human data, a health-based guideline value cannot be derived; however, practicable levels based on optimization of the coagulation process in drinking-water plants using aluminium-based coagulants are derived: $\leq$0.1 mg/L in large water treatment facilities, and $\leq$0.2 mg/L in small facilities.
[c]TWA: the value is for particulate matter containing no asbestos and <1% crystalline silica.
[d]AEGL-1 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. AEGL-2 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape. AEGL-3 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.
[e]A4: not classifiable as a human carcinogen.
[f]Pesticide classified as restricted use: limited to use by or under the direct supervision of a certified applicator for agricultural crop uses. Criteria influencing restriction includes inhalation hazard to humans.
[g]Pesticide exemptions from the requirement of a tolerance: residues of the following materials are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops or to raw agricultural commodities after harvest.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = Acute Exposure Guideline Level; Al = aluminum; CERCLA = Comprehensive Environmetnal Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; CCC = Criterion Continuous Concentration; CMC = Criteria Maximum Concentration; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NOS = not otherwise specified; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

This page is intentionally blank.

9. REFERENCES

Abbate C, Giorgianni C, Brecciaroli R, et al. 2003. Spirometric function in non-smoking workers exposed to aluminum. Am J Ind Med 44(4):400-404.

Abd-Elghaffar SK, El-Sokkary GH, Sharkawy AA. 2005. Aluminum-induced neurotoxicity and oxidative damage in rabbits: Protective effect of melatonin. Neuro Endocrinol Lett 26(5):609-616.

Abd El-Rahman SS. 2003. Neuropathology of aluminum toxicity in rats (glutamate and GABA impairment). Pharmacol Res 47(3):189-194.

Abercrombie DE, Fowler RC. 1997. Possible aluminum content of canned drinks. Toxicol Ind Health 13(5):649-654.

Abraham JL, Burnett BR. 1983. Quantitative analysis of inorganic particulate burden in situ in tissue sections. Scan Electron Microsc 2:681-696.

Abramson MJ, Wlodarczyk JH, Saunders NA, et al. 1989. Does aluminum smelting cause lung disease? Am Rev Respir Dis 139:1042-1057.

ACGIH. 2005. Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

Adinolfi M. 1985. The development of the human blood-CSF-brain barrier. Dev Med Child Neurol 27:532-537.

Adlercreutz H. 1995. Phytoestrogens: Epidemiology and a possible role in cancer protection. Environ Health Perspect Suppl 103(7):103-112.

Advenier E, Landry C, Colomb V, et al. 2003. Aluminum contamination of parenteral nutrition and aluminum loading in children on long-term parenteral nutrition. J Pediatr Gastroenterol Nutr 36(4):448-453.

AEC. 1971. Sources of trace elements in aerosols - approach to clean air. Argonne, IL: U.S. Atomic Energy Commission. ORA Project 089030. Contract No. AT1111705.

Agarwal SK, Ayyash L, Gourley CS, et al. 1996. Evaluation of the developmental neuroendocrine and reproductive toxicology of aluminum. Food Chem Toxicol 34(1):49-53.

Agency for Toxic Substances and Disease Registry. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles. Atlanta, GA: Agency for Toxic Substances and Disease Registry, Division of Toxicology.

Agency for Toxic Substances and Disease Registry. 1990. Biomarkers of organ damage or dysfunction for the renal, hepatobiliary, and immune systems. Subcommittee on Biomarkers of Organ Damage and Dysfunction. Atlanta, GA: Agency for Toxic Substances and Disease Registry.

---

* Not cited in text

9. REFERENCES

Ahn H-W, Fulton B, Moxon D, et al. 1995. Interactive effects of fluoride and aluminum uptake and accumulation in bones of rabbits administered both agents in their drinking water. J Toxicol Environ Health 44(3):337-350.

Akila R, Stollery BT, Riihimaki V. 1999. Decrements in cognitive performance in metal inert gas welders exposed to aluminum. Occup Environ Med 56(9):632-639.

Akira M. 1995. Uncommon pneumoconioses: CT and pathologic findings. Radiology 197(2):403-409.

Albers PH, Camardese MB. 1993. Effects of acidification on metal accumulation by aquatic plants and invertebrates. 1. Constructed wetlands. Environ Toxicol Chem 12:959-967.

Alder JF, Samuel AJ, West TS. 1976. The single element determination of trace metals in hair by carbon-furnace atomic absorption spectrometry. Anal Chim Acta 87(2):313-321.

Alder JF, Samuel AJ, West TS. 1977. The anatomical and longitudinal variation of trace element concentration in human hair. Anal Chim Acta 92:217-221.

Alderman FR, Gitelman HJ. 1980. Improved electrothermal determination of aluminum in serum by atomic absorption spectroscopy. Clin Chem 26:258-260.

Alfrey AC. 1980. Aluminum metabolism in uremia. Neurotoxicology 1:43-53.

Alfrey AC. 1981. Aluminum and tin. In: Bronner F, Coburn JW, eds. Disorders of mineral metabolism. Vol. 1. Trace minerals. New York, NY: Academic Press, 353-368.

Alfrey AC. 1984. Aluminum intoxication. N Engl J Med 310(17):1113-1115.

Alfrey AC. 1987. Aluminum metabolism and toxicity in uremia. J UOEH 9 Suppl:123-132.

Alfrey AC. 1993. Aluminum toxicity in patients with chronic renal failure. Ther Drug Monit 15(6):593-597.

Alfrey AC, Hegg A, Craswell P. 1980. Metabolism and toxicity of aluminum in renal failure. Am J Clin Nutr 33(7):1509-1516.

Alfrey AC, LeGendre GR, Kaehny WD. 1976. The dialysis encephalopathy syndrome: Possible aluminum intoxication. N Engl J Med 294(4):184-188.

Allain P, Mauras Y. 1979. Determination of aluminum in blood, urine, and water by inductively coupled plasma emission spectrometry. Anal Chem 51(13):2089-2091.

Allen DD, Orvig C, Yokel RA. 1995. Evidence for energy-dependent transport of aluminum out of brain extracellular fluid. Toxicology 98:31-39.

Allen SK, Allen JM, Lucas S. 1996. Dissolved metal concentrations in surface waters from west-central Indiana contaminated with acidic mine drainage. Bull Environ Contam Toxicol 56:240-243.

Al-Masalkhi A, Walton SP. 1994. Pulmonary fibrosis and occupational exposure to aluminum. J Ky Med Assoc 92:59-61.

9. REFERENCES

Al-Saleh I, Shinwari N. 1996. Aluminum in Saudi children. Biometals 9:385-392.

Altman PK, Dittmer DS. 1974. Biological handbooks: Biology data book. Vol. III. 2nd ed. Bethesda, MD: Federation of American Societies for Experimental Biology, 1987-2008, 2041.

Alvarez E, Perez A, Calvo R. 1993. Aluminum speciation in surface waters and soil solutions in areas of sulphide mineralization in Galicia (N.W. Spain). Sci Total Environ 133:17-37.

Amaducci LA, Fratiglioni L, Rocca WA, et al. 1986. Risk factors for clinically diagnosed Alzheimer's disease: A case-control study of an Italian population. Neurology 36(7):922-931.

Anane R, Bonini M, Creppy EE. 1997. Transplacental passage of aluminum from pregnant mice to fetus organs after maternal transcutaneous exposure. Hum Exp Toxicol 16(9):501-504.

Anane R, Bonini M, Grafeille MJ, et al. 1995. Bioaccumulation of water soluble aluminum chloride in the hippocampus after transdermal uptake in mice. Arch Toxicol 69(8):568-571.

Andersen JR. 1987. Graphite furnace atomic absorption spectrometric screening methods for determination of aluminum in hemodialysis concentrates. J Anal Atom Spectrom 2:257-259.

Andersen JR. 1988. Aluminum in peritoneal dialysis fluids as determined by stabilized temperature platform furnace atomic absorption spectrometry. J Pharm Biomed Anal 6(1):29-33.

Andersen ME, Krishnan K. 1994. Relating in vitro to in vivo exposures with physiologically based tissue dosimetry and tissue response models. In: Salem H, ed. Animal test alternatives: Refinement, reduction, replacement. New York: Marcel Dekker, Inc., 9-25.

Andersen ME, Clewell HJ 3rd, Gargas ML, et al. 1987. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. Toxicol Appl Pharmacol 87(2):185-205.

Andreoli SP. 1990. Aluminum levels in children with chronic renal failure who consume low-phosphorus infant formula. J Pediatr 116(2):282-285.

Andreoli SP, Bergstein JM, Sherrard DJ. 1984. Aluminum intoxication from aluminum-containing phosphate binders in children with azotemia not undergoing dialysis. N Engl J Med 310:1079-1084.

*Anthony J, Fadl S, Mason C, et al. 1986. Absorption, deposition and distribution of dietary aluminum in immature rats: Effects of dietary vitamin D3 and food-borne chelating agent. J Environ Sci Health B 21(2):191-205.

AOAC. 1990. Method 990.08: Metals in solid wastes. Inductively coupled plasma atomic emission method. First action 1990. In: Helrich K, ed. Changes in official methods of analysis of the Association of Official Analytical Chemists. First Supplement. Arlington, VA: Association of Official Analytical Chemists, Inc., 14-17, 43.

APHA. 1998a. Method 3113 B: Metals by atomic absorption spectroscopy. In: Clesceri LS, Greenberg AE, Eaton AD, et al., eds. Standard methods for the examination of water and wastewater. Washington, DC: American Public Health Association/American Water Works Association/Water Environment Federation, 3-24 to 3-31.

APHA. 1998b. Method 3120 B: Metals by plasma emission spectroscopy. In: Clesceri LS, Greenberg AE, Eaton AD, et al., eds. Standard methods for the examination of water and wastewater. Washington, DC: American Public Health Association/American Water Works Association/Water Environment Federation, 3-37 to 3-43.

APHA. 1998c. Method 3125: Metals by inductively coupled plasma/mass spectroscopy. In: Clesceri LS, Greenberg AE, Eaton AD, et al., eds. Standard methods for the examination of water and wastewater. Washington, DC: American Public Health Association/American Water Works Association/Water Environment Federation, 3-44 to 3-52.

APHA. 1998d. Method 3500-Al: Aluminum. In: Clesceri LS, Greenberg AE, Eaton AD, et al., eds. Standard methods for the examination of water and wastewater. Washington, DC: American Public Health Association, American Water Works Association, Water Environment Federation, 3-56 to 3-59.

Arieff AI, Cooper JD, Armstrong D, et al. 1979. Dementia, renal failure, and brain aluminum. Ann Intern Med 90(5):741-747.

Banasik A, Lankoff A, Piskulak A, et al. 2005. Aluminum-induced micronuclei and apoptosis in human peripheral-blood lymphocytes treated during different phases of the cell cycle. Environ Toxicol 20(4):402-406.

Banks WA, Kastin AJ, Fasold MB. 1988. Differential effect of aluminum on the blood-brain barrier transport of peptides, technetium and albumin. J Pharmacol Exp Ther 244:579-585.

*Banks WA, Maness LM, Banks MF, et al. 1996. Aluminum-sensitive degradation of amyloid beta-protein-40 by murine and human intracellular enzymes. Neurotoxicol Teratol 81:671-677.

Barnes DG, Dourson M. 1988. Reference dose (RfD) description and use in health risk assessments. Regul Toxicol Pharmacol 8:471-486.

Bast-Pettersen R, Drablos PA, Goffeng LO, et al. 1994. Neuropsychological deficit among elderly workers in aluminum production. Am J Ind Med 25(5):649-662.

Bast-Pettersen R, Skaug V, Ellingsen D, et al. 2000. Neurobehavioral performance in aluminum welders. Am J Ind Med 37(2):184-192.

Baxter MJ, Burrell JA, Crews HM, et al. 1989. Aluminium in infant formulae and tea and leaching during cooking. In: Massey RC, Taylor D, eds. Aluminium in food and the environment: Proceedings of a symposium organised by the Environment and Food Chemistry groups of the Industrial Division of the Royal Society of Chemistry, London, 17th May 1988. Special publication No. 73. London, England: The Royal Society of Chemistry, Thomas Graham House, 77-87.

Baxter MJ, Burrell JA, Crews H, et al. 1991. Aluminum levels in milk and infant formulae. Food Addit Contam 8(5):653-660.

Baxter MJ, Burrell JA, Massey RC. 1990. The aluminium content of infant formula and tea. Food Addit Contam 7(1):101-107.

9. REFERENCES

Baxter DC, Frech W, Lundberg E. 1985. Determination of aluminum in biological materials by constant-temperature graphite furnace atomic-emission spectrometry. Analyst 110:475-482.

Baydar T, Nagymajtenyi L, Isimer A, et al. 2005. Effect of folic acid supplementation on aluminum accumulation in rats. Nutrition 21(3):406-410.

Baylor NW, Egan W, Richman P. 2002. Aluminum salts in vaccines–US perspective. Vaccine 20(Suppl 3):S18-S23.

Bellia JP, Birchall JD, Roberts NB. 1996. The role of silicic acid in the renal excretion of aluminum. Ann Clin Lab Sci 26:227-233.

*Benett RW, Persaud TVN, Moore KL. 1975. Experimental studies on the effects of aluminum on pregnancy and fetal development. Anat Anz 138:365-378.

Benson RL, Worsfold PJ, Sweeting FW. 1990. On-line determination of residual aluminum in potable and treated waters by flow-injection analysis. Anal Chim Acta 238:177-182.

Berger GS. 1994. Epidemiology of endometriosis. In: Berger GS, ed. Endometriosis: Advanced management and surgical techniques. New York, NY: Springer-Verlag, 3-7.

Bergfors E, Bjorkelund C, Trollfors B. 2005. Nineteen cases of persistent pruritic nodules and contact allergy to aluminum after injection of commonly used aluminum-absorbed vaccines. Eur J Pediatr 164(11):691-697.

Berlyne GM, Ben-Ari J, Pest D, et al. 1970. Hyperaluminaemia from aluminum resins in renal failure. Lancet 2(7671):494-496.

Bernuzzi V, Desor D, Lehr PR. 1986. Effects of prenatal aluminum exposure on neuromotor maturation in the rat. Neurobehav Toxicol Teratol 8:115-119.

Bernuzzi V, Desor D, Lehr PR. 1989a. Effects of postnatal aluminum lactate exposure on neuromotor maturation in the rat. Bull Environ Contam Toxicol 42(3):451-455.

Bernuzzi V, Desor D, Lehr PR. 1989b. Developmental alterations in offspring of female rats intoxicated by aluminum chloride or lactate during gestation. Teratology 40(1):21-27.

Bettinelli M, Baroni U, Fontana F, et al. 1985. Evaluation of the L'vov platform and matrix modification for the determination of aluminum in serum. Analyst 110:19-22.

Biego GH, Joyeux M, Hartemann P, et al. 1998. Daily intake of essential minerals and metallic micropollutants form foods in France. Sci Total Environ 217(1-2):27-36.

Bilkei-Gorzo A. 1993. Neurotoxic effect of enteral aluminum. Food Chem Toxicol 31(5):357-361.

Birchall JD, Chappell JS. 1988. The chemistry of aluminum and silicon in relation to Alzheimer's disease. Clin Chem 34:265-267.

Bishop NJ. 1992. Aluminium in infants feeding: Is it a problem? Eur J Clin Nutr 46(Suppl 4):S37-S39.

9. REFERENCES

Bishop NJ, Morley R, Day JP, et al. 1997. Aluminum neurotoxicity in preterm infants receiving intravenous-feeding solutions. N Engl J Med 336:1557-1561.

*Bjertness E, Alexander J, Taylor G, et al. 1992. Aluminum and the causation of Alzheimer's disease: A combined clinical, neuropathological, and trace element study. J Trace Elem Exp Med 5:73.

Bloodworth BC, Hock CT, Boon TO. 1991. Aluminium content in milk powders by inductively-coupled argon plasma-optical emission spectrometry. Food Addit Contam 8(6):749-754.

Blotcky AJ, Hobson D, Leffler JA, et al. 1976. Determination of trace aluminum in urine by neutron activation analysis. Anal Chem 48:1084-1088.

Bodek I, Lyman WJ, Reehl WF, et al., eds. 1988. Aluminum (Al). Environmental inorganic chemistry: Properties, processes, and estimation methods. New York, NY: Pergamon Press, 6.7-1 to 6.7-9.

Böhler-Sommeregger K, Lindemayr H. 1986. Contact sensitivity to aluminum. Contact Dermatitis 15(5):278-281.

*Bolla KI, Briefel G, Spector D, et al. 1992. Neurocognitive effects of aluminum. Arch Neurol 49(10):1021-1026.

Bost TW, Newman LS. 1993. Metal-induced interstitial lung diseases: A clinicopathologic approach. Semin Resp Med 14(3):197-211.

Bougle D, Bureau F, Voirin J, et al. 1991. Aluminum levels in term and premature infants on enteral nutrition. Trace Elem Med 8:172-174.

Bouman AA, Platenkamp AJ, Posma FD. 1986. Determination of aluminum in human tissues by flameless atomic absorption spectroscopy and comparison of references values. Ann Clin Biochem 23(Part 1):97-101.

Bozynski ME, Sedman AB, Naglie RA, et al. 1989. Serial plasma and urinary aluminum levels and tissue loading in preterm twins. JPEN J Parenter Enteral Nutr 13(4):428-431.

Broe GA, Henderson AS, Creasey H, et al. 1990. A case-control study of Alzheimer's disease in Australia. Neurology 40(11):1698-1707.

Brooks AW, White KN, Bailey SE. 1992. Accumulation and excretion of aluminium and iron by the terrestrial snail Helix aspersa. Comp Biochem Physiol 103C:577-583.

Browning E. 1969. Aluminum. In: Browning E, ed. Toxicity of industrial metals. New York, NY: Appleton-Century-Crofts, 3-22.

Brumbaugh WG, Kane DA. 1985. Variability of aluminum in organs and whole bodies of smallmouth bass (Micropterus dolomieui). Environ Sci Technol 19:828-831.

Brusewitz S. 1984. Aluminum. Vol. 203. Stockholm, Sweden: University of Stockholm, Institute of Theoretical Physics.

9. REFERENCES

Buchta M, Kiesswetter E, Otto A, et al. 2003. Longitudinal study examining the neurotoxicity of occupational exposure to aluminum-containing welding fumes. Int Arch Occup Environ Health 76(7):539-548.

Buchta M, Kiesswetter E, Schaper M, et al. 2005. Neurotoxicity of exposures to aluminium welding fumes in the truck trailer construction industry. Environ Toxicol Pharmacol 19(3):677-685.

Buckler DR, Cleveland L, Little EE, et al. 1995. Survival, sublethal responses, and tissue residues of Atlantic salmon exposed to acidic pH and aluminum. Aquat Toxicol 31:203-216.

Buergel PM, Soltero RA. 1983. The distribution and accumulation of aluminum in rainbow trout following a whole-lake alum treatment. J Freshwater Ecol 2(1):37-44.

Burge PS, Scott JA, McCoach J. 2000. Occupational asthma caused by aluminum. Allergy 55(8):779-780.

*Burgess E. 1991. Aluminum toxicity from oral sucralfate therapy. Nephron 59(3):523-524.

*Burnatowska-Hledin MA, Doyle TM, Eadie MJ, et al. 1986. 1, 25-Dihydroxy-vitamin D3 increase serum and tissue accumulation of aluminum in rats. J Lab Clin Med 108(2):96-102.

Burt R, Wilson MA, Mays MD, et al. 2003. Major and trace elements of selected pedons in the USA. J Environ Qual 32(6):2109-2121.

Butte W, Heinzow B. 2002. Pollutants in house dust as indicators of indoor contamination. Rev Environ Contam Toxicol 175:1-46.

Cai HR, Cao M, Meng FQ, et al. 2007. Pulmonary sarcooid-like granulomatosis induced by aluminum dust: Report of a case and literature review. Chin Med J 120(17):1556-1560.

Campbell PGC, Hansen HJ, Dubreuil B, et al. 1992. Geochemistry of Quebec north shore salmon rivers during snowmelt: Organic acid pulse and aluminum mobilization. Can J Fish Aquat Sci 49:1938-1952.

*Candy JM, Mountfort SA, McArthur FK, et al. 1991. Aluminum accumulation and senile plaque formation in the brains. Neurotoxicology 12:123.

Cann CE, Prussin SG, Gordan GS. 1979. Aluminum uptake by the parathyroid glands. J Clin Endocrinol Metab 49(4):543-545.

Capar SG, Yess NJ. 1996. U.S. Food and Drug Administration survey of cadmium, lead and other elements in clams and oysters. Food Addit Contam 13:553-560.

Carmichael KA, Fallon MD, Dalinka M, et al. 1984. Osteomalacia and osteitis fibrosa in a man ingesting aluminum hydroxide antacid. Am J Med 76(6):1137-1143.

Caroli S, Alimonti A, Coni E, et al. 1994. The assessment of reference values for elements in human biological tissues and fluids: A systematic review. Crit Rev Anal Chem 24:363-398.

Carrillo F, Perez C, Camara C. 1992. Sensitive flow-injection-spectrofluorimetric method to determine aluminium III in water. Anal Chim Acta 262:91-96.

Castelain PY, Castelain M, Vervloet D, et al. 1988. Sensitization to aluminium by aluminium-precipitated dust and pollen extracts. Contact Dermatitis 19(1):58-60.

CEC. 1984. Aluminum. In: Alessio L, Berlin A, Boni M, et al., eds. Biological indicators for the assessment of human exposure to industrial chemicals. Brussels, Luxembourg: Commission of the European Communities, 21-29. PB86229242.

Cech I, Montera J. 2000. Spatial variations in total aluminum concentrations in drinking water supplies studied by geographic information system (GIS) methods. Water Res 34(10):2703-2712.

*Chan JCM, Jacob M, Brown S, et al. 1988. Aluminum metabolism in rats: Effects of vitamin-D, dihydrotachysterol, 1,25-dihydroxyvitamin-D and phosphate binders. Nephron 48(1):61-64.

Chan-Yeung M, Wong R, MacLean L, et al. 1983. Epidemiologic health study of workers in an aluminum smelter in British Columbia, Canada: Effects on respiratory system. Am Rev Respir Dis 127:465-469.

Chappuis P, de Vernejoul MC, Paolaggi F, et al. 1989. Relationship between hair, serum and bone aluminium in hemodialyzed patients. Clin Chim Acta 179(3):271-278.

Chappuis P, Duhaux L, Paolaggl F, et al. 1988. Analytical problems encountered in determining aluminum status from hair in controls and hemodialyzed patients. Clin Chem 34(11):2253-2255.

Chedid F, Fudge A, Teubner J, et al. 1991. Aluminium absorption in infancy. J Paediatr Child Health 27(3):164-166.

ChemFinder. 2008. Aluminum and compounds. ChemFinder.com database and internet searching. http://chemfinder.camsoft.com/. January 9, 2008.

ChemIDplus. 2008. Aluminum and compounds. ChemIDplus. Bethesda, MD: U.S. National Library of Medicine. http://sis.nlm.nih.gov/chemical.html. January 9, 2008.

Chen W-J, Monnat RJJ, Chen M, et al. 1978. Aluminum induced pulmonary granulomatosis. Hum Pathol 9(6):705-711.

Chiba M, Sera K, Hashizume M, et al. 2004. Element concentrations in hair of children living in environmentally degraded districts of the East Aral Sea region. J Radioanal Nucl Chem 259(1):149-152.

Chines A, Pacifici R. 1990. Antacid and sucralfate-induced hypophosphatemic osteomalacia: A case report and review of the literature. Calcif Tissue Int 47(5):291-295.

Chinoy NJ, Sharma AK, Patel TN, et al. 2004. Recovery from fluoride and aluminum induced free radical liver toxicity in mice. Fluoride 37(4):257-263.

Chopra JS, Kalra OP, Malik VS, et al. 1986. Aluminum phosphide poisoning: A prospective study of 16 cases in one year. Postgrad Med J 62:1113-1116.

Christie H, MacKay RJ, Fisher AM. 1963. Pulmonary effects of inhalation of aluminum by rats and hamsters. Am Ind Hyg Assoc J 24:47-56.

Chung FHY. 1992. Bakery processes (chemical leavening). In: Kroschwitz JI, Howe-Grant M, eds. Kirk-Othmer encyclopedia of chemical technology. Vol. 3. Antibiotics (b-lactams) to batteries. New York, NY: John Wiley & Sons, Inc., 892-902.

*Clayton RM, Sedowofia SKA, Rankin JM, et al. 1992. Long-term effects of aluminum on the fetal mouse brain. Life Sci 51(25):1921-1928.

Cleveland L, Buckler DR, Brumbaugh WG. 1991. Residue dynamics and effects of aluminum on growth and mortality in brook trout. Environ Toxicol Chem 10:243-248.

Cleveland L, Little EE, Wiedmeyer RH, et al. 1989. Chronic no-observed-effect concentrations of aluminum for brook trout exposed in low-calcium, dilute acidic water. In: Lewis TE, ed. Environmental chemistry and toxicology of aluminum. Chelsea, MI: Lewis Publishers, Inc., 229-246.

Clewell HJ III, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1:111-113.

Colin-Jones D, Langman MJ, Lawson DH, et al. 1989. Alzheimer's disease in antacid users. Lancet 1(8652):1453.

Colomina MT, Esparza JL, Corbella J et al. 1998. The effect of maternal restraint on developmental toxicity of aluminum in mice. Neurotoxicol Teratol 20(6):651-656.

Colomina MT, Gomez M, Domingo JL, et al. 1992. Concurrent ingestion of lactate and aluminum can result in developmental toxicity in mice. Res Commun Chem Pathol Pharmacol 77(1):95-106.

Colomina MT, Gomez M, Domingo JL, et al. 1994. Lack of maternal and developmental toxicity in mice given high doses of aluminum hydroxide and ascorbic acid during gestation. Pharmacol Toxicol 74(4-5):236-239.

Colomina MT, Roig JL, Sanchez DJ, et al. 2002. Influence of age on aluminum-induced neurobehavioral effects and morphological changes in rat brain. Neurotoxicology 23(6):775-781.

Colomina MT, Roig JL, Torrente M, et al. 2005. Concurrent exposure to aluminum and stress during pregnancy in rats: Effects on postnatal development and behavior of the offspring. Neurotoxicol Teratol 27(4):565-574.

Colomina MT, Sanchez DJ, Domingo JL, et al. 1999. Exposure of pregnant mice to aluminum and restraint stress: Effects on postnatal development and behavior of the offspring. Psychobiology 27(4):521-529.

Commissaris RL, Cordon JJ, Sprague S, et al. 1982. Behavioral changes in rats after chronic aluminum and parathyroid hormone administration. Neurobehav Toxicol Teratol 4(3):403-410.

Connor DJ, Harrell LE, Jope RS. 1989. Reversal of an aluminum-induced behavioral deficit by administration of deferoxamine. Behav Neurosci 103(4):779-783.

*Connor DJ, Jope RS, Harrell LE. 1988. Chronic, oral aluminum administration to rats: Cognition and cholinergic parameters. Pharmacol Biochem Behav 31:467-474.

Connor JJ, Shacklette HT. 1975. Background geochemistry of some rocks, soils, plants, and vegetables in the conterminous United States. United States Geological Survey. Professional Paper 574-F.

Cooke K, Gould MH. 1991. The health effects of aluminium-a review. J R Soc Health 111:163-168.

Cooper JA, Watson JG, Huntzicker JJ. 1979. Summary of the Portland Aerosol Characterization Study (PACS). Presented at the 72nd Annual Meeting of the Air Pollution Control Association, Cincinnati, Ohio, June 24-29, 1979. Cincinnati, OH: Air Pollution Control Association, 1-16.

Cotton FA, Wilkinson G, Murillo CA, et al., eds. 1999. The group 13 elements: Al, Ga, In, Tl. Advanced inorganic chemistry. 6th ed. New York, NY: John Wiley & Sons, Inc., 175-207.

Couri D, Liss L, Ebner K. 1980. Determination of aluminum in biological samples. Neurotoxicology 1:17-24.

Cournot-Witmer G, Zingraff J, Plachot JJ, et al. 1981. Aluminum localization in bone from hemodialyzed patients: Relationship to matrix mineralization. Kidney Int 20(3):375-385.

Cranmer JM, Wilkins JD, Cannon DJ, et al. 1986. Fetal-placental-maternal uptake of aluminum in mice following gestational exposure: Effect of dose and route of administration. Neurotoxicology 7(2):601-608.

Crapper DR, DeBoni U. 1978. Brain aging and Alzheimer's disease. Can Psychiatr Assoc J 23:229-233.

Crapper McLachlan DR. 1989. Aluminum neurotoxicity: Criteria for assigning a role in Alzheimer's disease. In: Lewis TE, ed. Environmental chemistry and toxicology of aluminum. Chelsea, MI: Lewis Publishers, Inc., 299-315.

Crombie DW, Blaisdell JL, MacPherson G. 1944. The treatment of silicosis by aluminum powder. Can Med Assoc J 50:318-328.

Cucarella C, Montoliu C, Hermenegildo C, et al. 1998. Chronic exposure to aluminum impairs neuronal glutamate-nitric oxide-cyclic GMP pathway. J Neurochem 70:1609-1614.

Dabeka RW, McKenzie AD. 1990. Aluminum levels in Canadian infant formulae and estimation of aluminum intakes from formulae by infants 0-3 months old. Food Addit Contam 7(2):275-282.

Dabeka RW, Conacher HBS, Salminen J, et al. 1992. Survey of bottled drinking water sold in Canada. Part 1. Lead, cadmium, arsenic, aluminum, and fluoride. J AOAC Int 75(6):949-953.

Dahlgren RA, Ugolini FC. 1989. Aluminum fractionation of soil solutions from unperturbed and tephra-treated spodosols, Cascade range, Washington, USA. Soil Sci Soc Am J 53:559-566.

Dantzman CL, Breland HL. 1970. Chemical status of some water sources in south central Florida. Soil Sci Soc Am Proc 29:18-28.

Dawson EB, Evans DR, Harris WA, et al. 2000. Seminal plasma trace metal levels in industrial workers. Biol Trace Elem Res 74(2):97-105.

Dawson EB, Ritter S, Harris WA, et al. 1998. Comparison of sperm viability with seminal plasma metal levels. Biol Trace Elem Res 64:215-219.

Day JP, Barker J, Evans LJA, et al. 1991. Aluminum absorption studied by 26Al tracer. Lancet 337(8753):1345.

Dean JR. 1989. Ion chromatographic determination of aluminum with ultraviolet spectrophotometric detection. Analyst 114:165-168.

*Dedman DJ, Treffry A, Candy JM, et al. 1992. Iron and aluminum in relation to brain ferritin in normal individuals and Alzheimer's-disease and chronic renal-dialysis patients. Biochem J 287(Part 2):509-514.

de Kom JFM, Dissels H MH, van der Voet GB, et al. 1997. Serum aluminum levels of workers in the bauxite mines. Clin Toxicol 35(6):645-651.

de la Flor St. Remy RR, Sanchez MLF, Sastre JBL, et al. 2004. Determination of essential and toxic total elements in premature human milk by inductively coupled plasma mass spectrometry (ICP-ORC-MS), using an octopole reaction cell. J Anal Atom Spectrom 19(5):616-622.

Deloncle R, Huguet F, Babin P, et al. 1999. Chronic administration of aluminium L-glutamate in young mature rats: Effects on iron levels and lipid peroxidation in selected brain areas. Toxicol Lett 104(1-2):65-73.

Deng Z, Coudray C, Gouzoux L, et al. 2000. Effects of acute and chronic coingestion of AlCl3 with citrate or polyphenolic acids on tissue retention and distribution of aluminum in rats. Biol Trace Elem Res 76(3):245-256.

DeVoto E, Yokel RA. 1994. The biological speciation and toxicokinetics of aluminum. Environ Health Perspect 102(11):940-951.

De Vuyst P, Dumortier P, Rickaert F, et al. 1986. Occupational lung fibrosis in an aluminum polisher. Eur J Respir Dis 68(2):131-140.

De Vuyst P, Dumortier P, Schandenè L, et al. 1987. Sarcoidlike lung granulomatosis induced by aluminum dusts. Am Rev Respir Dis 135(2):493-497.

D'Haese PCD, Couttenye MM, Goodman WG, et al. 1995. Use of the low-dose desferrioxamine test to diagnose and differentiate between patients with aluminum-related bone disease, increased risk for aluminum toxicity, or aluminum overload. Nephrol Dial Transplant 10:1874-1884.

Dick RB, Krieg EFJ, Sim MA, et al. 1997. Evaluation of tremor in aluminum production workers. Neurotoxicol Teratol 19(6):447-453.

Dinman BD. 1983. Aluminum, alloys, and compounds. In: Encyclopaedia of occupational health and safety. Vol. 1. Geneva: International Labour Office, 131-135.

Dinman BD. 1987. Aluminum in the lung: The pyropowder conundrum. J Occup Med 29(11):869-876.

DiPaolo JA, Casto BC. 1979. Quantitative studies of in vitro morphological transformation of Syrian hamster cells by inorganic metal salts. Cancer Res 39(3):1008-1013.

Dixon RL, Sherins RJ, Lee IP. 1979. Assessment of environmental factors affecting male fertility. Environ Health Perspect 30:53-68.

Dlugaszek M, Fiejka MA, Graczyk A, et al. 2000. Effects of various aluminum compounds given orally to mice on Al tissue distribution and tissue concentrations of essential elements. Pharmacol Toxicol 86(3):135-139.

DOE. 1984. A review and analysis of parameters for assessing transport of environmentally released radionuclides through agriculture. U.S. Department of Energy. ORNL-5786.

DOI. 1970. Trace metals in waters of the United States. A five year summary of trace metals in rivers and lakes of the United States (Oct. 1, 1962- Sept. 30, 1967). Cincinnati, OH: U.S. Department of the Interior, Federal Water Pollution Control Administration, Division of Pollution Surveillance.

DOI. 1971. Geochemical cycles involving flora, lake water, and bottom sediments. Washington, DC: U.S. Department of the Interior, Office of Water Resources Research. PB206197.

DOI. 1983. Removal of leachable metals and recovery of alumina from utility coal ash. Washington, DC: U.S. Department of the Interior, Bureau of Mines. PB83191650.

DOI. 1984. Study of availability and composition of metal bearing wastes (generated in titanium extraction and fabrication, aluminum smelters, chromite bearing refractory and foundry sands and mercury battery industries). Washington, DC: U.S. Department of the Interior, Bureau of Mines. PB84207091.

Domingo JL, Gomez M, Bosque MA, et al. 1989. Lack of teratogenicity of aluminum hydroxide in mice. Life Sci 45(3):243-247.

Domingo JL, Gomez M, Llobet JM, et al. 1991. Influence of some dietary constituents on aluminum absorption and retention in rats. Kidney Int 39(4):598-601.

Domingo JL, Gomez M, Sanchez DJ, et al. 1993. Effect of various dietary constituents on gastrointestinal absorption of aluminum from drinking water and diet. Res Commun Chem Pathol Pharmacol 79(3):377-380.

Domingo JL, Llobet JM, Gomez M, et al. 1987b. Nutritional and toxicological effects of short-term ingestion of aluminum by the rat. Res Commun Chem Pathol Pharmacol 56(3):409-419.

Domingo JL, Llorens J, Sanchez DJ, et al. 1996. Age-related effects of aluminum ingestion on brain aluminum accumulation and behavior in rats. Life Sci 58(17):1387-1395.

Domingo JL, Paternain JL, Llobet JM, et al. 1987c. The effects of aluminum ingestion of reproduction and postnatal survival in rats. Life Sci 41(9):1127-1131.

Domingo JL, Paternain JL, Llobet JM, et al. 1987a. Effects of oral aluminum administration on perinatal and postnatal development in rats. Res Commun Chem Pathol Pharmacol 57(1):129-132.

Donald JM, Golub MS, Gershwin ME, et al. 1989. Neurobehavioral effects in offspring of mice given excess aluminum in diet during gestation and lactation. Neurotoxicol Teratol 11(4):345-351.

Dong D, Xie Z, Du Y, et al. 1999. Influence of soil pH on aluminum availability in the soil and aluminum in tea leaves. Commun Soil Sci Plant Anal 30(5/6):873-883.

Drablos PA, Hetland S, Schmidt F et al. 1992. Uptake and excretion of aluminum in workers exposed to aluminum fluoride and aluminum oxide. Proceedings of the second international conference on aluminum and health, Tampa, Fl, February 2-6, 1992. New York, NY: Aluminum Association, 157-160.

Dreetz CD, Lund W. 1992. Air-intake filters used for multi-element analysis of airborne particulate matter by inductively coupled plasma atomic emission spectrometry. Anal Chim Acta 262:299-305.

Drew RT, Gupta BN, Bend JR, et al. 1974. Inhalation studies with a glycol complex of aluminum-chloride-hydroxide. Arch Environ Health 28(6):321-326.

Driscoll CT, Letterman RD. 1988. Chemistry and fate of aluminum (III) in treated drinking water. J Environ Eng 114:21-37.

Drueke TB, Jouhanneau P, Banide H, et al. 1997. Effects of silicon, citrate and the fasting state on the intestinal absorption of aluminum in rats. Clin Sci 92(1):63-67.

Du Val G, Grubb BR, Bently PJ. 1986. Tissue distribution of subcutaneously administered aluminum chloride in weanling rabbits. J Toxicol Environ Health 19:97-104.

Duggan JM, Dickeson JE, Tynan PF, et al. 1992. Aluminium beverage cans as a dietary source of aluminium. Med J Aust 156(9):604-605.

*Dwyer CM, Kerr RE. 1993. Contact allergy to aluminum in 2 brothers. Contact Dermatitis 29:36-38.

Dyrssen D, Haraldsson C, Nyberg E, et al. 1987. Complexation of aluminum with DNA. J Inorg Biochem 29(1):67-75.

Dzubay TG. 1980. Chemical element balance method applied to dichotomous sampler data. Ann NY Acad Sci 338:126-144.

*Ecelbarger CA, MacNeil GG, Greger JL. 1994. Aluminum retention by aged rats fed aluminum and treated with desferrioxamine. Toxicol Lett 73(3):249-257.

Edling NPG. 1961. Aluminum pneumoconiosis: A roentgendiagnostic study of five cases. Acta Radiol 56:170-178.

Edwardson JA, Moore PB, Ferrier IN, et al. 1993. Effect of silicon on gastrointestinal absorption of aluminum. Lancet 342(8865):211-212.

Eisenreich SJ. 1980. Atmospheric input of trace metals to Lake Michigan (USA). Water Air Soil Pollut 13(3):287-301.

El-Demerdash FM. 2004. Antioxidant effect of vitamin E and selenium on lipid peroxidation, enzyme activities and biochemical parameters in rats exposed to aluminum. J Trace Elem Med Biol 18(1):113-121.

*Elinder CG, Ahrengart L, Lidums V, et al. 1991. Evidence of aluminum accumulation in aluminum welders. Br J Ind Med 48(11):735-738.

Elliott JE. 2005. Trace metals, stable isotope ratios, and trophic relations in seabirds from the North Pacific Ocean. Environ Toxicol Chem 24(12):3099-3105.

Ellis H, Scurr JH. 1979. Axillary hyperhidrosis - topical treatment with aluminium chloride hexahydrate. Postgrad Med J 55:868-869.

Elmore D, Phillips FM. 1987. Accelerator mass spectrometry for measurement of long-lived radioisotopes. Science 236:543-550.

*Engelbrecht FM, Byers PD, Stacy BD, et al. 1959. Tissue reactions to injected aluminum and alumina in the lungs and livers of mice, rats, guinea-pigs and rabbits. J Pathol Bacteriol 77:407-416.

EPA. 1983a. Method 202.1: Aluminum (atomic absorption, direct aspiration). Methods for the chemical analysis of water and wastes. Cincinnati, OH: U.S. Environmental Protection Agency. EPA600479020. http://web1.er.usgs.gov/nemi/method_pdf/5267.pdf. March 21, 2006.

EPA. 1983b. Method 202.2: Aluminum (AA, furnace technique). Methods for chemical analysis of water and wastes. Cincinnati, OH: U.S. Environmental Protection Agency. EPA600479020. http://web1.er.usgs.gov/nemi/method_pdf/5268.pdf. March 21, 2006.

EPA. 1988. Recommendations for and documentation of biological values for use in risk assessment. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office. EPA600687008.

EPA. 1990. Interim methods for development of inhalation reference doses. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. EPA600888066F.

EPA. 1994a. Method 200.7: Inductively coupled plasma-atomic emission spectrometric method for trace element analysis of water and wastes. In: Methods for the determination of metals in environmental samples. Supplement 1. Cincinnati, OH: U.S. Environmental Protection Agency. EPA600R94111. http://web1.er.usgs.gov/nemi/method_pdf/4690.pdf. March 21, 2006.

EPA. 1994b. Method 200.8: Determination of trace elements in waters and wastes by inductively coupled plasma - mass spectrometry. In: Methods for the determination of metals in environmental samples. Supplement 1. Cincinnati, OH: U.S. Environmental Protection Agency. EPA600R94111. http://web1.er.usgs.gov/nemi/method_pdf/4665.pdf. March 21, 2006.

EPA. 1994c. Method 200.9: Trace elements in water, solids, and biosolids by stabilized temperature graphite furnace atomic absorption spectrometry. In: Methods for the determination of metals in environmental samples. Supplement 1. Cincinnati, OH: U.S. Environmental Protection Agency. EPA600R94111. http://web1.er.usgs.gov/nemi/method_pdf/4797.pdf. March 21, 2006.

EPA. 1995. Toxic Chemical Release Inventory Reporting Form R and Instructions- Revised 1994 version. Washington, DC: Office of Pollution Prevention, U.S. Environmental Protection Agency. EPA745K95051.

EPA. 1997. Special report on environmental endocrine disruption: An effects assessment and analysis. Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. EPA630R96012.

EPA. 1998. Reregistration eligibility decision (RED): Al and Mg phosphide. Washington, DC: U.S. Environmental Protection Agency. EPA738R98017.

EPA. 2000. Method 6010C: Inductively coupled plasma-atomic emission spectrometry. In: Test methods for evaluating solid waste, physical/chemical methods. Washington, DC: U.S. Environmental Protection Agency. SW846. http://www.epa.gov/sw-846/pdfs/6010c.pdf. March 21, 2006.

EPA. 2003. National primary drinking water regulations. Washington, DC: Office of Ground Water and Drinking Water, U.S. Environmental Protection Agency. EPA816F03016. http://www.epa.gov/safewater/mcl.html. March 07, 2006.

EPA. 2005. Toxic chemical release inventory reporting forms and instructions: Revised 2004 version. Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986). U.S. Environmental Protection Agency. Office of Environmental Information. EPA260B05001.

EPA. 2006a. Acute Exposure Guideline Levels (AEGLs) Washington, DC: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. http://www.epa.gov/oppt/aegl/chemlist.htm. March 07, 2006.

EPA. 2006b. Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 116.4. http://a257.g.akamaitech.net/7/257/2422/22jul20061500/edocket.access.gpo.gov/cfr_2006/julqtr/pdf/40cfr116.4.pdf. January 8, 2008.

EPA. 2006c. Hazardous air pollutants. Clean Air Act. U.S. Environmental Protection Agency. United States Code. 42 USC 7412. http://www.epa.gov/ttn/atw/orig189.html. March 07, 2006.

EPA. 2006d. Identification and listing of hazardous waste. Washington, DC: U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261, Appendix VIII. http://www.epa.gov/epacfr40/chapt-I.info/chi-toc.htm. March 08, 2006.

EPA. 2006e. National recommended water quality criteria. Washington, DC: U.S. Environmental Protection Agency, Office of Water, Office of Science and Technology. http://www.epa.gov/waterscience/criteria/nrwqc-2006.pdf. January 8, 2008.

EPA. 2006f. 2006 Drinking water standards and health advisories. Washington, DC: Office of Water, U.S. Environmental Protection Agency. EPA822R06013. http://www.epa.gov/waterscience/criteria/drinking/dwstandards.pdf. April 11, 2007.

EPA. 2006g. Pesticides classified for restricted use. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 152.175. http://www.epa.gov/epacfr40/chapt-I.info/chi-toc.htm. March 07, 2006.

EPA. 2006h. Table 117.3. Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 117.3. http://a257.g.akamaitech.net/7/257/2422/22jul20061500/edocket.access.gpo.gov/cfr_2006/julqtr/pdf/40cfr117.3.pdf. January 8, 2008.

EPA. 2006i. Designation of hazardous substances. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4. http://a257.g.akamaitech.net/7/257/2422/22jul20061500/edocket.access.gpo.gov/cfr_2006/julqtr/pdf/40cfr302.4.pdf. January 08, 2008.

EPA. 2006j. Superfund, emergency planning, and community right-to-know programs. Extremely hazardous substances and their threshold planning quantities. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 355, Appendix A. http://www.epa.gov/epacfr40/chapt-I.info/chi-toc.htm. March 08, 2006.

EPA. 2006k. Toxic chemical release reporting: Community right-to-know. Chemicals and chemical categories to which this part applies. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.65. http://a257.g.akamaitech.net/7/257/2422/22jul20061500/edocket.access.gpo.gov/cfr_2006/julqtr/pdf/40cfr372.65.pdf. January 08, 2008.

EPA. 2006l. Tolerances and exemptions from tolerances for pesticide chemicals in food. Aluminum hydroxide. Aluminum oxide. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 180.910. http://www.epa.gov/epacfr40/chapt-I.info/chi-toc.htm. March 08, 2006.

EPA. 2006m. Tolerances and exemptions from tolerances for pesticide chemicals in food. Aluminum sulfate. Phenol. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 180.920. http://www.epa.gov/epacfr40/chapt-I.info/chi-toc.htm. March 08, 2006.

EPA. 2008. National secondary drinking water regulations. Secondary maximum contaminant levels. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 143.3. http://www.epa.gov/lawsregs/search/40cfr.html. July 30, 2008.

Erasmus RT, Savory J, Wills MR, et al. 1993. Aluminum neurotoxicity in experimental animals. Ther Drug Monit 15:588-592.

Ermolenko LV, Dedkov YM. 1988. Photometric determination of aluminum in water with the sulfonitrazo DAF reagent. J Anal Chem USSR 43:815-820.

Exley C, Burgess E, Day JP, et al. 1996. Aluminum toxicokinetics. J Toxicol Environ Health 48:569-584.

Fairweather-Tait SJ, Faulks RM, Fatemi SJA, et al. 1987. Aluminium in the diet. Hum Nutr Food Sci Nutr 41F:183-192.

Farina M, Rotta LN, Soares FA, et al. 2005. Hematological changes in rats chronically exposed to oral aluminum. Toxicology 209(1):29-37.

FDA. 2002. Antacid products for over-the-counter (OTC) human use. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR Part 331, 222-226.

FDA. 2005. Beverages. Bottled water. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 165.110. http://a257.g.akamaitech.net/7/257/2422/01apr20051500/edocket.access.gpo.gov/cfr_2005/aprqtr/pdf/21cfr165.110.pdf. January 08, 2008.

FEDRIP. 2006. Aluminum. Federal Research in Progress database. Springfield, VA: National Technical Information Service.

Feinroth M, Feinroth MV, Berlyne GM. 1982. Aluminum absorption in the rat everted gut sac. Miner Electrolyte Metab 8(1):29-35.

Fernandez de la Campa MR, Garcia MED, Sanz-Medel A. 1988. Room-temperature liquid phosphorimetry of the aluminum-ferron chelate in micellar media. Determination of aluminum. Anal Chim Acta 212:235-243.

Fernandez-Lorenzo JR, Cocho JA, Rey-Goldar ML, et al. 1999. Aluminum contents of human milk, cow's milk, and infant formulas. J Pediatr Gastroenterol Nutr 28(3):270-275.

Fernández-Martin JL, Canteros A, Serrano M, et al. 1998. Prevention of aluminium exposure through dialysis fluids. Analysis of changes in the last 8 years. Nephrol Dial Transplant 13(Suppl 3):78-81.

Filipek LH, Nordstrom DK, Ficklin WH. 1987. Interaction of acid mine drainage with waters and sediments of West Squaw Creek in the West Shasta mining district, California. Environ Sci Technol 21:388-396.

Fimreite N, Hansen OO, Pettersen HC. 1997. Aluminum concentrations in selected foods prepared in aluminum cookware, and its implications for human health. Bull Environ Contam Toxicol 58(1):1-7.

Finberg L, Dweck HS, Holmes F, et al. 1986. Aluminum toxicity in infants and children. Pediatrics 78:1150-1154.

Finelli VN, Que Hee SS, Niemeier RW. 1981. Influence of exposure to aluminum chloride and fluoride dusts on some biochemical and physiological parameters in rats. In: Brown SS, Davies DS, eds. Organ-directed toxicity: Chemical indices and mechanisms. New York, NY: Pergamon Press, 291-295.

Fisher DW, Gambell AW, Likens GE, et al. 1968. Atmospheric contributions to water quality of streams in the Hubbard Brook Experimental Forest, New Hampshire. Water Resour Res 4:1115-1126.

Flarend RE, Elmore D. 1997. Aluminium-26 as a biological tracer using accelerator mass spectrometry. In: Zatta PF, Alfrey AC, eds. Aluminum toxicity in infants health and disease. Singapore: World Scientific, 16-39.

Flarend R, Bin T, Elmore D, et al. 2001. A preliminary study of the dermal absorption of aluminum from antiperspirants using aluminum-26. Food Chem Toxicol 39(2):163-168.

Flarend RE, Hem SL, White JL, et al. 1997. In vivo absorption of aluminum-containing vaccine adjuvants using 26Al. Vaccine 15(12-13)1314-1317.

Flaten TP. 1990. Geographical associations between aluminum in drinking water and death rates with dementia (including Alzheimer's disease), Parkinson's disease and amyotrophic lateral sclerosis in Norway. Environ Geochem Health 12(1-2):152-167.

Flaten TP. 2001. Aluminium as a risk factor in Alzheimer's disease, with emphasis on drinking water. Brain Res Bull 55(2):187-196.

Flaten TP, Odegard M. 1988. Tea, aluminium and Alzheimer's disease. Food Chem Toxicol 26(11-12):959-960.

Fleming J, Joshi JG. 1987. Ferritin: Isolation of aluminum-ferritin complex from brain. Proc Natl Acad Sci USA 84(22):7866-7870.

Fleming RF, Lindstrom RM. 1987. Precise determination of aluminum by instrumental neutron activation. J Radioanal Nucl Chem 113:35-42.

Flendrig JA, Kruis H, Das HA. 1976. Aluminum intoxication: The cause of dialysis dementia? Proc Eur Dial Transplant Assoc 13:355-363.

Florence AL, Gauthier A, Ponsar C, et al. 1994. An experimental animal model of aluminum overload. Neurodegeneration 3(4):315-323.

Fomon SJ. 1966. Body composition of the infant. Part I: The male reference infant. In: Falkner F, ed. Human development. Philadelphia, PA: WB Saunders, 239-246.

Fomon SJ, Haschke F, Ziegler EE, et al. 1982. Body composition of reference children from birth to age 10 years. Am J Clin Nutr 35:1169-1175.

Forbes WF, Hayward LM, Agwani N. 1992. Geochemical risk factors for mental functioning, based on the Ontario Longitudinal Study of Aging (LSA). I. Results from a preliminary investigation. Can J Aging 13(2):269-281.

Forbes WF, McAiney CA, Hayward LM, et al. 1994. Geochemical risk factors for mental functioning, based on the Ontario Longitudinal Study of Aging (LSA). II. The role of pH. Can J Aging 13(2):249-266.

Forster DP, Newens AJ, Kay DWK, et al. 1995. Risk factors in clinically diagnosed presenile dementia of the Alzheimer type: A case-control study in northern England. J Epidemiol Commun Health 49(3):253-258.

Fraga CG, Oteiza PI, Golub MS, et al. 1990. Effects of aluminum on brain lipid peroxidation. Toxicol Lett 51(2):213-219.

Freda J, McDonald DG. 1990. Effects of aluminum on the leopard frog, rana pipiens: Life stage comparisons and aluminum uptake. Can J Fish Aquat Sci 47:210-216.

Frick KG, Herrmann J. 1990. Aluminum accumulation in a lotic mayfly at low pH-a laboratory study. Ecotoxicol Environ Saf 19:81-88.

Froment DH, Buddington B, Miller NL, et al. 1989a. Effect of solubility on the gastrointestinal absorption of aluminum from various aluminum compounds in the rat. J Lab Clin Med 114(3):237-242.

Froment DPH, Molitoris BA, Buddington B, et al. 1989b. Site and mechanism of enhanced gastrointestinal absorption of aluminum by citrate. Kidney Int 36(6):978-984.

Fu HJ, Hu QS, Lin ZN, et al. 2003. Aluminum-induced apoptosis in cultured cortical neurons and its effect on SAPK/JNK signal transduction pathway. Brain Res 980(1):11-23.

Fuchs C, Brasche M, Paschen K, et al. 1974. [Aluminum determination in serum by flameless atomic absorption.] Clin Chim Acta 52:71-80. (German)

Gaffuri E, Donna A, Pietra R, et al. 1985. Pulmonary changes and aluminum levels following inhalation of alumina dust: A study on four exposed workers. Med Lav 76(3):222-227.

Gallego H, Lewis EJ, Crutchfield CE. 1999. Crystal deodorant dermatitis: Irritant dermatitis to alum-containing deodorant. Cutis 64(1):65-66.

Gandolfi L, Stella MP, Zambenedetti P, et al. 1998. Aluminum alters intracellular calcium homeostasis in vitro. Biochim Biophys Acta 1406(3):315-320.

Ganrot PO. 1986. Metabolism and possible health effects of aluminum. Environ Health Perspect 65:363-441.

Garbossa G, Galvez G, Castro ME, et al. 1998. Oral aluminum administration to rats with normal renal function. 1. Impairment of erythropoiesis. Hum Exp Toxicol 17(6):312-317.

Garbossa G, Gutnisky A, Nesse A. 1996. Depressed erythroid progenitor cell activity in aluminum-overloaded mice. Miner Electrolyte Metab 22(4):214-218.

Gardiner PE, Stoeppler M. 1987. Optimisation of the analytical conditions for the determination of aluminum in human blood plasma and serum by graphite furnace atomic absorption spectrometry. Part 2. Assessment of the analytical method. J Anal Atom Spectrom 2:401-404.

Gardiner PE, Ottaway JM, Fell GS, et al. 1981. Determination of aluminum in blood plasma or serum by electrothermal atomic absorption spectrometry. Anal Chim Acta 128:57-66.

Gardiner PE, Schierl R, Kreutzer K. 1987. Aluminum speciation in soil solutions as studied by size exclusion chromatography. Plant Soil 103(1):151-154.

Garruto RM, Shankar SK, Yanagihara R, et al. 1989. Low-calcium, high-aluminum diet-induced motor neuron pathology in cynomolgus monkeys. Acta Neuropathol 78(2):210-219.

Gauthier E, Fortier I, Courchesne F, et al. 2000. Aluminum forms in drinking water and risk of Alzheimer's disease. Environ Res 84(3):234-246.

Ghribi O, Dewitt DA, Forbes MS, et al. 2001. Co-involvement of mitochondria and endoplasmic reticulum in regulation of apoptosis: Changes in cytochrome c, Bcl-2 and Bax in the hippocampus of aluminum-treated rabbits. Brain Res 903(1-2):66-73.

*Gibbs GW. 1985. Mortality of aluminum reduction plant workers, 1950 through 1977. J Occup Med 27(10):761-770.

Gibbs GW, Horowitz I. 1979. Lung cancer mortality in aluminum reduction plant workers. J Occup Med 21:347-353.

Gilks B, Churg A. 1987. Aluminum-induced pulmonary fibrosis: Do fibers play a role? Am Rev Respir Dis 136(1):176-179.

Giordano R, Lombardi G, Ciaralli L, et al. 1999. Major and trace and elements in sediments from Terra Nova Bay, Antartica. Sci Total Environ 227(1):29-40.

Gitelman HJ, Alderman FR, Kurs-Lasky M, et al. 1995. Serum and urinary aluminum levels of workers in the aluminum industry. Ann Occup Hyg 39(2):181-191.

Giwercman A, Carlsen E, Keiding N, et al. 1993. Evidence for increasing incidence of abnormalities of the human testis: A review. Environ Health Perspect Suppl 101(2):65-71.

Goenaga X, Williams DJA. 1988. Aluminum speciation in surface waters from a Welsh upland area. Environ Pollut 52:131-149.

Goh CL. 1990. Aluminum chloride hexahydrate versus palmar hyperhidrosis. Evaporimeter assessment. Int J Dermatol 29(5):368-370.

Golden NH, Rattner BA, McGowan PC, et al. 2003. Concentrations of metals in feathers and blood of nestling Black-Crowned Night-Herons (Nycticorax mycticorax) in Chesapeake and Delaware Bays. Bull Environ Contam Toxicol 70(2):385-393.

Golomb D, Ryan D, Eby N, et al. 1997. Atmospheric deposition of toxics onto Massachusetts Bay-I. Metals. Atmos Environ 31:1349-1359.

Golub MS, Domingo JL. 1996. What we know and what we need to know about developmental aluminum toxicity. J Toxicol Environ Health 48(6):585-597.

Golub MS, Germann SL. 1998. Aluminum effects on operant performance and food motivation of mice. Neurotoxicol Teratol 20(4):421-427.

Golub MS, Germann SL. 2001. Long-term consequences of developmental exposure to aluminum in a suboptimal diet for growth and behavior of Swiss Webster mice. Neurotoxicol Teratol 23(4):365-372.

Golub MS, Tarara RP. 1999. Morphometric studies of myelination in the spinal cord of mice exposed developmentally to aluminum. Neurotoxicology 20(3):953-959.

Golub MS, Donald JM, Gershwin ME, et al. 1989. Effects of aluminum ingestion on spontaneous motor activity of mice. Neurotoxicol Teratol 11(3):231-235.

Golub MS, Germann SL, Han B, et al. 2000. Lifelong feeding of a high aluminum diet to mice. Toxicology 150(1-3):107-117.

Golub MS, Gershwin ME, Donald JM, et al. 1987. Maternal and developmental toxicity of chronic aluminum exposure in mice. Fundam Appl Toxicol 8(3):346-357.

Golub MS, Han B, Keen CL, et al. 1992b. Effects of dietary aluminum excess and manganese deficiency on neurobehavioral endpoints in adult mice. Toxicol Appl Pharmacol 112(1):154-160.

Golub MS, Han B, Keen CL, et al. 1994. Auditory startle in Swiss Webster mice fed excess aluminum in diet. Neurotoxicol Teratol 16(4):423-425.

Golub MS, Han B, Keen CL, et al. 1995. Behavioral performance of Swiss Webster mice exposed to excess dietary aluminum during development or during development and as adults. Toxicol Appl Pharmacol 133(1):64-72.

Golub MS, Han B, Keen CL. 1996. Iron and manganese uptake by offspring of lactating mice fed a high aluminum diet. Toxicology 109(2-3):111-118.

Golub MS, Keen CL, Gershwin ME. 1992a. Neurodevelopmental effect of aluminum in mice: Fostering studies. Neurotoxicol Teratol 14(3):177-182.

Golub MS, Takeuchi PT, Gershwin ME, et al. 1993. Influence of dietary aluminum cytokine production by mitogen-stimulated spleen cells from Swiss Webster mice. Immunopharmacol Immunotoxicol 15(5):605-619.

Gomez M, Domingo JL, Llobet JM, et al. 1986. Short-term oral toxicity study of aluminum in rats. Arch Farmacol Toxicol 12(2-3):145-151.

Gomez M, Domingo JL, Llobet JM. 1991. Developmental toxicity evaluation of oral aluminum in rats: Influence of citrate. Neurotoxicol Teratol 13(3):323-328.

Gomez M, Esparza JL, Domingo JL, et al. 1999. Chelation therapy in aluminum-loaded rats: Influence of age. Toxicology 137(3):161-168.

Gomez M, Sanchez DJ, Llobet JM, et al. 1997a. The effect of age on aluminum retention in rats. Toxicology 116(1-3):1-8.

Gomez M, Sanchez DJ, Llobet JM, et al. 1997b. Concentrations of some essential elements in the brain of aluminum-exposed rats in relation to the age of exposure. Arch Gerontol Geriatr 24:287-294.

Gonzalez-Munoz MJ, Mesenguer I, Sanchez-Reus MI, et al. 2007. Beer consumption reduces cerebral oxidation caused by aluminum toxicity by normalizing gene expression of tumor necrotic factor alpha and several antioxidant enzymes. Food Chem Toxicol 46(3):1111-1118.

Goralewski G. 1947. [The aluminium lung: A new industrial disease.] Z Gesamte Inn Med 2:665-673. (German)

Gorsky JE, Dietz AA. 1978. Determination of aluminum in biological samples by atomic absorption spectrophotometry with a graphite furnace. Clin Chem 24:1485-1490.

Gorsky JE, Dietz AA, Spencer H, et al. 1979. Metabolic balance of aluminum studied in six men. Clin Chem 25(10):1739-1743.

Gosink TA. 1975. Rapid simultaneous determination of picogram quantities of aluminum and chromium from water by gas phase chromatography. Anal Chem 47:165-168.

Goyens P, Brasseur D. 1990. Aluminum and infants. (Comment on: Pediatrics 84(6):1105-1107). Pediatrics 86(4):650-652.

Grams GW. 1992. Aluminum compounds: Aluminum halides and aluminum nitrate. In: Kroschwitz JI, Howe-Grant M, eds. Kirk-Othmer encyclopedia of chemical technology. Vol. 2: Alkanolamines to antibiotics (glycopeptides). New York, NY: John Wiley & Sons, Inc., 281-290.

Gräske A, Thuvander A, Johannisson A, et al. 2000. Influence of aluminum on the immune system – an experimental study on volunteers. Biometals 13(2):123-133.

Graves AB, Rosner D, Echeverria D, et al. 1998. Occupational exposures to solvents and aluminum and estimated risk of Alzheimer's disease. Occup Environ Med 55:627-633.

Graves AB, White E, Koepsell TD, et al. 1990. The association between aluminum-containing products and Alzheimer's disease. J Clin Epidemiol 43:35-44.

Greger JL. 1992. Dietary and other sources of aluminum intake. Aluminum in biology and medicine. Ciba Found Symp 169:26-49.

Greger JL, Baier MJ. 1983. Excretion and retention of low or moderate levels of aluminum by human subjects. Food Chem Toxicol 21(4):473-477.

Greger JL, Donnaubauer SE. 1986. Retention of aluminum in the tissues of rats after the discontinuation of oral exposure to aluminum. Food Chem Toxicol 24(12):1331-1334.

Greger JL, Sutherland JE. 1997. Aluminum exposure and metabolism. Crit Rev Clin Lab Sci 34(5):439-474.

Greger JL, Goetz W, Sullivan D. 1985. Aluminum levels in foods cooked and stored in aluminum pans, trays and foil. J Food Prot 48(9):772-777.

Griswold WR, Reznik V, Mendoza SA et al. 1983. Accumulation of aluminum in a nondialyzed uremic child receiving aluminum hydroxide. Pediatr 71(1):56-58.

Gross P, Harley RA Jr, deTreville RTP. 1973. Pulmonary reaction to metallic aluminum powders. Arch Environ Health 26:227-236.

Guerold F, Giamberini L, Tourmann JL, et al. 1995. Occurrence of aluminum in chloride cells of Perla marginata (plecoptera) after exposure to low pH and elevated aluminum concentration. Bull Environ Contam Toxicol 54:620-625.

Guillard O, Fauconneau B, Olichon D, et al. 2004. Hyperaluminemia in a woman using an aluminum-containing antiperspirant for 4 years. Am J Med 117(12):956-959.

Guillard O, Tiphaneau K, Reiss D, et al. 1984. Improved determination of aluminum in serum by electrothermal atomic absorption spectrometry and zeeman background correction. Anal Lett 17:1593-1605.

*Gupta SK, Waters DH, Gwilt PR. 1986. Absorption and disposition of aluminum in the rat. J Pharm Sci 75(6):586-589.

Guzelian PS, Henry CJ, Olin SS, eds. 1992. Similarities and differences between children and adults: Implications for risk assessment. Washington, DC: International Life Sciences Institute Press.

Hackenberg U. 1972. Chronic ingestion by rats of standard diet treated with aluminum phosphide. Toxicol Appl Pharmacol 23:147-158.

Haddad CM, Shannon MW, Winchester JF. 1998. Clinical management of poisoning and drug overdose. 3rd ed. Philadelphia, PA: WB Saunders, 186.

Halatek T, Sinczuk-Walczak H, Rydzynski K. 2005. Prognostic significance of low serum levels of Clara cell phospholipid-binding protein in occupational aluminium neurotoxicity. J Inorg Biochem 99(9):1904-1911.

Halatek T, Trzcinka-Ochocka M, Matczak W, et al. 2006. Serum Clara cell protein as an indicator of pulmonary impairment in occupational exposure at aluminum foundry. Int J Occup Med Environ Health 19(4):211-223.

Hamdy RD. 1993. The accumulation of dietary aluminum by rainbow trout, Oncorhynchus mykiss, at high exposure concentrations. J Fish Biol 42:603-606.

Hamilton EI, Minski MJ, Cleary JJ. 1973. The concentration and distribution of some stable elements in healthy human tissues from the United Kingdom - an environmental study. Sci Total Environ 1(4):341-374.

Hänninen H, Matikainen E, Kovala T, et al. 1994. Internal load of aluminum and the central nervous system function of aluminum welders. Scand J Work Environ Health 20(4):279-285.

Harris WR, Messori L. 2002. A comparative study of aluminum(III), gallium(III), indium(III), and thallium(III) binding to human serum transferrin. Coord Chem Rev 228:237-262.

Hawkins NM, Coffey S, Lawson MS, et al. 1994. Potential aluminum toxicity in infants fed special infant formula. J Pediatr Gastroenterol Nutr 19(4)377-381.

HazDat. 2008. Aluminum. HazDat Database: ATSDR's Hazardous Substance Release and Health Effects Database. Atlanta, GA: Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/hazdat.html. June 19, 2008.

He SC, Qiao N, Sheng W. 2003. Neurobehavioral, autonomic nervous function and lymphocyte subsets among aluminum electrolytic workers. Int J Immunopathol Pharmacol 16(2):139-144.

Hellou J, Fancey LL, Payne JF. 1992a. Concentrations of twenty-four elements in bluefin tuna, Thunnus thynnus from the Northwest Atlantic. Chemosphere 24(2):211-218.

Hellou J, Warren WG, Payne JF, et al. 1992b. Heavy metals and other elements in three tissues of cod, Gadus morhua from the Northwest Atlantic. Mar Pollut Bull 24(9):452-458.

Henshaw PF, Bewtra JK, Biswas N. 1993. Occurrence of aluminum, lead, and trihalomethanes in drinking water from the Great Lakes. J Great Lakes Res 19:521-532.

Herbert A, Sterling G, Abraham J, et al. 1982. Desquamative interstitial pneumonia in an aluminum welder. Hum Pathol 13(8):694-699.

Hermenegildo C, Saez R, Minoia C, et al. 1999. Chronic exposure to aluminum impairs the glutamate-nitric oxide-cyclic GMP pathway in the rat in vivo. Neurochem Int 34(3):245-253.

*Hewitt CD, Innes DJ, Herman MM, et al. 1992. Hematological changes after long-term aluminum administration to normal adult rabbits. Ann Clin Lab Sci 22(2):85-94.

Heyman A, Wilkinson WE, Stafford JA, et al. 1984. Alzheimer's disease: A study of epidemiological aspects. Ann Neurol 15(4):335-341.

His E, Beiras R, Seaman MN, et al. 1996. Sublethal and lethal toxicity of aluminum industry effluents to early developmental stages of the Crassostrea gigas oyster. Arch Environ Contam Toxicol 30:335-339.

Hoel DG, Davis DL, Miller AB, et al. 1992. Trends in cancer mortality in 15 industrialized countries, 1969-1986. J Natl Cancer Inst 84(5):313-320.

Hoffman GL, Duce RA, Zoller WH. 1969. Vanadium, copper, and aluminum in the lower atmosphere between California and Hawaii. Environ Sci Technol 3:1207-1210.

Hohl C, Gerisch P, Korschinek G, et al. 1994. Medical application of 26Al. Nucl Instr Meth Phys Res B 92:478-482.

Hosovski E, Mastelica Z, Sunderic D, et al. 1990. Mental abilities of workers exposed to aluminum. Med Lav 81(2):119-123.

Hostynek JJ, Hinz RS, Lorence CR, et al. 1993. Metals and the skin. Crit Rev Toxicol 23:171-235.

House RA. 1992. Factors affecting plasma aluminum concentrations in nonexposed workers. J Occup Med 34:1013-1017.

Hovatta O, Venalainen E-R, Kuusimaki L, et al. 1998. Aluminum, lead and cadmium concentrations in seminal plasma and spermatozoa, and semen quality in Finnish men. Hum Reprod 13(1):115-119.

HSDB. 2008. Aluminum and compounds. Hazardous Substances Data Bank. Bethesda, MD: National Library of Medicine. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB. January 9, 2008.

Huang JY, Wu MS, Wu CH. 2001. The effect of an iron supplement on serum aluminum level and desferrioxamine mobilization test in hemodialysis patients. Ren Fail 23(6):789-95.

Hull MJ, Abraham JL. 2002. Aluminum welding fume-induced pneumoconiosis. Hum Pathol 33(8):819-825.

IARC. 1984. Polynuclear aromatic compounds. Part 3: Industrial exposures in aluminum production, coal gasification, coke production, and iron and steel founding. Vol. 34. Lyon, France: World Health Organization, International Agency for Research on Cancer, 37-64.

IARC. 1987. Aluminum production. Overall evaluation of carcinogenicity: An updating of IARC monographs (Volumes 1 to 42). Supplement 7. Lyon, France: World Health Organization, International Agency for Research on Cancer, 89-91.

ICRP. 1994. Human respiratory tract model for radiological protection. ICRP publication 66. Oxford: Pergamon Press, 1-120.

*Ijomah G, Corrigan FM, Holliday J, et al. 1993. Aluminum, cadmium, lipids and prevalence of dementia in people living near an aluminum smelter. Trace Elem Med 10:6-12.

Ikem A, Nwankwoala A, Odueyungbo S, et al. 2002. Levels of 26 elements in infant formula from USA, UK, and Nigeria by microwave digestion and ICP-OES. Food Chem 77(4):439-447.

Imahori A, Fukushima I, Shiobara S, et al. 1979. Multielement neutron activation analysis of human scalp hair. A local population survey in the Tokyo metropolitan area. J Radioanal Chem 52(1):167-180.

Iregren A, Sjogren B, Gustafsson K, et al. 2001. Effect on the nervous system in different groups of workers exposed to aluminium. Occup Environ Med 58(7):453-460.

IRIS. 2008. Aluminum phosphide. Integrated Risk Information System. Washington, DC: U.S. Environmental Protection Agency. http://www.epa.gov/iris/subst/index.html. March 08, 2006.

Ittel TH, Buddington B, Miller NL, et al. 1987. Enhanced gastrointestinal absorption of aluminum in uremic rats. Kidney Int 32(6):821-826.

Jacqmin H, Commenges D, Letenneur L, et al. 1994. Components of drinking water and risk of cognitive impairment in the elderly. Am J Epidemiol 139(1):48-57.

Jacqmin-Gadda H, Commenges D, Letenneur L, et al. 1996. Silica and aluminum in drinking water and cognitive impairment in the elderly. Epidemiology 7:281-285.

James BR, Riha SJ. 1989. Aluminum leaching by mineral acids in forest soils: I. Nitric-sulfuric acid differences. Soil Sci Soc Am J 53:259-264.

Jansen S, Broadley MR, Robbrecht E, et al. 2002. Aluminum hyperaccumulation in angiosperms: A review of its phylogenetic significance. Bot Rev 68(2):235-269.

Jederlinic PJ, Abraham JL, Churg A, et al. 1990. Pulmonary fibrosis in aluminum oxide workers. Investigation of nine workers with pathologic examination and microanalysis in three of them. Am Rev Respir Dis 142:1179-1184.

Jeffery EH, Abreo K, Burgess E, et al. 1996. Systemic aluminum toxicity: Effects on bone, hematopoietic tissue, and kidney. J Toxicol Environ Health 48(6):649-665.

Jephcott CM. 1948. Fume exposure in the manufacture of alumina abrasives. Occup Med 5:701-709.

Jernelov A. 1971. Phosphate reduction in lakes by precipitation with aluminum sulphate. In: Jenkins SH, ed. Advances in water pollution research: Proceedings of the Fifth International Conference held in San Francisco and Hawaii, 1970. New York, NY: Pergamon Press, I-15/1 to I-15/6.

Jing Y, Wang Z, Song Y. 2004. Quantitative study of aluminum-induced changes in synaptic ultrastructure in rats. Synapse 52(4):292-298.

Johanson CE. 1980. Permeability and vascularity of the developing brain: Cerebellum vs cerebral cortex. Brain Res 190:3-16.

Johnson VJ, Kim SH, Sharma RP. 2005. Aluminum-maltolate induces apoptosis and necrosis in Neuro-2a cells: Potential role for p53 signaling. Toxicol Sci 83(2):329-339.

Jones KC, Bennett BG. 1986. Exposure of man to environmental aluminum-An exposure commitment assessment. Sci Total Environ 52(1-2):65-82.

Jope RS, Johnson GVW. 1992. Neurotoxic effects of dietary aluminum. Aluminum in biology and medicine. Ciba Found Symp 169:254-267.

*Jordan JW. 1961. Pulmonary fibrosis in a worker using an aluminum powder. Br J Ind Med 18:21-23.

Joshi SP, Toma RB, Medora N, et al. 2003. Detection of aluminum residue in sauces packaged in aluminum pouches. Food Chem 83(3):383-386.

Jouhanneau P, Lacour B, Raisbeck G, et al. 1993. Gastrointestinal absorption of aluminum in rats using 26Al and accelerator mass spectrometry. Clin Nephrol 40(4):244-248.

Jouhanneau P, Raisbeck GM, Yiou F, et al. 1997. Gastrointestinal absorption, tissue retention, and urinary excretion of dietary aluminum in rats determined by using 26Al. Clin Chem 43(6 Part 1):1023-1028.

Jugdaohsingh R, Reffitt DM, Oldham C, et al. 2000. Oligomeric but not monomeric silica prevents aluminum absorption in humans. Am J Clin Nutr 71(4):944-949.

Julka D, Gill KD. 1995. Development of a possible peripheral marker for aluminum neurotoxicity. Med Sci Res 23:311-314.

Julka D, Vasishta RK, Gill KD. 1996. Distribution of aluminum in different brain regions and body organs of rat. Biol Trace Elem Res 52(2):181-192.

Jyoti A, Sharma D. 2006. Neuroprotective role of Bacopa monniera extract against aluminium-induced oxidative stress in the hippocampus of the brain. Neurotoxicology 27(4):451-457.

Kabata-Pendias A, Pendias H, eds. 1984. Trace elements in soils and plants. Boca Raton, FL: CRC Press, Inc., 134-136.

Kada T, Hirano K, Shirasu Y. 1980. Screening of environmental chemical mutagens by the rec-assay system with Bacillus subtilis. Chem Mutagen 6:149-173.

Kaehny WD, Hegg AP, Alfrey AC. 1977. Gastrointestinal absorption of aluminum from aluminum-containing antacids. N Engl J Med 296(24):1389-1390.

Kaizer RR, Correa MC, Spanevello RM, et al. 2005. Acetylcholinesterase activation and enhanced lipid peroxidation after long-term exposure to low levels of aluminum on different mouse brain regions. J Inorg Biochem 99(9):1865-1870.

*Kandiah J, Kies C. 1994. Aluminum concentrations in tissues of rats: Effect of soft drink packaging. BioMetals 7(1):57-60.

Kanematsu N, Hara M, Kada T. 1980. Rec assay and mutagenicity studies on metal compounds. Mutat Res 77:109-116.

Karlik SJ, Eichhorn GL, Crapper-McLachlan DR. 1980. Molecular interactions of aluminum with DNA. Neurotoxicology 1:83-88.

Katz AC, Frank DW, Sauerhoff MW, et al. 1984. A 6-month dietary toxicity study of acidic sodium aluminum phosphate in beagle dogs. Food Chem Toxicol 22(1):7-9.

Keeler R. 1991. ICP mass spectrometry shows its mettle. Res Dev 33:44-48.

Keirsse H, Smeyers-Verbeke J, Verbeelen D, et al. 1987. Critical study of the speciation of aluminum in biological fluids by size-exclusion chromatography and electrothermal atomic absorption spectrometry. Anal Chim Acta 196:103-114.

Khanna P, Nehru B. 2007. Antioxidant enzymatic system in neuronal and glial cells enriched fractions of rat brain after aluminum exposure. Cell Mol Neurobiol 27(7):959-969.

Khosla SN, Nand N, Khosla P. 1988. Aluminum phosphide poisoning. J Trop Med Hyg 91:196-198.

Kiesswetter E, Schoeper M, Buchta M, et al. 2007. Longitudinal study on potential neurotoxic effects of aluminium: I. Assessment of exposure and neurobehavioural performance of Al welders in the train and truck construction industry over 4 years. Int Arch Occup Environ Health 81(1):41-67.

Kilburn KH. 1998. Pulmonary and neurological effects of aluminum. In: Rom WN, ed. Environmental and occupational medicine. Philadelphia, PA: Lippincott-Raven, 1065-1073.

King SW, Savory J, Wills MR. 1981. The clinical biochemistry of aluminum. CRC Crit Rev Clin Lab Sci 14:1-20.

Kinney PL, Chillrud SN, Ramstrom S, et al. 2002. Exposures to multiple air toxics in New York City. Environ Health Perspect 110(Suppl 4):539-546.

*Kirsner JB. 1942. The effect of calcium carbonate, aluminum phosphate, and aluminum hydroxide on mineral excretion in man. J Clin Invest 22:47-52.

Kislinger G, Steinhausen C, Alvarez-Bruckmann M, et al. 1997. Investigations of the human aluminium biokinetics with 26Al and AMS. Nucl Instrum Methods Phys Res B 123:259-265.

Klein GL, Snodgrass WR, Griffin MP, et al. 1989. Hypocalcemia complicating deferoxamine therapy in an infant with parenteral nutrition-associated aluminum overload: Evidence for a role of aluminum in the bone disease of infants. J Pediatr Gastroenterol Nutr 9:400-403.

Klosterkotter W. 1960. Effects of ultramicroscopic gamma-aluminum oxide on rats and mice. AMA Arch Ind Health 21:458-472.

*Kobayashi N, Ide G, Katsuki H, et al. 1968. Effects of aluminum compound on the development of experimental lung tumor in mice. Jpn J Cancer Res 59:433-436.

Kobayashi S, Fujiwara S, Arimoto S, et al. 1989. Hair aluminium in normal aged and senile dementia of Alzheimer type. Prog Clin Biol Res 317:1095-1109.

Koch KR, Pougnet MAB, De Villiers S. 1989. Determination of aluminium levels in tea and coffee by inductively coupled plasma optical emission spectrometry and graphite furnace atomic absorption spectrometry. Analyst 114:911.

Kohila T, Parkkonen E, Tahti H. 2004. Evaluation of the effects of aluminum, ethanol and their combination on rat brain synaptosomal integral proteins in vitro and after 90-day oral exposure. Arch Toxicol 78(5):276-282.

Komori M, Nishio K, Kitada M, et al. 1990. Fetus-specific expression of a form of cytochrome P-450 in human liver. Biochemistry 29:4430-4433.

Konishi Y, Yagyu K, Kinebuchi H, et al. 1996. Chronic effect of aluminum ingestion on bone in calcium-deficient rats. Pharmacol Toxicol 78:429-434.

Koo WWK, Kaplan LA, Bendon R, et al. 1986. Response to aluminum in parenteral nutrition during infancy. J Pediatr 109(5):877-883.

Koo WWK, Kaplan LA, Krug-Wispe SK. 1988. Aluminum contamination of infant formulas. J Parenter Enteral Nutr 12(2):170-173.

Koo WWK, Krug-Wispe SK, Succop P, et al. 1992. Sequential serum aluminum and urine aluminum: Creatinine ratio and tissue aluminum loading in infants with fractures/rickets. Pediatrics 89(5 Part 1):877-881.

Korogiannos C, Babatsikou F, Tzimas S, et al. 1998. Aluminum compounds and occupational lung disease. Eur Respir J 12(Suppl 28):139S.

*Kovalchik MT, Kaehny WD, Hegg AP, et al. 1978. Aluminum kinetics during hemodialysis. J Lab Clin Med 92:712-720.

Kowalczyk GS, Gordon GE, Rheingrover SW. 1982. Identification of atmospheric particulate sources in Washington, DC, using chemical element balances. Environ Sci Technol 16:79-90.

Krantzberg G, Stokes PM. 1990. Metal concentrations and tissues distribution in larvae of Chironomus with reference to x-ray microprobe analysis. Arch Environ Contam Toxicol 19:84-93.

Krasovskii GN, Vasukovich LY, Chariev OG. 1979. Experimental study of biological effects of lead and aluminum following oral administration. Environ Health Perspect 30:47-51.

Kraus T, Schaller KH, Angerer J, et al. 2000. Aluminum dust-induced lung disease in the pyro-powder-producing industry: Detection by high-resolution computed tomography. Int Arch Occup Environ Health 73(1):61-64.

Krishnan K, Andersen ME. 1994. Physiologically-based pharmacokinetic modeling in toxicology. In: Hayes AW, ed. Principles and methods of toxicology. New York, NY: Raven Press, Ltd., 149-188.

Krishnan K, Andersen ME, Clewell H, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures. In: Yang R, ed. Toxicology of chemical mixtures. New York: Academic Press, 399-437.

Lal B, Gupta A, Gupta A, et al. 1993. Aluminum ingestion alters behaviour and some neurochemicals in rats. Indian J Exp Biol 31(1):30-35.

Lansdown AB. 1973. Production of epidermal damage in mammalian skins by some simple aluminum compounds. Br J Dermatol 89:67-76.

Lantzy RJ, MacKenzie FT. 1979. Atmospheric trace metals: Global cycles and assessment of man's impact. Geochim Cosmochim Acta 43(4):511-525.

Lauricella AM, Garbossa G, Nesse A. 2001. Dissimilar behavior of lymph cells in response to the action of aluminum. In vitro and in vivo studies. Int Immunopharmacol 1(9-10):1725-1732.

Leblondel G, Allain P. 1980. Blood and brain aluminum concentrations in mice after intraperitoneal injection of different aluminum compounds. Res Commun Chem Pathol Pharmacol 27(3):579-586.

Lee RE Jr, Von Lehmden DJ. 1973. Trace metal pollution in the environment. J Air Pollut Control Assoc 23(1):853-857.

Leeder JS, Kearns GL. 1997. Pharmacogenetics in pediatrics: Implications for practice. Pediatr Clin North Am 44:55-77.

LeGendre GR, Alfrey AC. 1976. Measuring picogram amounts of aluminum in biological tissue by flameless atomic absorption analysis of a chelate. Clin Chem 22:53-56.

Leikin JB, Paloucek FP. 2002. Leikin and Paloucek’s poisoning and toxicology handbook. 3rd ed. Hudson, OH: Lexi-Comp, Inc., 214-217.

Letterman RD, Driscoll CT. 1988. Survey of residual aluminum in filtered water. J Am Water Works Assoc 80(4):154-158.

Letzel S, Schaller KH, Angerer J, et al. 1996. Biological monitoring of occupational aluminium powder exposure. Occup Hyg 3:271-280.

Leung H-W. 1993. Physiologically-based pharmacokinetic modelling. In: Ballentine B, Marro T, Turner P, eds. General and applied toxicology. New York: Stockton Press, 153-164.

Lewis C, Macias ES. 1980. Composition of size-fractionated aerosol in Charleston, West Virginia. Atmos Environ 14:185-194.

Lewis RJ, ed. 2001. Hawley's condensed chemical dictionary. New York, NY: John Wiley & Sons, Inc., 39-46, 118, 555.

Liao YH, Yu HS, Ho CK, et al. 2004. Biological monitoring of exposures to aluminium, gallium, indium, arsenic, and antimony in optoelectronic industry workers. J Occup Environ Med 46(9):931-936.

Lichte FE, Hopper S, Osborn TW. 1980. Determination of silicon and aluminum in biological matrices by inductively coupled plasma emission spectrometry. Anal Chem 52(1):120-124.

Lide DR, ed. 2005. CRC handbook of chemistry and physics. New York, NY: CRC Press, 4-3 to 4-4, 4-44 to 4-46, 4-79.

Lim B, Jickells TD. 1990. Dissolved, particulate and acid-leachable trace metal concentrations in North Atlantic precipitation collected on the Global Change expedition. Global Biogeochem Cycles 4:445-458.

Lin JL, Yang YJ, Yang SS, et al. 1997. Aluminum utensils contribute to aluminum accumulation in patients with renal disease. Am J Kidney Dis 30:653-665.

Lione A. 1983. The prophylactic reduction of aluminum intake. Food Chem Toxicol 21(1)103-109.

Lione A. 1985a. Aluminum intake from non-prescription drugs and sucralfate. Gen Pharmacol 16(3):223-228.

Lione A. 1985b. Aluminum toxicology and the aluminum-containing medications. Pharmacol Ther 29(2):255-285.

Lione A, Allen PV, Smith JC. 1984. Aluminum coffee percolators as a source of dietary aluminum. Food Chem Toxicol 22(4):265-268.

Liss L, Thornton DJ. 1986. The rationale for aluminum absorption control in early stages of Alzheimer's disease. Neurobiol Aging 7(6):552-554.

Litaor MI. 1987. Aluminum chemistry: Fractionation, speciation, and mineral equilibria of soil interstitial waters of an alpine watershed, Front Range, Colorado. Geochim Cosmochim Acta 51:1285-1295.

Litov RE, Sickles VS, Chan GM, et al. 1989. Plasma aluminum measurements in term infants fed human milk or a soy-based infant formula. (Comment in: Pediatrics 86(4):650-652). Pediatrics 84(6):1105-1107.

Livingston AL. 1978. Forage plant estrogens. J Toxicol Environ Health 4(2-3):301-324.

Ljunggren KG, Lidums V, Sjogren B. 1991. Blood and urine concentrations of aluminum among workers exposed to aluminum flake powders. Br J Ind Med 48:106-109.

Llansola M, Minana MD, Montoliu C, et al. 1999. Prenatal exposure to aluminum reduces expression of neuronal nitric oxide synthase and of soluble guanylate cyclase and impairs glutamatergic neurotransmission in rat cerebellum. J Neurochem 73(2):712-718.

Llobet JM, Domingo JL, Gomez M, et al. 1987. Acute toxicity studies of aluminum compounds: Antidotal efficacy of several chelating agents. Pharmacol Toxicol 60:280-283.

Lopez FF, Cabrera C, Lorenzo ML, et al. 1998. Aluminium levels in wine, beer and other alcoholic beverages consumed in Spain. Sci Total Environ 220(1):1-9.

López FF, Cabrera C, Lorenzo ML, et al. 2000. Aluminium levels in spices and aromatic herbs. Sci Total Environ 257(2-3):191-197.

Lovell MA, Ehmann WD, Markesbery WR. 1993. Laser microprobe analysis of brain aluminum in Alzheimer's disease. Ann Neurol 33(1):36-42.

Lowe TP, Day DD. 2002. Metal concentrations in zebra mussels and sediments from embayments and riverine environments of eastern Lake Erie, southern Lake Ontario, and the Niagara River. Arch Environ Contam Toxicol 43(3):301-308.

Ma LQ, Tan F, Harris WG. 1997. Concentrations and distributions of eleven metals in Florida soils. J Environ Qual 26:769-775.

Macdonald TL, Martin RB. 1988. Aluminum ion in biological systems. Trends Biochem Sci 13(1):15-19.

Madigosky SR, Alvarez-Hernandez X, Glass J. 1991. Lead, cadmium, and aluminum accumulation in the Red Swamp crayfish (Procambarus clarkii g.) collected from roadside drainage ditches in Louisiana. Arch Environ Contam Toxicol 20:253-258.

MAFF. 1999. MAFF UK - 1997 Total diet study: Aluminium, arsenic, cadmium, chromium, copper, lead, mercury, nickel, selenium, tin and zinc. Ministry of Agriculture, Fisheries and Food. Joint Food Safety and Standards Group. Food Surveillance Information Sheet Number 191. http://archive.food.gov.uk/maff/archive/food/infsheet/1999/no191/191tds.htm. June 06, 2006.

Mahieu S, Calvo ML, Millen N, et al. 1998. Crecimiento y metabolismo del calcio en ratas sometidas a intoxicacion cronica con hidroxido de aluminio. Acta Physiol Pharmacol Ther Latinoam 48:32-40.

Mahieu S, Millen N, Contini Mdel C, et al. 2006. Urinary concentrating mechanism and Aquaporin-2 abundance in rats chronically treated with aluminum lactate. Toxicology 223(3):209-218.

Mahieu S, Millen N, Gonzalez M, et al. 2005. Alterations of the renal function and oxidative stress in renal tissue from rats chronically treated with aluminum during the initial phase of hepatic regeneration. J Inorg Biochem 99:1858-1864.

Mahieu ST, Gionotti M, Millen N, et al. 2003. Effect of chronic accumulation of aluminum on renal function, cortical renal oxidative stress and cortical renal organic anion transport in rats. Arch Toxicol 77(11):605-612.

Main J, Ward MK. 1992. Potentiation of aluminum absorption by effervescent analgesic tablets in a haemodialysis patient. Br Med J 304(6843):1686.

Maitani T, Kubota H, Hori N, et al. 1994. Distribution and urinary excretion of aluminum injected with several organic acids into mice: Relationship with chemical state in serum studied by the HPLC-ICP method. J Appl Toxicol 14(4):257-261.

Makjanic J, McDonald B, Chen CPLH, et al. 1998. Absence of aluminum in neurofibrillary tangles in Alzheimer's disease. Neurosci Lett 240(3):123-126.

Malakoff D. 2000. Public health. Aluminum is put on trial as a vaccine booster. Science 288(5470):1323-1234.

Mameli O, Caria MA, Melis P, et al. 2006. Effect of aluminum consumption on the vestibulo-ocular reflex. Metab Brain Dis 21(2-3):89-107.

Mandić ML, Grgic J, Grgic Z, et al. 1995. Aluminum levels in human milk. Sci Total Environ 170:165-170.

Manna GK, Das RK. 1972. Chromosome aberrations in mice induced by aluminum chloride. Nucleus 15:180-186.

Markesbery WR, Ehmann WD, Alauddin M, et al. 1984. Brain trace element concentrations in aging. Neurobiol Aging 5:19-28.

Markesbery WR, Ehmann WD, Hossain TIM, et al. 1981. Instrumental neutron activation analysis of brain aluminum in Alzheimer disease and aging. Ann Neurol 10:511-516.

Martell AE, Motekaitis RJ. 1989. Coordination chemistry and speciation of Al (III) in aqueous solution. In: Lewis TE, ed. Environmental chemistry and toxicology of aluminum. Chelsea, MI: Lewis Publishers, Inc., 3-17.

Martin RB. 1986. The chemistry of aluminum as related to biology and medicine. Clin Chem 32(10):1797-1806.

Martino FAR, Fernandez-Sanchez ML, Sanz-Medel A. 2000. Total determination of essential and toxic elements in milk whey by double focusing ICP-MS. J Anal Atom Spectrom 15(2):163-168.

Martyn CN, Coggon DN, Inskip H, et al. 1997. Aluminum concentrations in drinking water and risk of Alzheimer’s disease. Epidemiol 8:281-286.

Martyn CN, Osmond C, Edwardson JA, et al. 1989. Geographical relation between Alzheimer's disease and aluminum in drinking water. Lancet 1(8629):59-62.

Marumo F, Tsukamoto Y, Iwanami S, et al. 1984. Trace element concentrations in hair, fingernails and plasma of patients with chronic renal failure on hemodialysis and hemofiltration. Nephron 38:267-272.

Marzin DR, Phi HV. 1985. Study of the mutagenicity of metal derivatives with Salmonella-typhimurium TA102m. Mutat Res 155(1-2):49-51.

*Mayor GH, Burnatowska-Hledin MA. 1983. Impaired renal function and aluminum metabolism. Fed Proc 42:2979-2983.

Mayor GH, Lohr TO, Sanchez TV, et al. 1985. Aluminum metabolism and toxicity in renal failure: A review. J Environ Pathol Toxicol Oncol 6(1):43-50.

Mayr U, Butsch A, Schneider S. 1992. Validation of two in vitro test systems for estrogenic activities with zearalenone, phytoestrogens and cereal extracts. Toxicology 74(2-3):135-149.

McCormack KM, Ottosen LD, Sanger VL, et al. 1979. Effect of prenatal administration of aluminum and parathyroid hormone on fetal development in the rat (40493). Proc Soc Exp Biol Med 161:74-77.

McDermott JR, Smith AI, Iqbal K, et al. 1979. Brain aluminum in aging and Alzheimer disease. Neurology 29(6):809-814.

McDermott JR, Smith AI, Ward MK, et al. 1978. Brain-aluminum concentration in dialysis encephalopathy. Lancet 1(8070):901-904.

McDonald DG, Wood CM, Rhem RG, et al. 1991. Nature and time course of acclimation to aluminum in juvenile brook trout (Salvelinus fontinalis). 1. Physiology. Can J Fish Aquat Sci 48:2006-2015.

McDowell I, Hill G, Lindsay J, et al. 1994. The Canadian study of health and aging: Risk factors for Alzheimer's disease in Canada. Neurology 44:2073-2080.

McKeever SWS, Moscovitch M, Townsend PD, eds. 1995. Aluminum oxide. Thermoluminescence dosimetry materials: Properties and uses. Kent, England: Nuclear Technology Publishing, 117-132.

McLachlan DRC, Bergeron C, Smith JE, et al. 1996. Risk for neuropathologically confirmed Alzheimer's disease and residual aluminum in municipal drinking water employing weighted residential histories. Neurology 46(2):401-405.

McLaughlin AIG, Kazantzis G, King E, et al. 1962. Pulmonary fibrosis and encephalopathy associated with the inhalation of aluminum dust. Br J Ind Med 19:253-263.

Meiklejohn A, Posner E. 1957. The effect of the use of calcined alumina in china biscuit placing on the health of the workman. Br J Ind Med 14:229-231.

Menounou N, Presley BJ. 2003. Mercury and other trace elements in sediment cores from central Texas lakes. Arch Environ Contam Toxicol 45(1):11-29.

Meyer-Baron M, Schaper M, Knapp G, et al. 2007. Occupational aluminum exposure: Evidence in support of its neurobehavioral impact. Neurotoxicology 28(6):1068-1078.

Michel P, Commenges D, Dartigues JF, et al. 1990. Study of the relationship between Alzheimer's disease and aluminum in drinking water. Neurobiol Aging 11:264.

Migliore L, Cocchi L, Nesti C, et al. 1999. Micronuclei assay and FISH analysis in human lymphocytes treated with six metal salts. Environ Mol Mutagen 34(4):279-284.

Milham S Jr. 1979. Mortality in aluminum reduction plant workers. J Occup Med 21(7):475-480.

Miller RG, Kopfler FC, Kelty KC, et al. 1984a. The occurrence of aluminum in drinking water. J Am Water Works Assoc 76:84-91.

Miller RR, Churg AM, Hutcheon M, et al. 1984b. Pulmonary alveolar proteinosis and aluminum dust exposure. Am Rev Respir Dis 130(2):312-315.

Milliner DS, Malekzadeh M, Lieberman E, et al. 1987. Plasma aluminum levels in pediatric dialysis patients: Comparison of hemodialysis and continuous ambulatory peritoneal dialysis. Mayo Clin Proc 62(4):269-274.

Misawa T, Shigeta S. 1992. Behavioral effects of repeated aluminum administration in the rat. Tokai J Exp Clin Med 17:155-159.

Missel JR, Schetinger MR, Gioda CR, et al. 2005. Chelating effect of novel pyrimidines in a model of aluminum intoxication. J Inorg Biochem 99(9):1853-1857.

Mitchell J, Manning GB, Molyneux M, et al. 1961. Pulmonary fibrosis in workers exposed to finely powdered aluminum. Br J Ind Med 18:10-20.

Molitoris BA, Froment DH, Mackenzie TA, et al. 1989. Citrate: A major factor in the toxicity of orally administered aluminum compounds. Kidney Int 36:949-953.

Molloy DW, Standish TI, Nieboer E, et al. 2007. Effects of acute exposure to aluminum on cognition in humans. J Toxicol Environ Health A 70(23):2011-2019.

*Monteagudo FSE, Isaacson LC, Wilson G, et al. 1988. Aluminum excretion by the distal tubule of the pig kidney. Nephron 49(3):245-250.

Montoliu C, Felipo V. 2001. Aluminum interferes with NMDA receptor-associated signal transduction and with the process of glutamate neurotoxicity in cerebellar neurons in culture. Neurotoxicology 22(4):535.

Moomaw JC, Nakamura MT, Sherman GD. 1959. Aluminum in some Hawaiian plants. Pac Sci 13:335-341.

Moreno A, Dominguez C, Ballabriga A. 1994. Aluminum in the neonate related to parenteral nutrition. Acta Paediatr 83(1):25-29.

Morris CM, Candy JM, Oakley AE, et al. 1989. Comparison of the regional distribution of transferrin receptors and aluminium in the forebrain of chronic renal dialysis patients. J Neurol Sci 94:295-306.

Morrow PE. 1988. Possible mechanisms to explain dust overloading of the lungs. Fundam Appl Toxicol 10:369-384.

Morselli PL, Franco-Morselli R, Bossi L. 1980. Clinical pharmacokinetics in newborns and infants. Clin Pharmacokin 5:485-527.

Moshtaghie AA, Skillen AW. 1986. Binding of aluminum to transferrin and lactoferrin. Biochem Soc Trans 14:916-917.

Moyers JL, Ranweiler LE, Hopf SB, et al. 1977. Evaluation of particulate trace species in Southwest desert atmosphere. Environ Sci Technol 11(8):789-795.

Mulder J, Vanbreemen N, Eijck HC. 1989. Depletion of soil aluminum by acid deposition and implications for acid neutralization. Nature 337:247-249.

Muller G, Bernuzzi V, Desor D, et al. 1990. Developmental alterations in offspring of female rats orally intoxicated by aluminum lactate at different gestation periods. Teratology 42(3):253-261.

*Muller G, Burnel D, Gery A, et al. 1993a. Element variations in pregnant and nonpregnant female rats orally intoxicated by aluminum lactate. Biol Trace Elem Res 39:211-219.

Muller G, Hutin M-F, Burnel D, et al. 1992. Aluminum transfer through milk in female rats intoxicated by aluminum chloride. Biol Trace Elem Res 34(1):79-87.

Muller JP, Steinegger A, Schlatter C. 1993b. Contribution of aluminum from packaging materials and cooking utensils to the daily aluminum intake. Z Lebensm Unters Forsch 197(4):332-341.

Müller M, Anke M, Illing-Gunther. 1998. Aluminium in foodstuffs. Food Chem 64(4):419-428.

Mundy WR, Freudenrich T, Shafer TJ, et al. 1995. In vitro aluminum inhibition of brain phosphoinositide metabolism: Comparison of neonatal and adult rats. Neurotoxicology 16:35-44.

Munoz DG. 1998. Is exposure to aluminum a risk factor for the development of Alzheimer disease?—No. Arch Neurol 55(5):737-739.

Mur JM, Moulin JJ, Meyer-Bisch C, et al. 1987. Mortality of aluminum reduction plant workers in France. Int J Epidemiol 16:257-264.

Musk AW, deKlerk NH, Beach JR, et al. 2000. Respiratory symptoms and lung function in alumina refinery employees. Occup Environ Med 57(4):279-283.

Musk AW, Greeville HW, Tribe AE. 1980. Pulmonary disease from occupational exposure to an artificial aluminum silicate used for cat litter. Br J Ind Med 37(4):367-372.

Mussi I, Calzaferri G, Buratti M, et al. 1984. Behaviour of plasma and urinary aluminum levels in occupationally exposed subjects. Int Arch Occup Environ Health 54(2):155-161.

Nagy S, Nikdel S. 1986. Tin, iron and aluminum contents of commercially canned single-strength grapefruit juice stored at varying temperatures. J Agric Food Chem 34:588-593.

NAS/NRC. 1989. Report of the oversight committee. In: Biologic markers in reproductive toxicology. Washington, DC: National Academy of Sciences, National Research Council, National Academy Press, 15-35.

Navarro-Blasco I, Alvarez-Galindo JI. 2003. Aluminum content of Spanish infant formula. Food Addit Contam 20(5):470-481.

Nayak P. 2002. Aluminum: Impacts and disease. Environ Res 89(2):101-115.

Naylor KE, Eastell R, Shattuck KE, et al. 1999. Bone turnover in preterm infants. Pediatr Res 45(3):363-363.

Nedzvetsky VS, Tuzcu M, Yasar A, et al. 2006. Effects of vitamin E against aluminum neurotoxicity in rats. Biochemistry 71(3):239-244.

Nehru B, Anand P. 2005. Oxidative damage following chronic aluminium exposure in adult and pup rat brains. J Trace Elem Med Biol 19(2-3):203-208.

Nehru B, Bhalla P. 2006. Reversal of an aluminium induced alteration in redox status in different regions of rat brain by administration of centrophenoxine. Mol Cell Biochem 290(1-2):185-191.

Nehru B, Bhalla P, Garg A, et al. 2007. Further evidence of centrophenoxine mediated protection in aluminum exposed rats by biochemical and light microscopy analysis. Food Chem Toxicol 45(12):2499-2505.

Nelson WO, Campbell PGC. 1991. The effects of acidification on the geochemistry of Al, Cd, Pb, and Hg in freshwater environments: A literature review. Environ Pollut 71:91-130.

Neri LC, Hewitt D. 1991. Aluminum, Alzheimer's disease, and drinking water. Lancet 338(8763):390.

Nieboer E, Gibson BL, Oxman AD, et al. 1995. Health effects of aluminum: A critical review with emphasis on aluminum in drinking water. Environ Rev 3(1):29-81.

*Nielsen FH, Shuler TR, Zimmerman TJ, et al. 1988. Dietary magnesium, manganese and boron affect the response of rats to high dietary aluminum. Magnesium 7(3):133-147.

NIH. 2004. Aluminum compounds: Household products database. National Institutes of Health. U.S. National Library of Medicine. http://hpd.nlm.nih.gov/cgi-bin/household/search. March 15, 2006.

NIOSH. 1991. National occupational exposure survey matrix. Cincinnati, OH: Department of Health and Human Services, National Institute for Occupational Safety and Health. December 11, 1996.

NIOSH. 1994. Method 7013: Aluminum and compounds, as Al. NIOSH manual of analytical methods (NMAM). Washington, DC: National Institute for Occupational Safety and Hazards. http://www.cdc.gov/niosh/nmam/pdfs/7013.pdf. March 21, 2006.

NIOSH. 1997. Aluminum phosphide. International chemical safety cards. Atlanta, GA: National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. http://www.cdc.gov/niosh/ipcsneng/neng0472.html. March 22, 2006.

NIOSH. 2003a. Method 7300: Elements by ICP (nitric/perchloric acid ashing). NIOSH manual of analytical methods (NMAM). Cincinnati, OH: National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication 94-113. http://www.cdc.gov/niosh/nmam/pdfs/7300.pdf. March 21, 2006.

NIOSH. 2003b. Method 7303: Elements by ICP (hot block/HCl/HNO3 digestion). NIOSH manual of analytical methods (NMAM). Washington, DC: National Institute for Occupational Safety and Hazards. http://www.cdc.gov/niosh/nmam/pdfs/7303.pdf. March 21, 2006.

NIOSH. 2003c. Method 7301: Elements by ICP (aqua regia ashing). NIOSH manual of analytical methods (NMAM). Washington, DC: National Institute for Occupational Safety and Hazards. http://www.cdc.gov/niosh/nmam/pdfs/7301.pdf. March 21, 2006.

NIOSH. 2005. Aluminum and aluminum oxide. NIOSH pocket guide to chemical hazards. Atlanta, GA: National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. http://www.cdc.gov/niosh/npg/. January 14, 2008.

Nishioka H. 1975. Mutagenic activities of metal compounds in bacteria. Mutat Res 31:185-189.

Nolte E, Beck E, Winklhofer C, et al. 2001. Compartmental model for aluminum biokinetics. Hum Exp Toxicol 20(2):111-117.

Nostrandt AC, Shafer TJ, Mundy WR, et al. 1996. Inhibition of rat brain phosphatidylinositol-specific phospholipase C by aluminum: Regional differences, interactions with aluminum salts, and mechanisms. Toxicol Appl Pharmacol 136(1):118-125.

NPIRS. 2008. Aluminum phosphide. Chemical ingredients database. National Pesticide Information Retrieval System. U.S. Environmental Protection Agency, U.S. Department of Agriculture. http://ppis.ceris.purdue.edu/htbin/cnamlist.com. January 7, 2008.

NRC. 1982. Aluminum (Al). Drinking water and health. Vol. 4. Washington, DC: National Academy of Sciences, National Research Council, National Academy Press, 155-167.

NRC. 1993. Pesticides in the diets of infants and children. Washington, DC: National Research Council, National Academy Press.

NTP. 2004. Report on carcinogens. 11th ed. Research Triangle Park, NC: National Toxicology Program, Department of Health and Human Services. http://ntp-server.niehs.nih.gov/ntp/roc/toc11.html. January 11, 2008.

Nyholm NE. 1981. Evidence of involvement of aluminum in causation of defective formation of eggshells and of impaired breeding in wild passerine birds. Environ Res 26(2):363-71.

Oberly TJ, Piper CE, McDonald DS. 1982. Mutagenicity of metal salts in the L5178Y mouse lymphoma assay. J Toxicol Environ Health 9:367-376.

Offit PA, Jew RK. 2003. Addressing parents' concerns: Do vaccines contain harmful preservatives, adjuvants, additives, or residuals? Pediatrics 112(6 Part 1):1394-1397.

Ogasawara Y, Sakamoto T, Ishii K, et al. 2002. Effects of the administration routes and chemical forms of aluminum on aluminum accumulation in rat brain. Biol Trace Elem Res 86(3):269-278.

Olivier P, Marzin D. 1987. Study of the genotoxic potential of 48 inorganic derivatives with the SOS chromotest. Mutat Res 189:263-269.

Omokhodion FO, Howard JM. 1994. Trace elements in the sweat of acclimatized persons. Clin Chim Acta 231(1):23-28.

Ondov JM, Zoller WH, Gordon GE. 1982. Trace element emissions of aerosols from motor vehicles. Environ Sci Technol 16(6):318-328.

Ondreicka R, Ginter E, Kortus J. 1966. Chronic toxicity of aluminum in rats and mice and its effects on phosphorus metabolism. Br J Ind Med 23(4):305-312.

Oneda S, Takasaki T, Kurowaki K, et al. 1994. Chronic toxicity and tumorigenicity study of aluminum potassium sulfate in B6C3F1 mice. In Vivo 8(3):271-278.

O'Neil MJ, Smith A, Heckelman PE, et al. 2001. Aluminum and aluminum compounds. The Merck index. An encyclopedia of chemicals, drugs, and biologicals. Whitehouse Station, NJ: Merck & Co., Inc., 59-65.

OSHA. 2001. Method ID-109-SG: Aluminum oxide in workplace atmospheres. Sampling and analytical methods. Occupational Safety and Health Administration. U.S. Department of Labor. http://www.osha.gov/dts/sltc/methods/inorganic/t-id109sg-pv-02-0110-m/t-id109sg-pv-02-0110-m.html. March 07, 2006.

OSHA. 2002. Method ID-121: Metal and metalloid particulates in workplace atmospheres (atomic absorption). Sampling and analytical methods. Occupational Safety and Health Administration. U.S. Department of Labor. http://www.osha.gov/dts/sltc/methods/inorganic/id121/id121.html. March 21, 2006.

OSHA. 2007a. Air contaminants. Occupational safety and health standards for shipyard employment. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1915.1000. http://edocket.access.gpo.gov/cfr_2007/julqtr/pdf/29cfr1915.1000.pdf. July 30, 2008.

OSHA. 2007b. Limits for air contaminants. Occupational safety and health standards. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000. http://edocket.access.gpo.gov/cfr_2007/julqtr/pdf/29cfr1910.1000.pdf. July 30, 2008.

OTA. 1990. Neurotoxicology: Identifying and controlling poisons of the nervous system. Washington, DC: Office of Technology Assessment. OTA-BA-438.

Oteiza PI, Golub MS, Gershwin ME, et al. 1989. The influence of high dietary aluminum on brain microtubule polymerization in mice. Toxicol Lett 47:279-285.

Oteiza PI, Keen CL, Han B, et al. 1993. Aluminum accumulation and neurotoxicity in Swiss-Webster mice after long-term dietary exposure to aluminum and citrate. Metabolism 42(10):1296-1300.

Owen GM, Brozek J. 1966. Influence of age, sex, and nutrition on body composition during childhood and adolescence. In: Falkner F, ed. Human development. Philadelphia, PA: WB Saunders, 222-238.

Owen LMW, Crews HM, Bishop NJ, et al. 1994. Aluminum uptake from some foods by guinea pigs and the characterization of aluminum in in vivo intestinal digesta by sec-ip-ms. Food Chem Toxicol 32(8):697-705.

Partridge NA, Regnier FE, White JL, et al. 1989. Influence of dietary constituents on intestinal absorption of aluminum. Kidney Int 35(6):1413-1417.

Paternain JL, Domingo JL, Llobet JM, et al. 1988. Embryotoxic and teratogenic effects of aluminum nitrate in rats upon oral administration. Teratology 38:253-257.

*Peng J-HF, Xu Z-C, Xu Z-X, et al. 1992. Aluminum-induced acute cholinergic neurotoxicity in rat. Mol Chem Neuropathol 17(1):79-89.

Pennington JAT. 1987. Aluminum content of foods and diets. Food Addit Contam 5(2):161-232.

Pennington JAT, Jones JW. 1989. Dietary intake of aluminum. In: Gitelman HJ, ed. Aluminum and health: A critical review. New York, NY: Marcel Dekker Inc., 67-100.

Pennington JAT, Schoen SA. 1995. Estimates of dietary exposure to aluminum. Food Addit Contam 12(1):119-128.

Perl DP, Brody AR. 1980. Alzheimer's disease: X-ray spectrometric evidence of aluminum accumulation in neurofibrillary tangle-bearing neurons. Science 208:297-299.

Perl DP, Good PF. 1987. Uptake of aluminum into central nervous system along nasal-olfactory pathways. Lancet 1(8540):1028.

*Perl DP, Good PF. 1988. Aluminum, environment and central nervous-system disease. Environ Technol Lett 9:901-906.

Perl DP, Gajdusek DC, Garruto RM, et al. 1982. Intraneuronal aluminum accumulation in amytotrophic lateral sclerosis and Parkinsonism-dementia of Guam. Science 217:1053-1055.

Pettersen JC, Hackett DS, Zwicker GM, et al. 1990. Twenty-six week toxicity study with KASAL (basic sodium aluminum phosphate) in beagle dogs. Environ Geochem Health 12(1-2):121-123.

Pierre F, Baruthio F, Diebold F, et al. 1995. Effect of different exposure compounds on urinary kinetics of aluminum and fluoride in industrially exposed workers. Occup Environ Med 52(6):396-403.

Pigott GH, Gaskell BA, Ishmael J. 1981. Effects of long term inhalation of alumina fibres in rats. Br J Exp Pathol 62(3):323-331.

Pillay KKS, Thomas CC Jr. 1971. Determination of the trace element levels in atmospheric pollutants by neutron activation analysis. J Radioanal Chem 7:107-118.

*Pineau A, Durand C, Guillard O, et al. 1992. Role of aluminum in skin reactions after diphtheria-tetanus-pertussis-poliomyelitis vaccination: An experimental study in rabbits. Toxicology 73(1):117-125.

Pivnick EK, Kerr NC, Kaufman RA, et al. 1995. Rickets secondary to phosphate depletion: A sequela of antacid use in infancy. Clin Pediatr 34(2):73-78.

Plankey BJ, Patterson HH. 1987. Kinetics of aluminum-fulvic acid complexation in acidic waters. Environ Sci Technol 21:595-601.

Pötzl K. 1970. Inorganic chemical analyses of nonpolluted aerosols sample at 1800 meters altitude. J Geophys Res 75:2347-2352.

Polizzi S, Pira E, Ferrara M, et al. 2001. Neurotoxic effects of aluminum among foundry workers. Neurotoxicology 22(4):540.

Polizzi S, Pira E, Ferrara M, et al. 2002. Neurotoxic effects of aluminum among foundry workers and Alzheimer's disease. Neurotoxicology 23(6):761-774.

Posner E, Kennedy MCS. 1967. A further study of china biscuit placers in Stoke-on-Trent. Br J Ind Med 24:133-142.

Powell JJ, Thompson RPH. 1993. The chemistry of aluminum in the gastrointestinal lumen and its uptake and absorption. Proc Nutr Soc 52:241-253.

Priest ND. 1993. Satellite symposium on 'Alzheimer's disease and dietary aluminum': The bioavailability and metabolism of aluminum compounds in man. Proc Nutr Soc 52:231-240.

Priest ND. 2004. The biological behaviour and bioavailability of aluminum in man, with special reference to studies employing aluminum-26 as a tracer: Review and study update. J Environ Monit 6(5):375-403.

Priest ND, Newton D, Day JP, et al. 1995. Human metabolism of aluminum-26 and gallium-67 injected as citrates. Hum Exp Toxicol 14(3):287-293.

Priest ND, Talbot RJ, Austin JG, et al. 1996. The bioavailability of 26Al-labelled aluminum citrate and aluminum hydroxide in volunteers. BioMetals 9(3):221-228.

Priest ND, Talbot RJ, Newton D, et al. 1998. Uptake by man of aluminum in a public water supply. Hum Exp Toxicol 17(6):296-301.

Progar JJ, May JC, Rains TC, et al. 1996. Preparation of an intra-laboratory reference material-determination of the aluminum content of a pooled 5% albumin (human) solution by ETAAS, MFS and ICP-AES. Biologicals 24:87-93.

Provan SD, Yokel RA. 1988. Influence of calcium on aluminum accumulation by the rat jejunal slice. Res Commun Chem Pathol Pharmacol 59(1):79-92.

Provan SD, Yokel RA. 1990. Reduced intestinal calcium and dietary calcium intake, increased aluminum absorption, and tissue concentration in the rat. Biol Trace Elem Res 23:119-132.

Que Hee SS, Boyle JR. 1988. Simultaneous multielemental analysis of some environmental and biological samples by inductively coupled plasma atomic emission spectrometry. Anal Chem 60:1033-1042.

Que Hee SS, Finelli VN, Fricke FL, et al. 1982. Metal content of stack emissions, coal and fly ash from some eastern and western power plants in the U.S.A. as obtained by ICP-AES. Int J Environ Anal Chem 13:1-18.

Que Hee SS, Igwe OJ, Boyle JR. 1988. Elemental alterations during the exposure of 1,2-dichloroethane (EDC), disulfiram (DSF), and EDC-DSF to male Sprague-Dawley rats. Biol Trace Elem Res 18:61-80.

Qureshi N, Malmberg RH. 1985. Reducing aluminum residuals in finished water. J Am Water Works Assoc 77(10):101-108.

Quiterio SL, Escaleira V, Sousa CRS, et al. 2004. Metals in airborne particulate matter in downtown Rio de Janeiro, Brazil. Bull Environ Contam Toxicol 72(5):916-922.

Radiation Safety Guide. 1999. Occupational radiation exposure monitoring - External monitoring. http://www.nih.gov/od/ors/ds/rsb/rsguide/orem.htm. June 15, 1999.

Radiation Safety Newsletter. 1998. Aluminum. Office of Radiological Safety, Georgia Tech. http://www.ors.gatech.edu/News9804.htm. June 15, 1999.

Radon K, Nowak D, Szadkowski D. 1999. Lack of combined effects of exposure and smoking on respiratory health in aluminium potroom workers. Occup Environ Med 56(7):468-472.

Rahman H, Skillen AW, Channon SM, et al. 1985. Methods for studying the binding of aluminum by serum protein. Clin Chem 31(12):1969-1973.

Rajasekaran K. 2000. Effects of combined exposure to aluminum and ethanol on food intake, motor behavior and a few biochemical parameters in pubertal rats. Environ Toxicol Pharmacol 9(1-2):25-30.

Ranau R, Oehlenschlager J, Steinhart H. 2001. Aluminium levels of fish fillets baked and grilled in aluminium foil. Food Chem 73(1):1-6.

Randall ME. 1983. Aluminium toxicity in an infant not on dialysis. Lancet 1(8337):1327-1328.

Razniewska G, Trzcinka-Ochocka M. 2003. ET-AAS as a method for determination of aluminum in blood serum and urine. Chem Analityczna 48:107-113.

Recker RR, Blotcky AJ, Leffler JA, et al. 1977. Evidence for aluminum absorption from the gastrointestinal tract and bone deposition by aluminum carbonate ingestion with normal renal function. J Lab Clin Med 90:810-815.

Reiber S, Kukull W, Standish-Lee P. 1995. Drinking water aluminum and bioavailability. J Am Water Works Assoc 87(5):86-100.

Rice KC. 1999. Trace-element concentrations in streambed sediment across the conterminous United States. Environ Sci Technol 33(15):2499-2504.

Riddell AR. 1948. Pulmonary changes encountered in employees engaged in the manufacture of alumina abrasives. Occup Med 5:710-717.

Rifat SL, Eastwood MR, Crapper-McLachlan DR, et al. 1990. Effect of exposure of miners to aluminum powder. Lancet 336(8724):1162-1165.

Riihimäki V, Hanninen H, Akila R. 2000. Body burden of aluminum in relation to central nervous system function among metal inert-gas welders. Scand J Work Environ Health 26(2):118-130.

Robinson MJ, Ryan SW, Newton CJ, et al. 1987. Blood aluminium levels in preterm infants fed parenterally or with cows' milk formulae. Lancet 2(8569):1206.

Rockette HE, Arena VC. 1983. Mortality studies of aluminum reduction plant workers: Potroom and carbon department. J Occup Med 25:549-557.

Rodella L, Ricci F, Borsani E, et al. 2004. Exposure to aluminium decreases nitric oxide synthetase expression in the rat cerebral cortex in time dependent manner. J Histochem Cytochem 52(Suppl 1):S25.

Rogers MA, Simon DG. 1999. A preliminary study of dietary aluminium intake risk of Alzheimer's disease. Age Ageing 28(2):205-209.

Roider G, Drasch G. 1999. Concentrations of aluminum in human tissues - investigations on an occupationally non-exposed population in Southern Bavaria (Germany). Trace Elem Electrolytes 16(2):77-86.

Roig JL, Fuentes S, Teresa CM, et al. 2006. Aluminum, restraint stress and aging: Behavioral effects in rats after 1 and 2 years of aluminum exposure. Toxicology 218(2-3):112-124.

*Roloff VLE, Platt B, Riedel G. 2002. Long-term study of chronic oral aluminum exposure and spatial working memory in rats. Behav Neurosci 116(2):351-356.

Rondeau V, Commenges D, Jacqmin-Gadda H, et al. 2000. Relation between aluminum concentrations in drinking water and Alzheimer's disease: An 8-year follow-up study. Am J Epidemiol 152(1):59-66.

Rondeau V, Jacamin-Gadda H, Commenges D, et al. 2001. Aluminum in drinking water and cognitive decline in elderly subjects: The Paquid cohort. (Comment on: Am J Epidemiol 153(7):695-703). Am J Epidemiol 154(3):288-290.

Roodhooft AM, van de Vyver FL, D'Haese PC, et al. 1987. Aluminum accumulation in children on chronic dialysis: Predictive value of serum aluminum levels and desferrioxamine infusion test. Clin Nephrol 28(3):125-129.

Rossbach B, Buchta M, Csanady GA, et al. 2006. Biological monitoring of welders exposed to aluminium. Toxicol Lett 162(2-3):239-245.

Rosseland BO, Eidhuset TD, Staurnes M. 1990. Environmental effects of aluminum. Environ Geochem Health 12:17-27.

Roy AK, Talukder G, Sharma A. 1990. Effects of aluminium sulphate on human leukocyte chromosomes in vitro. Mutat Res 244:179-183.

Saba-El-Rigal N. 2004. Effect of ascorbic acid on enzymatic and non-enzymatic antioxidants in mice liver after aluminum sulphate intoxication. Bull Natl Res Cent 29(4):483-496.

*Sahin G, Varol I, Temizer A, et al. 1994. Determination of aluminum levels in the kidney, liver, and brain of mice treated with aluminum hydroxide. Biol Trace Elem Res 41(1-2):129-135.

Saiyed SM, Yokel RA. 2005. Aluminum content of some foods and food products in the USA, with aluminum food additives. Food Addit Contam 22(3):234-244.

Salib E, Hillier V. 1996. A case-control study of Alzheimer's disease and aluminum occupation. Br J Psychiatry 168(2):244-249.

Salusky IB, Coburn JW, Foley J, et al. 1986. Effects of oral calcium carbonate on control of serum phosphorus and changes in plasma aluminum levels after discontinuation of aluminum-containing gels in children receiving dialysis. J Pediatr 108(5 Part 1):767-770.

Salusky IB, Coburn JW, Nelson P, et al. 1990. Prospective evaluation of aluminum loading from formula in infants with uremia. J Pediatr 116:726-729.

Sanchez DJ, Gomez M, Llobet JM, et al. 1997. Effects of aluminum on the mineral metabolism of rats in relation to age. Pharmacol Toxicol 80(1):11-17.

Santos F, Chan JCM, Yang MS, et al. 1987. Aluminum deposition in the central nervous system. Preferential accumulation in the hippocampus in weanling rats. Med Biol 65(1):53-55.

*Santucci D, Rankin J, Laviola G, et al. 1994. Early exposure to aluminum affects eight-arm maze performance and hippocampal nerve growth factor in adult mice. Neurosci Lett 166:89-92.

Sanz-Medel A, Roza RR, Alonso RG, et al. 1987. Atomic spectrometric methods (atomic absorption and inductively coupled plasma atomic emission) for the determination of aluminum at the parts per billion level in biological fluids. J Anal Atom Spectrom 2(2):177-184.

Sarin S, Julka D, Gill KD. 1997. Regional alterations in calcium homeostasis in the primate brain following chronic aluminum exposure. Mol Cell Biochem 168:95-100.

Saunders FM. 1988. Heavy metal impact on disposal and reclamation of aluminum-anodizing residues. Environ Technol Lett 9:945-956.

Savory J, Wills MR. 1986. Analytical methods for aluminum measurement. Kidney Int 29(Suppl 18):S24-S27.

Schaller KH, Csanady G, Filser J, et al. 2007. Elimination kinetics of metals after an accidental exposure to welding fumes. Int Arch Occup Environ Health 80(7):635-641.

Schenk RU, Bjorksten J, Yeager L. 1989. Composition and consequences of aluminum in water, beverages and other ingestibles. In: Lewis TE, ed. Environmental chemistry and toxicology of aluminum. Chelsea, MI: Lewis Publishers, Inc., 247-269.

Schmid K, Angerer J, Letzel S, et al. 1995. Use of bone mineral content determination by x-ray absorptiometry in the evaluation of osteodystrophy among workers exposed to aluminum powders. Sci Total Environ 163(1-3):147-151.

Schönholzer KW, Sutton RAL, Walker VR, et al. 1997. Intestinal absorption of trace amounts of aluminum in rats studied with 26aluminum and accelerator mass spectrometry. Clin Sci 92(4):379-383.

Schonwald S. 2004. Aluminum. In: Dart RC, ed. Medical toxicology. 3rd ed. New York, NY: Lippincott, Williams, and Wilkins, 1387-1390.

Schroeder HA, Mitchener M. 1975a. Life-term studies in rats: Effects of aluminum, barium beryllium and tungsten. J Nutr 105(4):421-427.

Schroeder HA, Mitchener M. 1975b. Life-term effects of mercury, methyl, mercury, and nine other trace metals on mice. J Nutr 105:452-458.

Schupf N, Silverman W, Zigman WB, et al. 1989. Aluminum and Alzheimer's disease [Letter]. Lancet 1(8632):267-269.

*Sedman AB, Alfrey AC, Miller NL, et al. 1987. Tissue and cellular basis for impaired bone formation in aluminum-related osteomalacia in the pig. J Clin Invest 79(1):86-92.

Setchell BP, Waites GMH. 1975. The blood testis barrier. In: Creep RO, Astwood EB, Geiger SR, eds. Handbook of physiology: Endocrinology V. Washington, DC: American Physiological Society, 143-172.

Shafer TJ, Mundy WR. 1995. Effects of aluminum on neuronal signal transduction: Mechanisms underlying disruption of phosphoinositide hydrolysis. Gen Pharmacol 26(5):889-895.

Sharma P, Mishra KP. 2006. Aluminum-induced maternal and developmental toxicity and oxidative stress in rat brain: Response to combined administration of Tiron and glutathione. Reprod Toxicol 21(3):313-321.

Shaver CG. 1948. Pulmonary changes encountered in employees engaged in the manufacture of alumina abrasives. Occup Med 5:718-728.

Shaver CG, Riddell AR. 1947. Lung changes associated with the manufacture of alumina abrasives. J Ind Hyg Toxicol 29:145-157.

Sheldon L, Umana M, Bursey J, et al. 1986. Biological monitoring techniques for human exposure to industrial chemicals: Analysis of human fat, skin, nails, hair, blood, urine, and breath. Park Ridge, NJ: Noyes Publications, 86-122.

Shore D, Wyatt RJ. 1983. Aluminum and Alzheimer's disease. J Nerv Ment Dis 171(9):553-558.

Sighinolfi GP, Gorgoni C, Bonori O, et al. 1989. Comprehensive determination of trace elements in human saliva by ETA-AAS. Mikrochim Acta 97(3-4):171-179.

Sim M, Dick R, Russo J, et al. 1997. Are aluminum potroom workers at increased risk of neurological disorders? Occup Environ Med 54(4):229-235.

Simmer K, Fudge A, Teubner J, et al. 1990. Aluminum concentrations in infant formulae. J Paediatr Child Health 26(1):9-11.

Simonsson BG, Sjoberg A, Rolf C, et al. 1985. Acute and long-term airway hyperreactivity in aluminum-salt exposed workers with nocturnal asthma. Eur J Respir Dis 66:105-118.

Sinczuk-Walczak H, Szymczak M, Razniewska G, et al. 2003. Effects of occupational exposure to aluminum on nervous system: Clinical and electroencephalographic findings. Int J Occup Environ Health 16(4):301-310.

Sjögren B, Elinder C-G, Lidums V, et al. 1988. Uptake and urinary excretion of aluminum among welders. Int Arch Occup Environ Health 60(2):77-79.

Sjögren B, Gustavsson P, Hogstedt C. 1990. Neuropsychiatric symptoms among welders exposed to neurotoxic metals. Br J Ind Med 47(10):704-707.

Sjögren B, Lidums V, Hakansson M, et al. 1985. Exposure and urinary excretion of aluminum during welding. Scand J Work Environ Health 11(1):39-43.

Sjögren B, Ljunggren KG, Almkvist O, et al. 1996. A follow-up study of five cases of aluminosis. Int Arch Occup Environ Health 68(3):161-164.

Slanina P, Falkeborn Y, Frech W, et al. 1984. Aluminum concentrations in the brain and bone of rats fed citric acid, aluminum citrate or aluminum hydroxide. Food Chem Toxicol 22(5):391-397.

Slanina P, Frech W, Bernhardson A, et al. 1985. Influence of dietary factors on aluminum absorption and retention in the brain and bone of rats. Acta Pharmacol Toxicol 56(4):331-336.

Slanina P, Frech W, Ekstrom L-G, et al. 1986. Dietary citric acid enhances absorption of aluminum in antacids. Clin Chem 32(3):539-541.

Snoeyink VL, Jenkins D, eds. 1980. Water chemistry. New York: John Wiley and Sons, 146, 209-210.

Sohn S-J, Shin J-H, Park Y-S, et al. 1996. Components of drinking water and risk of cognitive impairment in the rural elderly. Chonnam J Med Sci 9(2):189-193.

Soni MG, White SM, Flamm WG, et al. 2001. Safety evaluation of dietary aluminum. Regul Toxicol Pharmacol 33(1):66-79.

Sorenson JRJ, Campbell IR, Tepper LB, et al. 1974. Aluminum in the environment and human health. Environ Health Perspect 8:3-95.

Sparling DW, Lowe TP. 1996. Environmental hazards of aluminum to plants, invertebrates, fish, and wildlife. Rev Environ Contam Toxicol 145:1-127.

SRI. 2007. 2007 Directory of chemical producers: United States. Menlo Park, CA: SRI Consulting, 451-454, 840, 873.

Staley JT, Haupin W. 1992. Aluminum and aluminum alloys. In: Kroschwitz JI, Howe-Grant M, eds. Kirk-Othmer encyclopedia of chemical technology. Vol. 2: Alkanolamines to antibiotics (glycopeptides). New York: John Wiley & Sons, Inc., 248-249.

Stauber JL, Florence TM, Davies CM, et al. 1999. Bioavailability of Al in alum-treated drinking water. J Am Water Works Assoc 91(11):84-93.

Steinhagen WH, Cavender FL, Cockrell BY. 1978. Six month inhalation exposures of rats and guinea pigs to aluminum chlorhydrate. J Environ Pathol Toxicol 1:267-277.

Steinhausen C, Kislinger G, Winklhofer C, et al. 2004. Investigation of the aluminum biokinetics in humans: A 26Al tracer study. Food Chem Toxicol 42(3):363-371.

Stevens RK, Dzubay TG, Russwurm G, et al. 1978. Sampling and analysis of atmospheric sulfates and related species. Atmos Environ 12:55-68.

Stitch SR. 1957. Trace elements in human tissue. I. A semi-quantitative spectrographic survey. Biochem J 67:97-109.

Stokinger HE. 1981. The metals. In: Clayton GD, Clayton FE, eds. Patty's industrial hygiene and toxicology. New York, NY: John Wiley Sons, 1493-1505.

Stone CJ, McLaurin DA, Steinhagen WH, et al. 1979. Tissue deposition patterns after chronic inhalation exposures of rats and guinea pigs to aluminum chlorhydrate. Toxicol Appl Pharmacol 49:71-76.

Strong MJ, Garruto RM, Joshi JG, et al. 1996. Can the mechanisms of aluminum neurotoxicity be integrated into a unified scheme? J Toxicol Environ Health 48:599-613.

Suarez-Fernandez MB, Soldado AB, Sanz-Medel A, et al. 1999. Aluminum-induced degeneration of astrocytes occurs via apoptosis and results in neuronal death. Brain Res 835(2):125-136.

Subcommittee on Flame-Retardant Chemicals. 2000. Toxicological risks of selected flame-retardant chemicals. Subcommittee on Flame-Retardant Chemicals, Committee on Toxicology, Board on Environmental Studies and Toxicology. Commission on Life Sciences, National Research Council. Washington, DC: National Academy Press, 99-100.

Sutherland JE, Greger JL. 1998. Effect of the size of an oral dose of aluminum on the relative importance of biliary v. urinary aluminium excretion in conscious rats. Food Chem Toxicol 36(6):505-512.

Sweet CW, Vermette SJ, Landsberger S. 1993. Sources of toxic trace elements in urban air in Illinois. Environ Sci Technol 27:2502-2510.

Talbot RJ, Newton D, Priest ND, et al. 1995. Inter-subject variability in the metabolism of aluminum following intravenous injection as citrate. Hum Exp Toxicol 14:595-599.

Taylor FB, Symons GE. 1984. Effects of acid rain on water supplies in the Northeast. J Am Water Works Assoc 76:34-42.

Taylor GA, Moore PB, Ferrier IN, et al. 1998. Gastrointestinal absorption of aluminum and citrate in man. J Inorg Biochem 69(3):165-169.

Teraoka H. 1981. Distribution of 24 elements in the internal organs of normal males and the metallic workers in Japan. Arch Environ Health 36(4):155-165.

Testolin G, Erba D, Ciappellano S, et al. 1996. Influence of organic acids on aluminum absorption and storage in rat tissues. Food Addit Contam 13(1):21-27.

*Theriault G, Cordier S, Harvey R. 1984b. Skin telangiectases in workers at an aluminum plant. N Engl J Med 303(22):1278-1281.

Theriault G, Cordier S, Tremblay C, et al. 1984a. Bladder cancer in the aluminum industry. Lancet 1(8383):947-950.

Thomson SM, Burnett DC, Bergmann JD, et al. 1986. Comparative inhalation hazards of aluminum and brass powders using bronchopulmonary lavage as an indicator of lung damage. J Appl Toxicol 6(3):197-209.

Thomas K, Colborn T. 1992. Organochlorine endocrine disruptors in human tissue. In: Colborn T, Clement C, eds. Chemically induced alterations in sexual and functional development: The wildlife/human connection. Princeton, NJ: Princeton Scientific Publishing, 365-394.

Thorne BM, Cook A, Donohoe T, et al. 1987. Aluminum toxicity and behavior in the weanling Long-Evans rat. Bull Pyschon Soc 25:129-132.

Thorne BM, Donohoe T, Lin K-N, et al. 1986. Aluminum ingestion and behavior in the Long-Evans rat. Physiol Behav 36(1):63-67.

Tipton IH, Cook MJ. 1963. Trace elements in human tissue. Part II. Adult subjects from the United States. Health Phys 9:103-145.

Tipton IH, Shafer JJ. 1964. Statistical analysis of lung trace element levels. Arch Environ Health 8:58-67.

TRI05. 2007. TRI explorer: Providing access to EPA's toxics release inventory data. Washington, DC: Office of Information Analysis and Access. Office of Environmental Information. U.S. Environmental Protection Agency. Toxics Release Inventory. http://www.epa.gov/triexplorer/. December 27, 2007.

Trieff NM, Romana LA, Esposito A, et al. 1995. Effluent from bauxite factory induces developmental and reproductive damage in sea urchins. Arch Environ Contam Toxicol 28:173-177.

Tsou VM, Young RM, Hart MH. 1991. Elevated plasma aluminum levels in normal infants receiving antacids containing aluminum. Pediatrics 87(2):148-151.

Ueda M, Mizoi Y, Maki Z, et al. 1958. A case of aluminum dust lung: A necropsy report. Kobe J Med Sci 4:91-99.

USGS. 1964. Chemical composition of snow in the Northern Sierra Nevada and other areas. Geochemistry of water. U.S. Geological Survey, U.S. Department of Interior. U.S. Geol Surv Water Supply Paper 1535-J.

USGS. 1984a. Characterization of aluminum chemistry for acid precipitation. Reston, VA: U.S. Geological Survey, Water Resources Division. PB85214542.

USGS. 1984b. Residual aluminum in potable water. Technical completion report. Reston, VA: U.S. Geological Survey, Water Resources Division. PB85214963.

USGS. 1984c. Element concentrations in soils and other surficial materials of the conterminous United States. Alexandria, VA: U.S. Geological Survey. Geological Survey Professional Paper 1270.

USGS. 1996. Method I-1472-95: Methods of analysis by the U.S. Geological Survey National Water Quality Laboratory. Determination of dissolved aluminum and boron in water by inductively coupled plasma-atomic emission spectrometry. Denver, CO: U.S. Geological Survey. Open-File Report 96-149. http://web1.er.usgs.gov/nemi/method_pdf/8915.pdf. March 21, 2006.

USGS. 2007a. Bauxite and alumina. Minerals yearbook: Vol. I. Metals and minerals. U.S. Geological Survey. http://minerals.usgs.gov/minerals/pubs/commodity/bauxite/myb1-2006-bauxi.pdf. January 14, 2008.

USGS. 2007b. Aluminum. Minerals yearbook: Vol. I. Metals and minerals. U.S. Geological Survey. http://minerals.usgs.gov/minerals/pubs/commodity/aluminum/myb1-2006-alumi.pdf. January 14, 2008.

USGS. 2007c. Aluminum. Mineral commodity summaries 2007. U.S. Geological Survey, 18-19. http://minerals.usgs.gov/minerals/pubs/mcs/2007/mcs2007.pdf. January 14, 2008.

USGS. 2007d. Bauxite and alumina. Mineral commodity summaries, January 2006. U.S. Geological Survey, 28-29. http://minerals.usgs.gov/minerals/pubs/mcs/2007/mcs2007.pdf. January 14, 2008.

Valkonen S, Aitio A. 1997. Analysis of aluminum in serum and urine for the biomonitoring of occupational exposure. Sci Total Environ 199:103-110.

Vallyathan V, Berferon WN, Robichaux PA, et al. 1982. Pulmonary fibrosis in an aluminum arc welder. Chest 81(3):372-374.

Vandenplas O, Delwiche JP, Vanbilsen ML, et al. 1998. Occupational asthma caused by aluminum welding. Eur Resp J 11(5):1182-1184.

van der Voet G. 1992. Intestinal absorption of aluminum. Aluminum in biology and medicine. Ciba Found Symp 169:109-117.

*van der Voet GB, de Wolff FA. 1987. The effect of di-and trivalent iron on the intestinal absorption of aluminum in rats. Toxicol Appl Pharmacol 90(2):190-197.

van der Voet GB, de Haas EJM, de Wolff FA. 1985. Monitoring of aluminum in whole blood, plasma, serum, and water by a single procedure using flameless atomic absorption spectrophotometry. J Anal Toxicol 9:97-100.

Van Landeghem GF, D'Haese PC, Lamberts LV, et al. 1994. Quantitative HPLC/ETAAS hybrid method with an on-line metal scavenger for studying the protein binding and speciation of aluminum and iron. Anal Chem 66(2):216-222.

Varner JA, Horvath WJ, Huie CW, et al. 1994. Chronic aluminum fluoride administration. 1. Behavioral observations. Behav Neural Biol 61(3):233-241.

Varner JA, Huie C, Horvath W, et al. 1993. Chronic AlF3 administration: II. Selected histological observations. Neurosci Res Commun 13(2):99-104.

Varner JA, Jensen KF, Horvath W, et al. 1998. Chronic administration of aluminum-fluoride or sodium-fluoride to rats in drinking water: Alterations in neuronal and cerebrovascular integrity. Brain Res 784(1-2):284-298.

9. REFERENCES

Varrica D, Aiuppa A, Dongarra G. 2000. Volcanic and anthropogenic contribution to heavy metal content in lichens from Mt. Etna and Vulcano Island (Sicily). Environ Pollut 108(2):153-162.

Veien NK, Hattel T, Justesen O, et al. 1986. Aluminum allergy. Contact Dermatitis 15:295-297.

Vela MM, Toma RB, Reiboldt W, et al. 1998. Detection of aluminum residue in fresh and stored canned beer. Food Chem 63(2):235-239.

Venugopal B, Luckey TD, eds. 1978. Metal toxicity in mammals. Vol 2. New York, NY: Plenum Press, 104-112.

Versieck J, Cornelis R. 1980. Measuring aluminum levels. N Engl J Med 302(8):468-469.

Vieira I, Sonnier M, Cresteil T. 1996. Developmental expression of CYP2E1 in the human liver: Hypermethylation control of gene expression during the neonatal period. Eur J Biochem 238:476-483.

Vittori D, Nesse A, Perez G, et al. 1999. Morphologic and functional alterations of erythroid cells induced by long-term ingestion of aluminum. J Inorg Biochem 76(2):113-120.

Vogt KA, Dahlgren R, Ugolini F, et al. 1987. Aluminum, Fe, Ca, Mg, K, Mn, Cu, Zn and P in above- and belowground biomass. II. Pools and circulation in a subalpine Abies amabilis stand. Biogeochem 4:295-311.

von Stockhausen HB, Schrod L, Bratter P, et al. 1990. Aluminum loading in premature infants during intensive care as related to clinical aspects. J Trace Elem Electrolytes Health Dis 4:209-213.

Vuori K-M, Witick A, Jokela S. 1990. Accumulation of aluminum in Fontinalis dalecarlica br. eur. in a brownwater river in western Europe. Aqua Fenn 20:203-204.

Waldron-Edward D, Chan P, Skoryna SC. 1971. Increased prothrombin time and metabolic changes with high serum aluminum levels following long-term exposure to Bayer-process alumina. Can Med Assoc J 105(12):1297-1299.

Walker WJ, Cronan CS, Patterson HH. 1988. A kinetic-study of aluminum adsorption by aluminosilicate clay-minerals. Geochim Cosmochim Acta 52:55-62.

Walton J, Tuniz C, Fink D, et al. 1995. Uptake of trace amounts of aluminum into the brain from drinking water. Neurotoxicology 16(1):187-190.

Wangen LE, Jones MM. 1984. The attenuation of chemical elements in acidic leachates from coal mineral wastes by soils. Environ Geol Water Sci 6:161-170.

Warady BA, Ford DM, Gaston CE, et al. 1986. Aluminum intoxication in a child: Treatment with intraperitoneal desferrioxamine. Pediatrics 78(4):651-655.

Ward NI. 1989. Environmental contamination of aluminum and other elements in North Cornwall as a result of the Lowermoor water treatment works incident. In: Vernet J-P, ed. Heavy metals in the environment. Edinburgh: CEP Consultants, 118-121.

Wawschinek O, Petek W, Lang J, et al. 1982. The determination of aluminum in human plasma. Mikrochim Acta 1:335-339.

Weberg R, Berstad A. 1986. Gastrointestinal absorption of aluminum from single doses of aluminum containing antacids in man. Eur J Clin Invest 16(5):428-432.

Wedrychowski A, Schmidt WN, Hnilica LS. 1986. The in-vivo cross-linking of proteins and DNA by heavy metals. J Biol Chem 261(7):3370-3376.

Weintraub R, Hams G, Meerkin M, et al. 1986. High aluminum content of infant milk formulas. Arch Dis Child 61(9):914-916.

West JR, Smith HW, Chasis H. 1948. Glomerular filtration rate, effective renal blood flow, and maximal tubular excretory capacity in infancy. J Pediatr 32:10-18.

Wettstein A, Aeppli J, Gautschi K, et al. 1991. Failure to find a relationship between mnestic skills of octogenarians and aluminum in drinking water. Int Arch Occup Environ Health 63(2):97-103.

White DM, Longstreth WTJ, Rosenstock L, et al. 1992. Neurologic syndrome in 25 workers from an aluminum smelting plant. Arch Intern Med 152:1443-1448.

WHO. 2000. Air quality guidelines. Geneva, Switzerland: World Health Organization. http://www.euro.who.int/Document/AIQ/AirQualRepMtg.pdf. March 08, 2006.

WHO. 2004. Guidelines for drinking-water quality. Geneva, Switzerland: World Health Organization. http://www.who.int/water_sanitation_health/dwq/gdwq3/en/. March 08, 2006.

Widdowson EM, Dickerson JWT. 1964. Chapter 17: Chemical composition of the body. In: Comar CL, Bronner F, eds. Mineral metabolism: An advanced treatise. Vol. II: The elements Part A. New York, NY: Academic Press.

*Wide M. 1984. Effect of short-term exposure to five industrial metals on the embryonic and fetal development of the mouse. Environ Res 33(1):47-53.

Wigle DT. 1977. Bladder cancer: Possible new high-risk occupation. Lancet 2(8082):83-84.

Wilhelm M, Jager DE, Ohnesorge FK. 1990. Aluminum toxicokinetics. Pharmacol Toxicol 66:4-9.

Wilhelm M, Ohnesorge FK, Lombeck I, et al. 1989. Uptake of aluminum, cadmium, copper, lead, and zinc by human scalp hair and elution of the adsorbed metals. J Anal Toxicol 13:17-21.

Wilkinson KJ, Campbell PGC. 1993. Aluminum bioconcentration at the gills surface of juvenile Atlantic salmon in acidic media. Environ Toxicol Chem 12:2083-2095.

Wills MR, Savory J. 1989. Aluminum and chronic renal failure: Sources, absorption, transport, and toxicity. CRC Crit Rev Clin Lab Sci 27(1):59-107.

*Wills MR, Hewitt CD, Sturgill BC, et al. 1993. Long-term oral or intravenous aluminum administration in rabbits. I. Renal and hepatic changes. Ann Clin Lab Sci 23(1):1-16.

Wilson CL, Arfsten DP, Carpenter RL, et al. 2002. Effect of Navy chaff release on aluminum levels in an area of the Chesapeake Bay. Ecotoxicol Environ Saf 52(2):137-142.

Winterberg B, Bertram H-P, Korte R, et al. 1987. Hair analysis for aluminum monitoring in patients on long-term hemodialysis. Trace Elem Med 4(2):72-74.

Wood CM, McDonald DG, Ingersoll CG, et al. 1990. Effects of water acidity, calcium, and aluminum on whole body ions of brook trout (Salvelinus fontinalis) continuously exposed from fertilization to swim-up: A study by instrumental neutron activation analysis. Can J Fish Aquat Sci 47(8):1593-1603.

Wood DJ, Cooper C, Stevens J, et al. 1988. Bone mass and dementia in hip fracture patients from areas with different aluminum concentrations in water supplies. Age Ageing 17(6):415-419.

Woodson GC. 1998. An interesting case of osteomalacia due to antacid use associated with stainable bone aluminum in a patient with normal renal function. Bone 22(6):695-698.

Woolfson AD, Gracey GM. 1988. Methods for the determination of trace aluminum contamination in dialysis fluids. J Clin Pharm Ther 13:243-248.

Wrobel K, Gonzalez EB, Wrobel K, et al. 1995. Aluminum and silicon speciation in human serum by ion-exchange high-performance liquid chromatography-electrothermal atomic absorption spectrometry and gel electrophoresis. Analyst 120(3):809-815.

Xu N, Majidi V, Markesbery WR, et al. 1992a. Brain aluminum in Alzheimer's disease using an improved GFAAS method. Neurotoxicology 13(4):735-743.

*Xu ZC, Tang J, Xu ZX, et al. 1992b. Kinetics of aluminum in rats. IV. Blood and cerebrospinal fluid kinetics. Toxicol Lett 63(1):7-12.

Yeardley RB, Lazorchak JM, Paulsen SG. 1998. Elemental fish tissue contamination in northeastern U.S. Lakes: Evaluation of an approach to regional assessment. Environ Toxicol Chem 17(9):1875-1884.

Yokel RA. 1985. Toxicity of gestational aluminum exposure to the maternal rabbit and offspring. Toxicol Appl Pharmacol 79(1):121-133.

Yokel RA. 1987. Toxicity of aluminum exposure to the neonatal and immature rabbit. Fundam Appl Toxicol 9(4):795-806.

Yokel RA, McNamara PJ. 1985. Aluminum bioavailability and disposition in adult and immature rabbits. Toxicol Appl Pharmacol 77(2):344-352.

Yokel RA, McNamara PJ. 1988. Influence of renal impairment, chemical form, and serum protein binding on intravenous and oral aluminum kinetics in the rabbit. Toxicol Appl Pharmacol 95(1):32-43.

Yokel RA, McNamara PJ. 1989. Elevated aluminum persists in serum and tissues of rabbits after a 6-hour infusion. Toxicol Appl Pharmacol 99(1):133-138.

Yokel RA, McNamara PJ. 2001. Aluminium toxicokinetics: An updated minireview. Pharmacol Toxicol 88(4):159-167.

Yokel RA, Allen DD, Ackley DC. 1999. The distribution of aluminum into and out of the brain. J Inorg Biochem 76(2):127-132.

Yokel RA, Meurer KA, Hong CB, et al. 1997. Short-term oral 3-hydroxypyridin-4-one dosing increases aluminum excretion and partially reverses aluminum-induced toxicity in the rabbit independent of chelator lipophilicity. Drug Metab Dispos 25(2):182-190.

Yokel RA, Rhineheimer SS, Brauer RD, et al. 2001a. Aluminum bioavailability from drinking water is very low and is not appreciably influenced by stomach contents or water hardness. Toxicology 161(1-2):93-101.

Yokel RA, Rhineheimer SS, Sharma P, et al. 2001b. Entry, half-life, and desferrioxamine-accelerated clearance of brain aluminum after a single 26Al exposure. Toxicol Sci 64(1):77-82.

Yokel RA, Wilson M, Harris WR, et al. 2002. Aluminum citrate uptake by immortalized brain endothelial cells: Implications for its blood-brain barrier transport. Brain Res 930(1-2):101-110.

Yoshida S, Gershwin ME, Keen CL, et al. 1989. The influence of aluminum on resistance to Listeria monocytogenes in Swiss-Webster mice. Int Arch Allergy Appl Immunol 89:404-409.

Yukawa M, Suzuki-Yasumoto M, Amano K, et al. 1980. Distribution of trace elements in the human body determined by neutron activation analysis. Arch Environ Health 35:36-44.

Yumoto S, Nagai H, Kobayashi K, et al. 2003. 26Al incorporation into the brain of suckling rats through maternal milk. J Inorg Biochem 97:155-160.

Yumoto S, Nagai H, Matsuzaki H, et al. 2000. Transplacental passage of 26Al from pregnant rats to fetuses and 26Al transfer through maternal milk to suckling rats. Nucl Instrum Methods Phys Res B 172:925-929.

Zafar TA, Weaver CM, Martin BR, et al. 1997. Aluminum (Al26) metabolism in rats. Proc Soc Exp Biol Med 216(1):81-85.

Zapatero MD, Garcia de Jalon A, Pascual F, et al. 1995. Serum aluminum levels in Alzheimer's disease and other senile dementias. Biol Trace Elem Res 47:235-240.

Zatta P, Favarato M, Nicolini M. 1993. Deposition of aluminum in brain tissues of rats exposed to inhalation of aluminum acetylacetonate. NeuroReport 4(9):1119-1122.

Zatta P, Ibn-Lkhayat-Idrissi M, Zambenedetti P, et al. 2002. In vivo and in vitro effects of aluminum on the activity of mouse brain acetylcholinesterase. Brain Res Bull 59(1):41-45.

Zhang ZJ, Qian YH, Hu HT, et al. 2003. The herbal medicine Dipsacus asper wall extract reduces the cognitive deficits and overexpression of β-amyloid protein induced by aluminum exposure. Life Sci 73(19):2443-2454.

Zheng W. 2001. Neurotoxicology of the brain barrier system: New implications. J Toxicol Clin Toxicol 39(7):711-719.

Zhou Y, Yokel RA. 2005. The chemical species of aluminum influence its paracellular flux across and uptake into Caco-2 cells, a model of gastrointestinal absorption. Toxicol Sci 87(1):15-26.

Ziegler EE, Edwards BB, Jensen RL et al. 1978. Absorption and retention of lead by infants. Pediatr Res 12:29-34.

9. REFERENCES

This page is intentionally blank.

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.

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.

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.

***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) that 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 OR 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 dynamic behavior of a material in the body, used to predict 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.

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

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration 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 group.

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

Toxicokinetic—The 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 LEVELS 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 100-fold 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 and Environmental Medicine, expert panel peer reviews, and agency-wide 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 and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Aluminum
CAS Numbers: 7429-90-5
Date: June 2008
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 46
Species: Mouse

Minimal Risk Level: 1 [X] mg/kg/day [ ] ppm

Reference: Golub MS, Germann SL. 2001. Long-term consequences of developmental exposure to aluminum in a suboptimal diet for growth and behavior in Swiss Webster mice. Neurotoxicol Teratol 23:365-372.

Experimental design: Groups of pregnant Swiss Webster mice were exposed to 0, 100, 500, or 1,000 mg Al/kg diet on gestational days 0–21 and during lactation until day 21. On PND 21, one male and one female pup from each litter were placed on the same diet as the dam. The offspring were exposed until PND 35. The composition of the diet was modified from the National Research Council's recommendations; the investigators noted that the nutrients were reduced to correspond to the usual intake of these nutrients by young women. The average daily intakes of phosphorus, calcium, magnesium, iron, and zinc in women aged 18–24 years are 83, 56, 71, 69, and 67% of the RDA; these percents were used to modify the recommended dietary intake for the mice used in this study. Doses of 26, 130, and 260 mg Al/kg/day are calculated by averaging reported estimated doses of 10, 50, and 100 mg Al/kg/day for adults (i.e., at beginning of pregnancy) and 42, 210, and 420 mg Al/kg/day maximal intake during lactation. The doses at lactation were calculated using doses estimated in previous studies with similar exposure protocols performed by the same group of investigators (Golub et al. 1995). At 3 months of age, the females were tested for neurotoxicity using the Morris water maze. At 5 months of age, males were tested for motor activity and function using rotarod, grip strength, wire suspension, mesh pole descent, and beam traversal tests.

Effect noted in study and corresponding doses: No alterations in pregnancy weight gain or pup birth weights were observed. At PND 21, significant decreases in pup body weights were observed at 130 and 260 mg/kg/day. No information on maternal weight gain during lactation was reported; however, the investigators noted that the decrease in pup weight was not associated with reduced maternal food intake. At PND 35, the decrease in body weight was only significant at 260 mg/kg/day. On PND 90, female mice in the 260 mg/kg/day group weighed 15% less than controls. Decreases in heart and kidney weights were observed at 260 mg/kg/day in the females. Also, decreases in absolute brain weight were observed in females at 260 mg/kg/day and relative brain weights were observed at 26 or 260 mg/kg/day. In the males, significant decreases in body weight were observed at 130 (10%) and 260 (18%) mg/kg/day at 5 months; an increase in food intake was also observed these doses. In the Morris maze (tested at 3 months in females), fewer animals in the 260 mg/kg/day group had escape latencies of <60 seconds during sessions 1–3 (learning phase) and a relocation of the visible cues resulted in increased latencies at 130 and 260 mg/kg/day. Body weight did not correlate with latency to find the platform or with the distribution of quadrant times. The investigators concluded that controls used salient and/or nonsalient cues, 26 and 130 mg/kg/day animals used both cues, but had difficulty using only one cue, and 260 mg/kg/day animals only used the salient cues. In the males tested at 5 months, a significant decrease in hindlimb grip strength was observed at 260 mg/kg/day, an increase in the number of rotations on the rotorod as observed at 260 mg/kg/day, and a shorter latency to fall in the wire suspension test as was

observed at 130 and 260 mg/kg/day. The investigators noted that there were significant correlations between body weight and grip strength and number of rotations. When hindlimb grip strength was statistically adjusted for body weight, the aluminum-exposed mice were no longer significantly different from controls.

Reference: Colomina MT, Roig JL, Torrente M, et al. 2005. Concurrent exposure to aluminum and stress during pregnancy in rats: effects on postnatal development and behavior of the offspring. Neurotoxicol Teratol 27:565-574.

Experimental design: Groups of female Sprague-Dawley rats were exposed to 0, 50, or 100 mg Al/kg/day aluminum nitrate nonahydrate in drinking water; citric acid (710, 355, and 710 mg/kg/day in the control, 50, and 100 ppm groups, respectively) was added to the drinking water to increase aluminum absorption. The adult rats were exposed to aluminum for 15 days prior to mating and the during gestation and lactation periods; after weaning, the pups were exposed to the same aluminum concentration as the mothers from postnatal day 21 through 68. The basal diet (Panlab rodent chow) contained 41.85 µg Al/g diet. Aluminum doses were calculated by adding the basal dietary aluminum doses (calculated using reference values for mature Sprague-Dawley rats) to reported aluminum doses from water; the total aluminum doses were 3, 53, and 103 mg Al/kg/day. In addition to aluminum exposure, some animals in each group underwent restraint stress for 2 hours/day on gestation days 6–20; the restraint consisted of placing the rats in cylindrical holders. The following neurobehavioral tests were performed on the offspring: righting reflex (PNDs 4, 5, 6), negative geotaxis (PNDs 7, 8, 9), forelimb grip strength (PNDs 10–13), open field activity (PND 30), passive avoidance (PND 35), and water maze (only tested at 53 mg/kg/day on PND 60). On PND 68, rats were killed and aluminum levels were measured in the cortex, hippocampus, striatum, cerebellum, and brainstem.

Effect noted in study and corresponding doses: No significant alterations in body weight, food consumption, or water consumption were observed during gestation in the dams exposed to aluminum. The investigators noted that decreases in water and food consumption were observed during the lactation period in the rats exposed to 103 mg Al/kg/day, but the data were not shown, and maternal body weight during lactation was not mentioned. No significant alterations in the number of litters, number of fetuses per litter, viability index, or lactation index were observed. Additionally, no differences in days at pinna detachment or eye opening were observed. Age at incisor eruption was significantly higher in males exposed to 53 mg/kg/day, but not in males exposed to 103 mg/kg/day or in females. A significant delay in age at testes descent was observed at 103 mg/kg/day and vagina opening was delayed at 53 and 103 mg/kg/day. A decrease in forelimb grip strength was observed at 103 mg/kg/day; no alterations in other neuromotor tests were observed. Additionally, no alterations in open field behavior or passive avoidance test were observed. In the water maze test, latency to find the hidden platform was decreased in the 53 mg/kg/day group on test day 2, but not on days 1 or 3; no significant alteration in time in the target quadrant was found.

Dose and end point used for MRL derivation: The Golub and Germann (2001) and Colomina et al. (2005) studies identify four end points that could be used as the point of departure for derivation of the intermediate-duration oral MRL:

(1) latency to fall off wire in wire suspension test; adverse effect level of 130 mg Al/kg/day, no effect level of 26 mg Al/kg/day (Golub and Germann 2001);
(2) latency to locate the platform following cue relocation in the water maze test; adverse effect level of 130 mg Al/kg/day, no effect level of 26 mg Al/kg/day (Golub and Germann 2001);
(3) decreased forelimb grip strength; adverse effect level of 103 mg Al/kg/day, no effect level of 53 mg Al/kg/day (Colomina et al. 2005); and

(4) delay in vagina opening; adverse effect level of 53 mg Al/kg/day, no effect level not identified (Colomina et al. 2005).

Benchmark dose modeling was considered for each of these end points. Continuous variable models in the EPA Benchmark Dose Software (BMDS version 1.3.2) were fit to the data. A change of 1 standard deviation from control was selected as the BMR. Benchmark dose modeling was not conducted for latency to fall from the wire and forelimb grip strength because it is unclear whether the data reported in Table 5 (Golub and Germann 2001) and Figure 2 (Colomina et al. 2005), respectively, was for the mean ±SEM or the mean ± standard deviation. For delay in maturation, none of the available models provided an adequate fit (as assessed by the p-values for variance); therefore, the data set is unsuitable for BMD modeling. For the change in the latency to find the platform, the constant variance linear model provided an adequate fit. However, the BMD (419 mg Al/kg/day) and BMDL (186 mg Al/kg/day) were higher than the dose at which the change in latency was statistically significant (130 mg Al/kg/day), suggesting that using the change of 1 standard deviation from controls may not be an appropriate BMR for these data.

Using a NOAEL/LOAEL approach, the NOAEL of 26 mg Al/kg/day identified in the Golub and Germann (2001) study was selected as the point of departure for the MRL.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

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

Modifying Factors used in MRL derivation:

[X] 0.3 to account for possible differences in the bioavailability of the aluminum lactate used in the Golub and Germann (2001) study and the bioavailability of aluminum from drinking water and a typical U.S. diet.

No studies were identified that estimated the bioavailability of aluminum lactate following long-term dietary exposure; however, a bioavailability of 0.63% was estimated in rabbits receiving a single dose of aluminum lactate (Yokel and McNamara 1988). Yokel and McNamara (2001) and Powell and Thompson (1993) suggested that the bioavailability of aluminum from the typical U.S. diet was 0.1%; the bioavailability of aluminum from drinking water ranges from 0.07 to 0.39% (Hohl et al. 1994; Priest et al. 1998; Stauber et al. 1999; Steinhausen et al. 2004). These data suggest that aluminum lactate has a higher bioavailability than aluminum compounds typically found in drinking water or the diet.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Golub and Germann (2001): Doses of 26, 130, and 260 mg Al/kg/day are calculated by averaging reported estimated doses of 10, 50 and 100 mg Al/kg/day for adults (i.e., at beginning of pregnancy), and 42, 210, and 420 mg Al/kg/day maximal intake during lactation. The doses at lactation were calculated using doses were estimated in previous studies with similar exposure protocols performed by the same group of investigators (e.g., Golub et al. 1995).

Colomina et al. (2005): Doses of 3, 53, and 103 mg Al/kg/day were calculated by adding the basal dietary aluminum doses (calculated using reference values for mature Sprague-Dawley rats) to reported aluminum doses from water.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: The neurotoxicity and neurodevelopmental toxicity of aluminum are well-documented effects of aluminum in orally-exposed in mice and rats. A wide variety of behavioral tests were conducted in rats and mice; alterations in motor function were the most consistently observed effects. Decreases in forelimb and/or hindlimb grip strength have been observed in adult mice exposed to 195 mg Al/kg/day as aluminum lactate in the diet for 90 days (Golub et al. 1992b), mice (6 weeks of age at study beginning) exposed to 195 mg Al/kg/day as aluminum lactate in the diet for 5–7 weeks (Oteiza et al. 1993), the offspring of mice exposed on gestation day 1 through lactation day 21 to 155 mg Al/kg/day (Donald et al. 1989; Golub et al. 1995) or 250 mg Al/kg/day (Golub et al. 1995) as aluminum lactate, and the offspring of rats exposed to 103 mg Al/kg/day as aluminum nitrate in drinking water (with added citric acid) for 15 days prior to mating and on gestation day 1 through lactation day 21 (Colomina et al. 2005). Decreases in spontaneous motor activity were observed in mice exposed to 130 mg Al/kg/day for 6 weeks (Golub et al. 1989) or 195 mg Al/kg/day for 90 days (Golub et al. 1992b). Motor impairments have also been detected in mice in the wire suspension test in which offspring exposed to 130 mg Al/kg/day had a shorter latency to fall from the wire and in the rotorod test in which offspring exposed to 260 mg Al/kg/day had a higher number of rotations (which occur when the animals lost its footing, clung to the rod, and rotated with it for a full turn) (Golub and Germann 2001). Neurobehavioral alterations that have occurred at similar dose levels include decreased responsiveness to auditory or air-puff startle (Golub et al. 1992b, 1995), decreased thermal sensitivity (Golub et al. 1992a), increased negative geotaxis latency (Golub et al. 1992a), and increased foot splay (Donald et al. 1989). Additionally, one study found significant impairment in performance of the water maze test in offspring of mice exposed to 130 mg Al/kg/day on gestation day 1 through lactation day 21 (Golub and Germann 2001). Colomina et al. (2005) did not find alterations in this test in rats exposed to 53 mg Al/kg/day; however, this study did not run probe tests, which showed significant alterations in the Golub and Germann (2001) study. Other studies have utilized passive avoidance tests or operant training tests to evaluate potential impairment of cognitive function. However, the interpretation of the results of these tests is complicated by an increase in food motivation in aluminum exposed mice (Golub and Germann 1998).

In addition to the neurodevelopmental effects, there is also strong evidence that gestational and/or lactational exposure can cause other developmental effects. Aluminum does not appear to result in an increase in the occurrence of malformations and anomalies and does not typically affect birth weight. Gestation and/or lactation exposure can result in significant decreases in pup body weight gain in rats and mice (Colomina et al. 2005; Golub and Germann 2001; Golub et al. 1992a). The decreases in pup body weight are often associated with decreases in maternal body weight during the lactation phase of the study; however, decreases in body weight have also been observed in a cross-fostering study when gestation-exposed pups were nursed by control mice (Golub et al. 1992a). Other studies involving gestation and lactation exposure to aluminum did not find changes in pup growth in mice (Donald et al. 1989; Golub and Germann 1998; Golub et al. 1995). In rats, a delay in physical maturation, particularly delays in vagina opening, testes descent, and incisor eruption, has been reported at 53 mg Al/kg/day (Colomina et al. 2005).

Agency Contacts (Chemical Managers): Sam Keith, Dennis Jones, Zemoria Rosemond

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Aluminum
CAS Numbers: 7429-90-5
Date: June 2008
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 56
Species: Mouse

Minimal Risk Level: 1 [X] mg/kg/day [ ] ppm

Reference: Golub MS, Germann SL, Han B, et al. 2000. Lifelong feeding of a high aluminum diet to mice. Toxicology 150:107-117.

Experimental design: Groups of 8 male and 10 female Swiss Webster mice were exposed to 7 or 1,000 μg Al/g diet as aluminum lactate in a purified diet. The investigators estimated adult doses of <1 and 100 mg/kg/day. The mice were exposed to aluminum from conception (via feeding the dams) through 24 months of age. Body weight, food intake, and clinical signs were determined during the last 6 months of the study. Neurobehavioral test battery (foot splay, temperature sensitivity, negative geotaxis, and grip strength), 1 hour spontaneous activity, and auditory startle tests were conducted at 18 and 24 months.

In a companion study, groups of 6–9 male and female Swiss Webster mice or 7 male and female C57BL/6J mice (number per sex were not reported) were exposed to 7 or 1,000 μg Al/g diet as aluminum lactate in a purified diet (<1 and 100 mg/kg/day) from conception (via feeding the dams) through 24 months of age. Body weight, food intake, and clinical signs were determined during the last 6 months of the study. Neurobehavioral test battery (foot splay, temperature sensitivity, negative geotaxis, and grip strength) and Morris maze testing were at 22–23 months of age.

Effect noted in study and corresponding doses: In the principal study, no significant alterations in mortality were observed. A significant decrease in body weight was observed in the female mice (approximately 20%). In the males, there was a significant increase in body weight (approximately 10%). No significant alterations in food intake were observed in either sex. However, food intake/g body weight was significantly higher in the aluminum exposed mice. No significant alterations in the occurrence of clinical signs or indications of neurodegenerative syndromes were found. Significant increases in relative spinal cord, heart, and kidney weights were found. Significant alterations in negative geotaxis and tail withdrawal time in the temperature sensitivity test (males only) were observed at 18 months. At 24 months, significant alterations in forelimb and hindlimb grip strength and temperature sensitivity were found in male and female mice. Forelimb and hindlimb grip strength was decreased and thermal sensitivity was decreased, as evidenced by an increase in tail withdrawal times. Auditory startle response tests could not be completed in the older mice. Similarly, vertical spontaneous movement could not be measured; no effect on horizontal movement was found.

In the companion study, no alterations in neurobehavioral battery test performance were observed; the investigators note that this may be due to the small number of animals per group. In general, aluminum-exposed mice performed better on the water maze test than controls.

Dose and end point used for MRL derivation: A LOAEL of 100 mg Al/kg/day for decreased forelimb and hindlimb grip strength and decreased thermal sensitivity. A benchmark dose approach for deriving an MRL was not utilized because the Golub et al. (2000) study only tested one aluminum group.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

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

Modifying Factors used in MRL derivation:

[X] 0.3 to account for possible differences in the bioavailability of the aluminum lactate used in the Golub and Germann (2001) study and the bioavailability of aluminum from drinking water and a typical U.S. diet.

No studies were identified that estimated the bioavailability of aluminum lactate following long-term dietary exposure; however, a bioavailability of 0.63% was estimated in rabbits receiving a single dose of aluminum lactate (Yokel and McNamara 1988). Yokel and McNamara (2001) and Powell and Thompson (1993) suggested that the bioavailability of aluminum from the typical U.S. diet was 0.1%; the bioavailability of aluminum from drinking water ranges from 0.07 to 0.39% (Hohl et al. 1994; Priest et al. 1998; Stauber et al. 1999; Steinhausen et al. 2004). These data suggest that aluminum lactate has a higher bioavailability than aluminum compounds typically found in drinking water or the diet.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No (doses corresponding to food ppm levels were reported by investigators).

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: A small number of animal studies examined the chronic toxicity of aluminum. Schroeder and Mitchener (1975a, 1975b) examined the systemic toxicity of aluminum following lifetime exposure of rats and mice to very low doses of aluminum sulfate in the drinking water. Although the levels of aluminum in diet were not reported, they are assumed to be low because the animals were fed a low-metal diet in metal-free environmental conditions. Studies conducted by Roig et al. (2006) and Golub et al. (2000) primarily focused on the neurotoxicity of aluminum following lifetime exposure (gestation day 1 through 24 months of age). In the Golub et al. (2000) study, significant decreases in forelimb and hindlimb grip strength, and a decrease in thermal sensitivity were observed in mice exposed to 100 mg Al/kg/day; negative geotaxis was significantly altered at 18 months, but not at 24 months. No effect on horizontal activity was observed. A 10% increase in body weight and a 20% decrease in body weight were observed in the males and females, respectively. In a companion study by this group, no significant cognitive impairments were found in the Morris water maze test; in fact, aluminum-exposed mice performed better than controls in the learning tasks. Roig et al. (2006) also found no significant alterations in performance on the Morris water maze in rats exposed to 100 mg Al/kg/day as aluminum nitrate in the drinking water (with added citric acid). Although significant differences were found between the two aluminum groups

(50 and 100 mg Al/kg/day), this was primarily due to the improved performance (as compared to controls, no significant differences) in the 50 mg Al/kg/day group. Roig et al. (2006) also found no significant alterations in open field activity.

Additional support for the selection of these end points, and neurotoxicity in general, comes from a number of intermediate-duration studies that indicate that this is one of most sensitive targets of aluminum toxicity (Colomina et al. 2005; Donald et al. 1989; Golub and Germann 2001; Golub et al. 1992a, 1995).

Agency Contacts (Chemical Managers): Sam Keith, Dennis Jones, Zemoria Rosemond

This page is intentionally blank.

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 exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 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 regimens 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 “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 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 acute and intermediate 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 38m 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

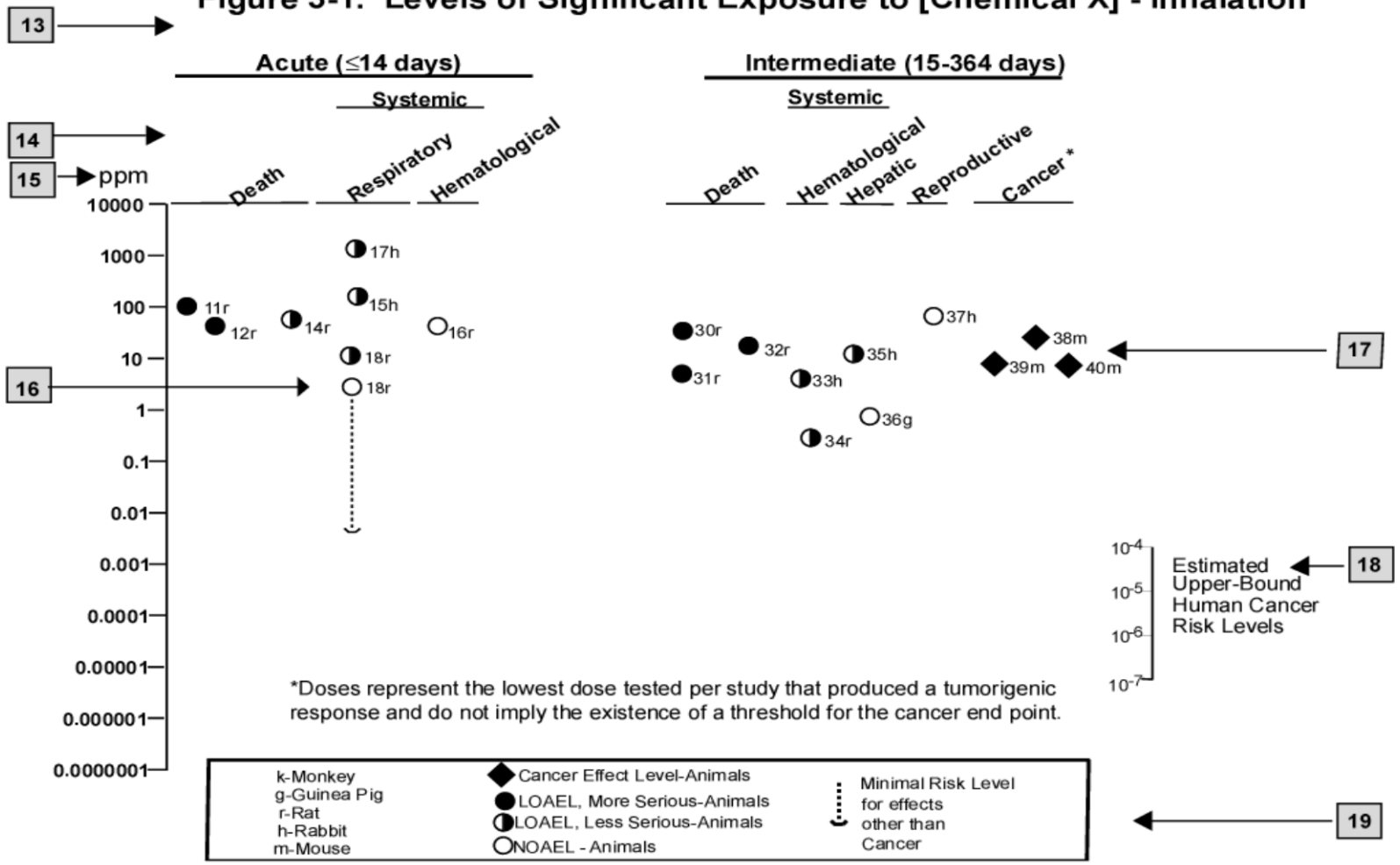
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

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



This page is intentionally blank.

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/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental 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
kkg	metric ton
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
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon

PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
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

This page is intentionally blank.

APPENDIX D. INDEX