TOXICOLOGICAL PROFILE FOR ALUMINUM

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

July 1999

ADMIN RECORD

1/490

SW-A-006129

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 was released in October 1995. This edition supersedes any previously released draft or final profile.

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

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

THIS PAGE

INTENTIONALLY

LEFT 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.

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

*Legislative Background

The toxicological profiles are developed in response to the Super-fund 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 Super-fund). 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 November 17, 1997 (62 FR 61332). For prior versions of the list of substances, see *Federal Register* notices dated April 29, 1996 (61 FR 18744); 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); and February 28, 1994 (59 FR 9486). 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: Health Effects: Specific health effects of a given hazardous compound are reported by *route of exposure,* by *type of health effect* (death, systemic, immunologic, reproductive), 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 2.6 Children's Susceptibility
Section 5.6 Exposures of Children

Other Sections of Interest:
Section 2.7 Biomarkers of Exposure and Effect
Section 2.10 Methods for Reducing Toxic Effects

ATSDR Information Center
Phone: 1-888-42-ATSDR or 404-639-6357 *Fax: 404-639-6359*
E-mail: atsdric@cdc.gov *Internet:* http://www.atsdr.cdc.gov

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

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

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

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

Other Agencies and Organizations

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

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

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

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. *Contact:* AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 •Phone: 202-347-4976 •FAX: 202-347-4950 •e-mail: aoec@dgs.dgsys.com •AOEC Clinic Director: http://occ-envmed..mc.duke.edu/oem/aoec.htm

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. *Contact:* ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 •Phone: 847-228-6850 •FAX: 847-228-1856.

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHORS(S):

Sam Keith, MS, CHP
ATSDR, Division of Toxicology, Atlanta, GA

Obaid Faroon, Ph.D.
ATSDR, Division of Toxicology, Atlanta, GA

James Corcoran, Ph.D.
Research Triangle Institute, Research Triangle Park, NC

Stephen Bosch
Syracuse Research Corporation, North Syracuse, NY

Lisa Ingerman, Ph.D.
Syracuse Research Corporation, Portland, OR

THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

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

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

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

THIS PAGE

INTENTIONALLY

LEFT BLANK

PEER REVIEW

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

1 . Dr. Charles Buncher, Director, Division of Epidemiology and Biostatistics, University of Cincinnati College of Medicine, Cincinnati, OH;

2 . Dr. Inge Harding-Barlow, Private Consultant, Palo Alto, CA;

3 . Dr. Norman Trieff, Professor, University of Texas Medical Branch, Galveston, TX;

4 . Dr. Allen Alfrey, Physician, Denver CO; and

5 . Dr. Mari Golub, Professor, California Regional Primate Research Center, University of California, Davis CA

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

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

THIS PAGE

INTENTIONALLY

LEFT BLANK

CONTENTS

FOREWORD v

QUICK REFERENCE FOR HEALTH CARE PROVIDERS vii

CONTRIBUTORS ix

PEER REVIEW xi

LIST OF FIGURES xvii

LIST OF TABLES xix

1. PUBLIC HEALTH STATEMENT 1
   1.1 WHAT IS ALUMINUM? 1
   1.2 WHAT HAPPENS TO ALUMINUM WHEN IT ENTERS THE ENVIRONMENT? 2
   1.3 HOW MIGHT I BE EXPOSED TO ALUMINUM? 3
   1.4 HOW CAN ALUMINUM ENTER AND LEAVE MY BODY? 5
   1.5 HOW CAN ALUMINUM AFFECT MY HEALTH? 5
   1.6 HOW CAN ALUMINUM AFFECT CHILDREN? 6
   1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO ALUMINUM? 7
   1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO ALUMINUM? 8
   1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH? 8
   1.10 WHERE CAN I GET MORE INFORMATION? 9

2. HEALTH EFFECTS 11
   2.1 INTRODUCTION 11
   2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE 11
      2.2.1 Inhalation Exposure 13
         2.2.1.1 Death 13
         2.2.1.2 Systemic Effects 14
         2.2.1.3 Immunological and Lymphoreticular Effects 28
         2.2.1.4 Neurological Effects 29
         2.2.1.5 Reproductive Effects 30
         2.2.1.6 Developmental Effects 31
         2.2.1.7 Genotoxic Effects 31
         2.2.1.8 Cancer 31
      2.2.2 Oral Exposure 33
         2.2.2.1 Death 50
         2.2.2.2 Systemic Effects 51
         2.2.2.3 Immunological and Lymphoreticular Effects 61
         2.2.2.4 Neurological Effects 62
         2.2.2.5 Reproductive Effects 70
         2.2.2.6 Developmental Effects 72
         2.2.2.7 Genotoxic Effects 76

2.2.2.8 Cancer . . . 77
2.2.3 Dermal Exposure . . . 77
2.2.3.1 Death . . . 77
2.2.3.2 Systemic Effects . . . 78
2.2.3.3 Immunological and Lymphoreticular Effects . . . 78
2.2.3.4 Neurological Effects . . . 82
2.2.3.5 Reproductive Effects . . . 82
2.2.3.6 Developmental Effects . . . 82
2.2.3.7 Genotoxic Effects . . . 82
2.2.3.8 Cancer . . . 82
2.3 TOXICOKINETICS . . . 83
2.3.1 Absorption . . . 84
2.3.1.1 Inhalation Exposure . . . 84
2.3.1.2 Oral Exposure . . . 85
2.3.1.3 Dermal Exposure . . . 88
2.3.1.4 Other Routes of Exposure . . . 89
2.3.2 Distribution . . . 89
2.3.2.1 Inhalation Exposure . . . 90
2.3.2.2 Oral Exposure . . . 90
2.3.2.3 Dermal Exposure . . . 93
2.3.2.4 Other Routes of Exposure . . . 93
2.3.3 Metabolism . . . 95
2.3.4 Elimination and Excretion . . . 95
2.3.4.1 Inhalation Exposure . . . 95
2.3.4.2 Oral Exposure . . . 96
2.3.4.3 Dermal Exposure . . . 97
2.3.4.4 Other Routes of Exposure . . . 97
2.3.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models . . . 97
2.4 MECHANISMS OF ACTION . . . 99
2.4.1 Pharmacokinetic Mechanisms . . . 99
2.4.2 Mechanisms of Toxicity . . . 102
2.4.3 Animal-to-Human Extrapolations . . . 105
2.5 RELEVANCE TO PUBLIC HEALTH . . . 106
2.6 CHILDREN'S SUSCEPTIBILITY . . . 126
2.7 BIOMARKERS OF EXPOSURE AND EFFECT . . . 131
2.7.1 Biomarkers Used to Identify or Quantify Exposure to Aluminum . . . 132
2.7.2 Biomarkers Used to Characterize Effects Caused by Aluminum . . . 132
2.8 INTERACTIONS WITH OTHER CHEMICALS . . . 132
2.9 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE . . . 134
2.10 METHODS FOR REDUCING TOXIC EFFECTS . . . 134
2.10.1 Reducing Peak Absorption Following Exposure . . . 135
2.10.2 Reducing Body Burden . . . 135
2.10.3 Interfering with the Mechanism of Action for Toxic Effects . . . 135
2.11 ADEQUACY OF THE DATABASE . . . 135
2.11.1 Existing Information on Health Effects of Aluminum . . . 136
2.11.2 Identification of Data Needs: Children's Susceptibility . . . 138
2.11.3 Identification of Data Needs . . . 138
2.11.4 Ongoing Studies . . . 147

3. CHEMICAL AND PHYSICAL INFORMATION 151
3.1 CHEMICAL IDENTITY 151
3.2 PHYSICAL AND CHEMICAL PROPERTIES 151

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL 173
4.1 PRODUCTION 173
4.2 IMPORT/EXPORT 177
4.3 USE 179
4.4 DISPOSAL 181

5. POTENTIAL FOR HUMAN EXPOSURE 183
5.1 OVERVIEW 183
5.2 RELEASES TO THE ENVIRONMENT 188
5.2.1 Air 188
5.2.2 Water 190
5.2.3 Soil 192
5.3 ENVIRONMENTAL FATE 192
5.3.1 Transport and Partitioning 192
5.3.2 Transformation and Degradation 198
5.3.2.1 Air 198
5.3.2.2 Water 198
5.3.2.3 Sediment and Soil 200
5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT 200
5.4.1 Air 200
5.4.2 Water 201
5.4.3 Sediment and Soil 205
5.4.4 Other Environmental Media 206
5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE 217
5.6 EXPOSURES OF CHILDREN 224
5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES 229
5.8 ADEQUACY OF THE DATABASE 230
5.8.1 Identification of Data Needs 231
5.8.2 Ongoing Studies 234

6. ANALYTICAL METHODS 241
6.1 BIOLOGICAL SAMPLES 241
6.2 ENVIRONMENTAL SAMPLES 247
6.3 ADEQUACY OF THE DATABASE 250
6.3.1 Identification of Data Needs 250
6.3.2 Ongoing Studies 252

7. REGULATIONS AND ADVISORIES 253

8. REFERENCES 271

9. GLOSSARY 347

APPPENDICES

A. ATSDR MINIMAL RISK LEVEL AND WORKSHEETS A-1

B. USER'S GUIDE B-1

C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS C-1

LIST OF FIGURES

2-1 Levels of Significant Exposure to Aluminum - Inhalation 19

2-2 Levels of Significant Exposure to Aluminum - Oral 45

2-3 Conceptional Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance 100

2-4 Existing Information on Health Effects of Aluminum and Compounds 137

5-1 Frequency of NPL Sites with Aluminum Contamination 189

THIS PAGE

INTENTIONALLY

LEFT BLANK

LIST OF TABLES

2-1 Levels of Significant Exposure to Aluminum and Compounds - Inhalation 15

2-2 Levels of Significant Exposure to Aluminum and Compounds - Oral 35

2-3 Levels of Significant Exposure to Aluminum and Compounds - Dermal 79

2-4 Genotoxicity of Aluminum *In Vitro* 127

2-5 Ongoing Studies for Aluminum Toxicity 148

3-1 Chemical Identity of Aluminum and Compounds 152

3-2 Physical and Chemical Properties of Aluminum and Compounds 162

4-1 Facilities That Manufacture or Process Aluminum and Its Compounds 176

4-2 Facilities That Manufacture or Process Aluminum Oxide 178

5-1 Releases to the Environment from Facilities That Manufacture or Process Aluminum and Its Compounds 185

5-2 Releases to the Environment from Facilities That Manufacture or Process Aluminum Oxide 187

5-3 Aluminum Concentrations Detected in Drinking Water in Various Regions of the United States 203

5-4 Estimated Aluminum Concentrations of Selected Foods 207

5-5 Comparison of Aluminum Levels (μg/L) in Breast Milk, Humanized Infant Formulae, and in Special Purpose Infant Formulae 213

5-6 Concentrations of Aluminum (ppm wet weight) in Foods Before and After Cooking in Aluminum and Stainless Steel Cookware 214

5-7 Aluminum-containing Non-prescription Drugs and Sucralfate 216

5-8 Estimated Number of Workers Potentially Exposed to Aluminum and Its Compounds in the Workplace 223

5-9 Dietary Intakes of Aluminum in Children 226

5-10 Major Sources of Aluminum in Food by Age-Sex Group 227

5-11 Ongoing Studies on Aluminum 235

6-1 Analytical Methods for Determining Aluminum in Biological Materials 242

6-2 Analytical Methods for Determining Aluminum in Environmental Samples 248

7-1 Regulations and Guidelines Applicable to Aluminum 254

1. PUBLIC HEALTH STATEMENT

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

The Environmental Protection Agency (EPA) has identified 1,445 hazardous waste sites as the most serious in the nation. These sites make up the National Priorities List (NPL) and are targeted for long-term federal clean-up activity. Aluminum has been found in at least 427 NPL sites. However, the total number of NPL sites evaluated for this substance is not known. As more sites are evaluated, the sites at which aluminum is found may increase. This information is important because exposure to this substance may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it by breathing, eating, touching, or drinking.

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

1.1 WHAT IS ALUMINUM?

Aluminum is the most abundant metal and the third most abundant element, after oxygen and silicon, in the earths crust. It is widely distributed and constitutes approximately 8 percent of the earth's surface layer. However, 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. These are the natural

forms of aluminum rather than the silvery metal. The metal is obtained from aluminum-containing minerals, primarily bauxite. Small amounts of aluminum are even found in water in dissolved or ionic form. (Ions are atoms, collections of atoms, or molecules containing a positive or negative electric charge.) The most commonly found ionic forms of aluminum are complexes formed with hydroxy (hydrogen attached to oxygen) ions.

Aluminum metal is light in weight and silvery-white in appearance. We are most familiar with aluminum in beverage cans, pots and pans, airplanes, siding and roofing, and foil. The reason why aluminum metal is so durable is that the aluminum atoms on the surface of the metal quickly combine with oxygen in the air to form a thin, strong, and protective coating of aluminum oxide or alumina. Since pure aluminum is very soft, aluminum is often mixed with small amounts of other metals to form aluminum alloys, which are stronger and harder.

Aluminum compounds are used in many diverse and important industrial applications such as alums in water-treatment and alumina in abrasives and furnace linings. They are found in consumer products such as antacids, astringents, buffered aspirin, food additives, and antiperspirants. Powdered aluminum metal is often used in explosives and fireworks. To learn more about the properties and uses of aluminum see Chapters 3 and 4.

1.2 WHAT HAPPENS TO ALUMINUM WHEN IT ENTERS THE ENVIRONMENT?

Aluminum occurs naturally in soil, water, and air. It is redistributed or moved by natural and human activities. High levels in the environment can be caused by the mining and processing of its ores and by the production of aluminum metal, alloys, and compounds. Small amounts of aluminum are released into the environment from coal-fired power plants and incinerators. Virtually all food, water, and air contain some aluminum which nature is well adapted to handle.

Aluminum cannot be destroyed in the environment. It can only change its form or become attached or separated from particles. Aluminum particles released from power plants and other combustion processes are usually attached to very small particles. Aluminum contained in

wind-borne soil is generally found in larger particles. These particles settle to the ground or are washed out of the air by rain. Aluminum that is attached to very small particles may stay in the air for many days. Most aluminum will ultimately end up in the soil or sediment. Aluminum in soil is taken up into plants, which are eaten by animals. Aluminum is not known to bioconcentrate up the food chain and therefore, vegetables, fruits, fish, and meat will not generally contain high concentrations of aluminum An exception is tea plants which can accumulate aluminum. Because of the toxicity of dissolved aluminum to many aquatic organisms, including fish, these animals would die before the amount of aluminum in the animal became very high.

Most aluminum-containing compounds do not dissolve much in water unless the water is acidic. However, when acid rain falls, aluminum compounds in the soil may dissolve and enter lakes and streams. Since the affected bodies of water are often acidic themselves from the acid rain, the dissolved aluminum does not combine with other elements in the water and settle out as it would under normal (i.e., non-acidic) conditions. In this situation, abnormally high concentrations of aluminum may occur. For more information on aluminum in the environment, see Chapter 5.

1.3 HOW MIGHT I BE EXPOSED TO ALUMINUM?

Aluminum is found naturally in the environment. You are always exposed to some aluminum by eating food; drinking water, ingesting medicinal products like certain antacids and buffered analgesics that contain aluminum, or breathing air. You may also be exposed by skin contact with soil, water, aluminum metal, antiperspirants, food additives (e.g., some baking powders) or other substances that contain aluminum Analytical methods used by scientists to determine the levels of aluminum in the environment generally do not determine the specific form of aluminum present. Therefore, we do not always know the form of aluminum a person may be exposed to. Similarly, we do not what forms of aluminum are present at hazardous waste sites. Some forms of aluminum may be insoluble or so tightly attached to particles or embedded in minerals that they are not taken up by plants and animals. Other forms, such as those found in acidic lakes, may be taken up by plants and animals and, therefore, be more hazardous.

Aluminum is the most abundant metal in the earth's crust. Its concentration in soils varies widely, ranging from about 0.07 percent by weight or 700 parts per million parts of soil (ppm) to over 10 percent by weight or 100,000 ppm, and the typical concentration is about 7.1% by weight or 71,000 ppm.

Levels of aluminum in the air generally range from 0.005 to 0.18 nanograms (1 nanogram ng, equals a billionth of a gram) of aluminum per cubic meter of air (0.005-0. 18 ng/m^3), depending on location, weather conditions, and the 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 can range from 0.4 to 10 ng/m^3. The amount of aluminum you breathe in a day is much less than you consume in food. You may breathe in higher levels of aluminum in dust if you live in areas where the air is dusty, where aluminum is mined or processed into aluminum metal or near certain hazardous waste sites.

The concentration of aluminum in natural waters is generally below 0.1 parts of aluminum per million parts of water (0.1 ppm) unless the water is very acidic. People generally consume very little aluminum from drinking water. Drinking water is sometimes treated with aluminum salts, but even then aluminum levels generally do not exceed 0.1 ppm although several cities have of 0.4 to 1 ppm of aluminum in their drinking water. Unprocessed foods like fresh fruits, vegetables, and meat contain very little aluminum However aluminum compounds may be added to foods (e.g., baking powder) during processing. Foods such as processed cheese and cakes may contain moderate amounts of aluminum as a result of its addition during processing. Soy-based infant formula may also contain moderate amounts of aluminum. An adult eats about 7 to 9 milligrams (1 milligram equals a thousandth of a gram) of aluminum per day in their food. People are exposed to aluminum in some cosmetics such as deodorants and in pharmaceuticals such as antacids, buffered aspirin, and intravenous fluids. The amount of aluminum ingested in antacids is as much as 200 milligram per tablet. For more information on how you might be exposed to aluminum see Chapter 5.

1.4 HOW CAN ALUMINUM ENTER AND LEAVE MY BODY?

When you eat aluminum in your food or drink it in liquids, very little goes from your stomach into your bloodstream Most aluminum leaves your body quickly in the feces. The small amount of aluminum that does enter the bloodstream leaves in the urine. You breathe in very little aluminum from the air, and very little can enter your body through the skin. To learn more, see Chapter 2.

1.5 HOW CAN ALUMINUM AFFECT MY HEALTH?

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

Exposure to aluminum is usually not harmful. Aluminum occurs naturally in many foods. Factory 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 eliminated this problem Some workers who breathe aluminum dusts or aluminum fumes have decreased performance in some tests that measure functions of the nervous system 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. 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

Holly Young

From: John Boylan
Sent: Monday, January 29, 2007 11:26 AM
To: Holly Young
Subject: Ash Pits

Hi Holly,

I'm looking for a written requirement that was issued in around late '04 or '05 (probably) regarding the Ash Pits. We were to install a benchmark or marker that would allow us to evaluate whether Woman Creek was encroaching on the Ash Pits. The marker got installed, but I don't know if we're supposed to resurvey it periodically, walk it down, or what. The requirement is not in the Ash Pits Closeout Report, so I'm not sure where to look next and thought you could help.

Some key words to try: Ash Pits, Woman Creek, marker or benchmark or survey location

Let me know if you find anything. I've seen the document I'm looking for, but it's been awhile and now I don't remember if it was in another report or a letter or what. Sorry!

Thank you,

John

John Boylan
John.Boylan@gjo.doe.gov
720-377-9678 (desk)
303-994-0310 (cell)
720-377-3829 (fax)

know for certain whether aluminum accumulation is a result of the disease or its cause. People may get skin rashes from the aluminum compounds in some underarm antiperspirants.

Rats and hamsters showed signs of lung damage after breathing very large amounts of aluminum as chlorohydrate or pure metal dust. Some animals died when they were given very large amounts of aluminum in water, and others gained less weight than normal. Animals exposed to aluminum appeared weaker and less active in their cages, and were less responsive to loud noises.

We do not know if aluminum will affect reproduction in people. Aluminum does not appear to affect reproduction in animals. Aluminum has not been shown to cause cancer in animals. To learn more about the health effects of aluminum exposure, see Chapter 2.

1.6 HOW CAN ALUMINUM AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on children resulting from exposures of the parents are also considered.

Children may be exposed to high levels of aluminum in drinking water. Brain and bone disease have been seen in children with kidney disease. Bone disease has also been seen in children taking some medicines containing aluminum. Animals exposed to aluminum appeared weaker and less active in their cages, and some movements appeared less coordinated than animals not exposed to aluminum. In addition, aluminum also made some animals unusually sensitive to high temperature. These effects are similar to those seen in adults. It does not appear that children are more sensitive than adults.

We do not know if aluminum will cause birth defects in people. Birth defects have been seen in animals. Effects on the nervous system have been seen in the newborn babies of animals exposed to aluminum in the diet.

There does not appear to be any difference between children and adults in terms of how much aluminum will enter the body, where aluminum can be found in the body, and how fast aluminum will leave the body. Aluminum from the mother can enter her unborn baby through the placenta. Aluminum is found in breast milk, but only a small amount of this aluminum will enter the infant's body through breastfeeding.

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

If your doctor finds that you have been exposed to significant amounts of aluminum, ask your doctor if children may also be exposed. When necessary your doctor may need to ask your state Department of Public Health to investigate.

The most important way families can lower exposures to aluminum is to know about the sources of aluminum that may affect their health and lessen their exposure to these sources. Since aluminum is so common and widespread in the environment, we cannot avoid exposure to aluminum In addition, exposure to the low 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 is generally not harmful. Eating large amounts of processed food containing aluminum additives, cooking acid food in aluminum pots, or taking aluminum-containing drugs is the most common way that families may be exposed to high levels of aluminum. Of these sources, avoiding taking large quantities of soluble forms of aluminum such as aluminum-containing antacids and buffered aspirin is the best way to reduce exposure to aluminum. In addition, the products should have child-proof caps so that children will not accidentally eat them. Families should also be aware that soy-based infant formula may contain high levels of aluminum and may want to consult with their physician on the choice of formula for their infant.

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

All people have small amounts of aluminum in their bodies. It can be measured in the blood, feces, or urine, Only the urine measurements can tell you whether you have been exposed to larger-than-normal amounts of aluminum. Your doctor would have to send a sample to a specialized laboratory to do this test. To learn more, see Chapters 2 and 6.

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

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

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

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

EPA requires industry to report spills of more than 5,000 pounds of aluminum sulfate. Special regulations are set for aluminum phosphide because it is a pesticide. EPA has recommended a Secondary Maximum Contaminant Level (SMCL) of 0.05 to 0.2 milligrams per liter (mg/L) for aluminum in drinking water. The SMCL is not a based on levels that will affect humans or animals. It can be based on taste, smell, or color. OSHA says that the amount of aluminum dusts that workers breathe should be not more than 15 milligrams per cubic meter (mg/m^3) of air. FDA has determined that ,aluminum cooking utensils, aluminum foil, antiperspirants, antacids, and other aluminum products are generally safe. To learn more, see Chapter 7.

1 .10 WHERE CAN I GET MORE INFORMATION?

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

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

* Information line and technical assistance

Phone: 1-888-42-ATSDR
Fax: (404) 639-6359 or 6324

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

* To order toxicological profiles, contact:

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: (800) 553-6847 or (703) 487-4650

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of 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 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.

2.2 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 (LOAEL) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for 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 organs(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancer health effects only and do not reflect a consideration of carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposure for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for derrnal 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 result from repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis.

As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

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

2.2.1 Inhalation Exposure

2.2.1.1 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 8 1% metallic aluminum and 17 % various oxides and hydroxides of aluminum The death of a male factory worker chronically exposed to aluminum flake powder has been described (McLaughlin et al. 1962). Prior to death, the man exhibited memory loss, speech difficulties, convulsions, weakness, EEG abnormalities, dysarthria, hemiparesis, and slowed reactions. Neurological symptoms were not found in 53 other male workers at the same factory. It is possible that other factors, such as impaired renal function, in addition to aluminum exposure, contributed to the neurological symptoms and death of the factory worker.

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). No studies were located that evaluated death from an intermediate-duration inhalation exposure in animals to aluminum or its compounds.

2.2.1.2 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 2-1 and plotted in Figure 2- 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 welding operations, and the production and use of finely powdered aluminum. Wheezing, dyspnea, and impaired lung function have been observed in potroom workers (Bast-Peetersen et al. 1994; Chan-Yeung et al. 1983; Simonsson et al. 1985). Because these workers were also exposed to a number of other toxic chemicals including sulfur dioxide, polycyclic aromatic hydrocarbons (PAHs), carbon monoxide, and hydrogen fluoride, it is difficult to ascribe the respiratory effects to aluminum.

Pulmonary fibrosis is the most commonly reported respiratory effect observed in workers exposed to fine aluminum dust (pyropowder), alumina (aluminum hydroxide), 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 (Devuyst et al. 1986; Gaffuri et al. 1985; Jephcott 1948; Musk et al. 1980; Riddell 1948; Shaver 1948); 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

Table 2-1. Levels of Significant Exposure to Aluminum and Compounds - Inhalation

Key to[a] figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
ACUTE EXPOSURE							
Systemic							
1	Rat (Fischer- 344)	5 d 4 hr	Resp	10 M	50 M (alterations in cytological and enzymatic content of lavage fluid)		Thomson et al. 1986 Aluminum powder
			Resp	100 M	200 M (multifocal microgranulomas in lungs)		
2	Hamster (Golden Syrian)	3 d 6 hr/d - day 1 4 hr/d - days 2 + 3	Resp		33 M (alveolar wall thickening and increased number of macrophages; bronchopneumonia)		Drew et al. 1974 alchlor
			Bd Wt		33 (unspecified decreased body weight)		
3	Hamster (Golden Syrian)	3 d 4 hr/d	Resp		31 (alveolar wall thickening and increased number of macrophages and heterophils)		Drew et al. 1974 alchlor
4	Hamster (Golden Syrian)	3 d 4 hr/d	Resp	3 M	7 M (15% increased lung weight)		Drew et al. 1974 alchlor
5	Hamster (Golden Syrian)	3 d 4 hr/d	Resp		10 M (approximately 24% increased lung weight)		Drew et al. 1974 alchlor

Table 2-1. Levels of Significant Exposure to Aluminum and Compounds - Inhalation (continued)

Key to[a] figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
6	Rabbit (New Zealand)	5 d 4 hr/d	Resp		43 (alveolar wall thickening, increased number of macrophages: 65% increase in lung weight)		Drew et al. 1974 alchlor
INTERMEDIATE EXPOSURE							
Systemic							
7	Rat (Fischer- 344)	6 mo 5 d/wk 6 hr/d	Resp	0.061	0.61 (increase in alveolar macrophages; granulomatous lesions in lungs)		Steinhagen et al. 1978 $Al_2(OH)_5Cl$
			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			
8	Rat (Fischer- 344)	6-12 mo 5 d/wk 6 hr/day	Resp	0.61	6.1 (48-112% increased relative lung wt)		Stone et al. 1979 $Al_2(OH)_5Cl$
			Bd Wt	6.1			
			Bd Wt	5.4			

Table 2-1. Levels of Significant Exposure to Aluminum and Compounds - Inhalation (continued)

Key to[a] figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
9	Gn Pig (Hartley)	6 mo 5 d/wk 6 hr/d	Resp	0.061	0.61 (increase in alveolar macrophages; granulomatous lesions in lungs)		Steinhagen et al. 1978 $Al_2(OH)_5Cl$
			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			
10	Gn Pig (Hartley)	6-12 mo 5 d/wk 6 hr/day	Resp	0.61	6.1 (22-30% increased relative lung weight)		Stone et al. 1979 $Al_2(OH)_5Cl$
			Bd Wt	6.1			
11	Hamster (Golden Syrian)	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 alchlor

Table 2-1. Levels of Significant Exposure to Aluminum and Compounds - Inhalation (continued)

Key to[a] figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
CHRONIC EXPOSURE							
Systemic							
12	Rat (Wistar)	86 wk 5 d/wk 6 hr/d	Resp	2.45			Pigott et al. 1981 Al_2O_3
13	Rat (Fischer- 344)	24 mo 5 d/wk 6 hr/day	Resp	0.61	6.1 (108-274% increased relative lung weight at 2 yrs)		Stone et al. 1979 $Al_2(OH)_5Cl$
			Hemato	6.1			
			Bd Wt		6.1 (10-20% decrease)		
14	Gn Pig (Hartley)	21 mo 5 d/wk 6 hr/day	Resp	0.061	6.1 (21-41% increased relative lung weight at 2 yrs)		Stone et al. 1979 $Al_2(OH)_5Cl$
			Hemato	6.1			
			Bd Wt	6.1			

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

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Gd = gestational day; Hemato = hematological; hr = hour(s); LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observable-adverse-effect level; LT_{50} = time to 50% kill; M = male; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; NS = not specified; RBC = red blood cell; Resp = respiratory; WBC = white blood cell; wk = week(s).

Figure 2-1. Levels of Significant Exposure to Aluminum - Inhalation

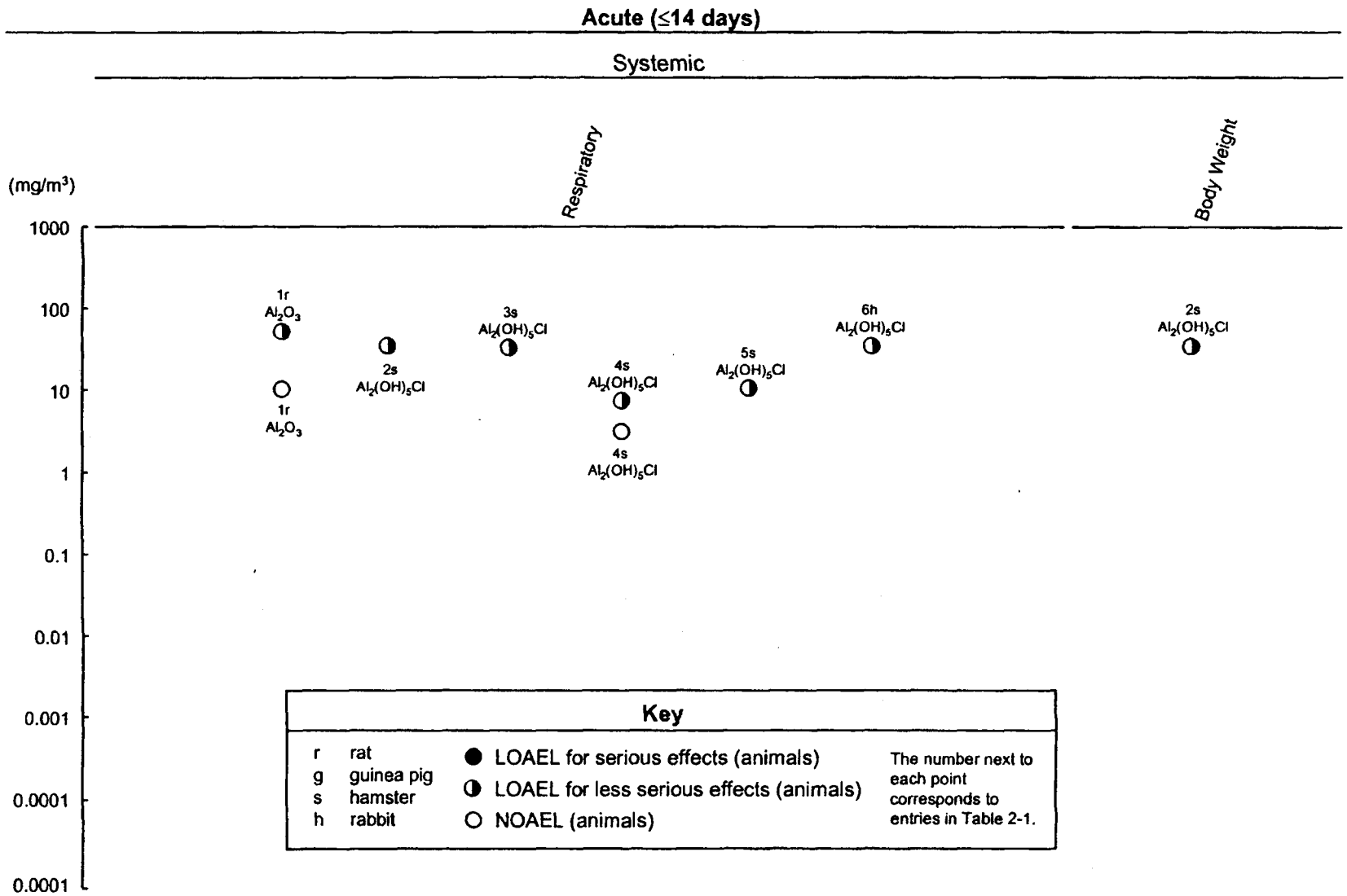


Figure 2-1. Levels of Significant Exposure to Aluminum - Inhalation (cont.)

Intermediate (15-364 days)

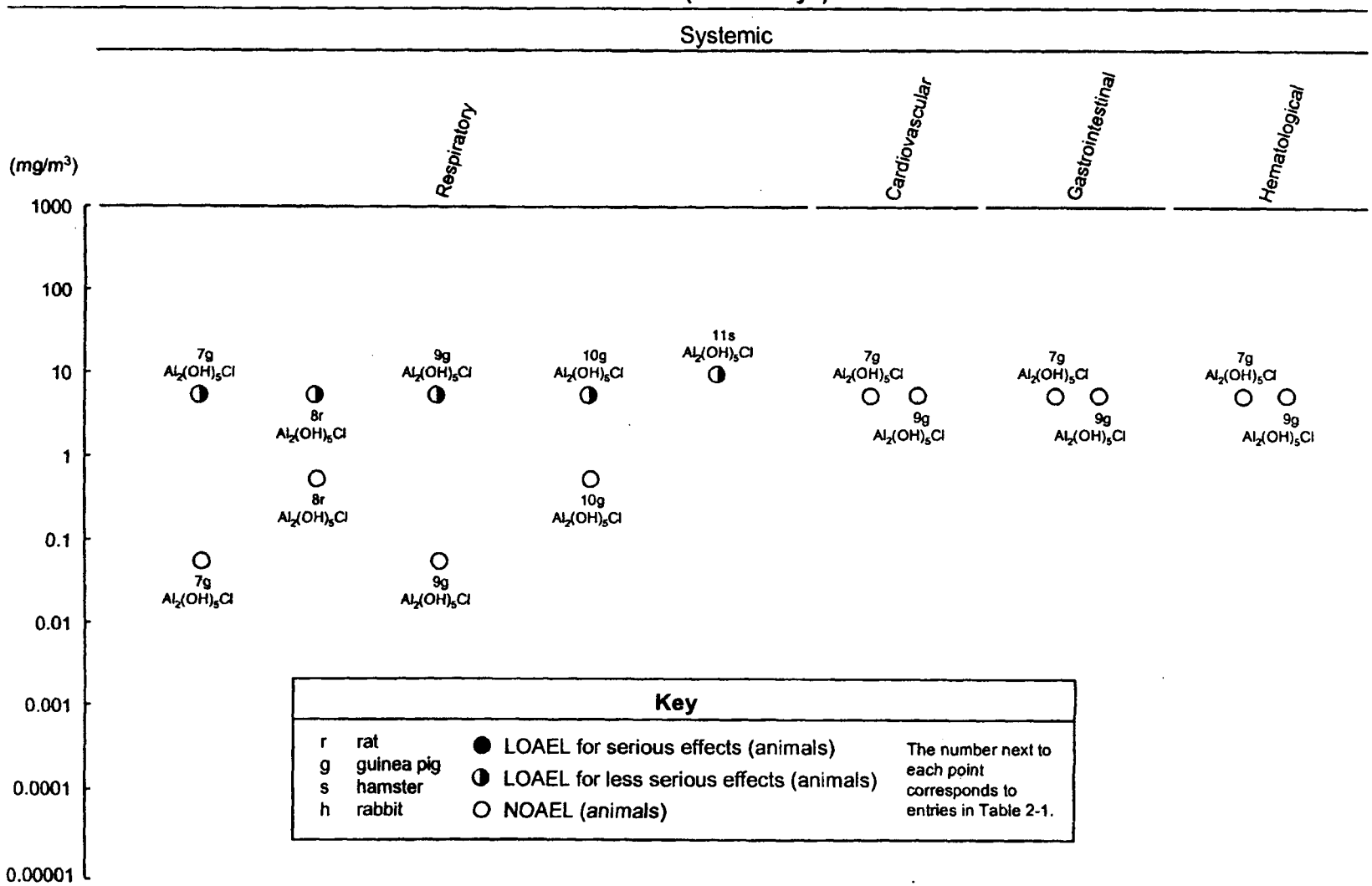


Figure 2-1. Levels of Significant Exposure to Aluminum - Inhalation (cont.)

Intermediate (15-364 days)

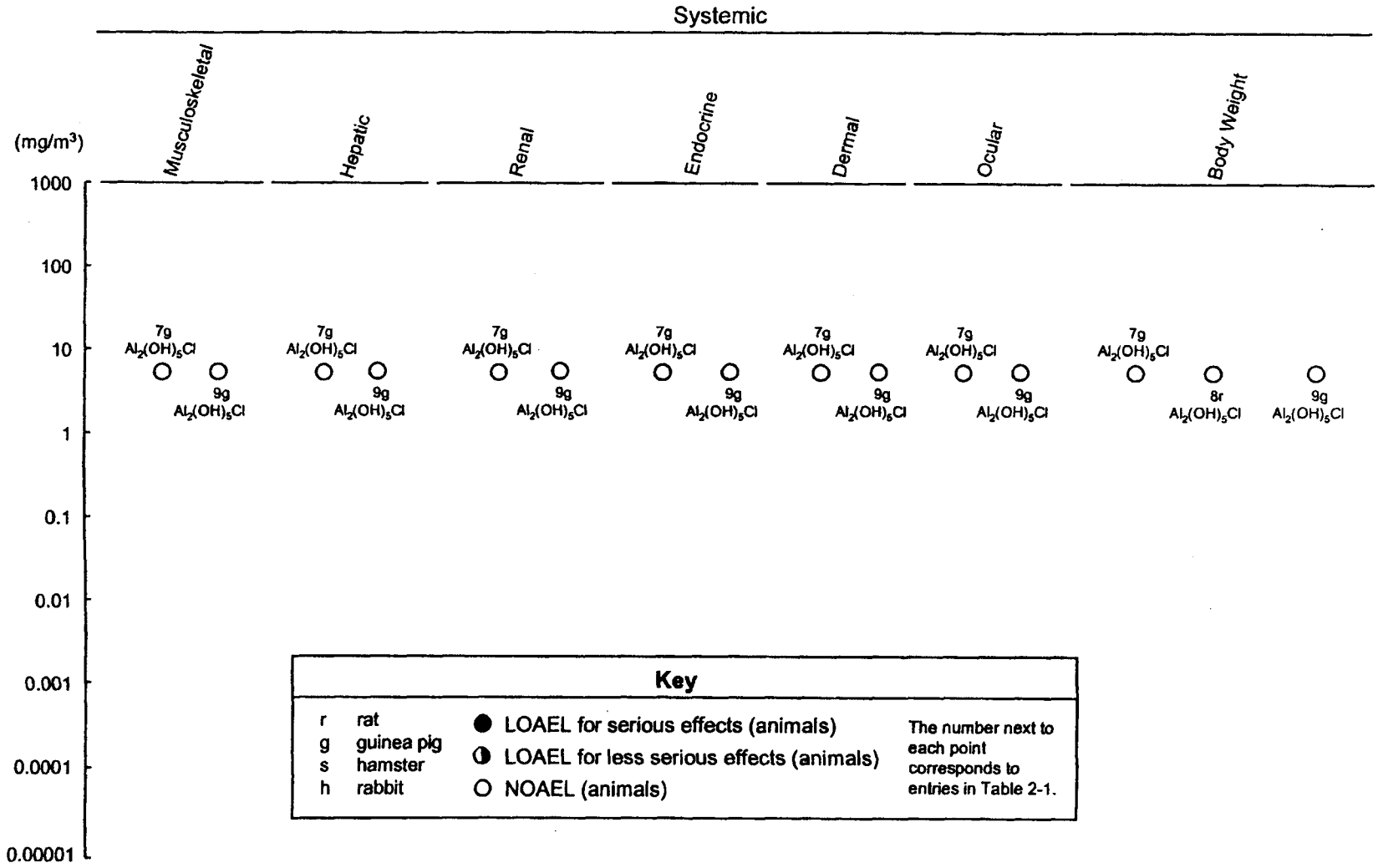
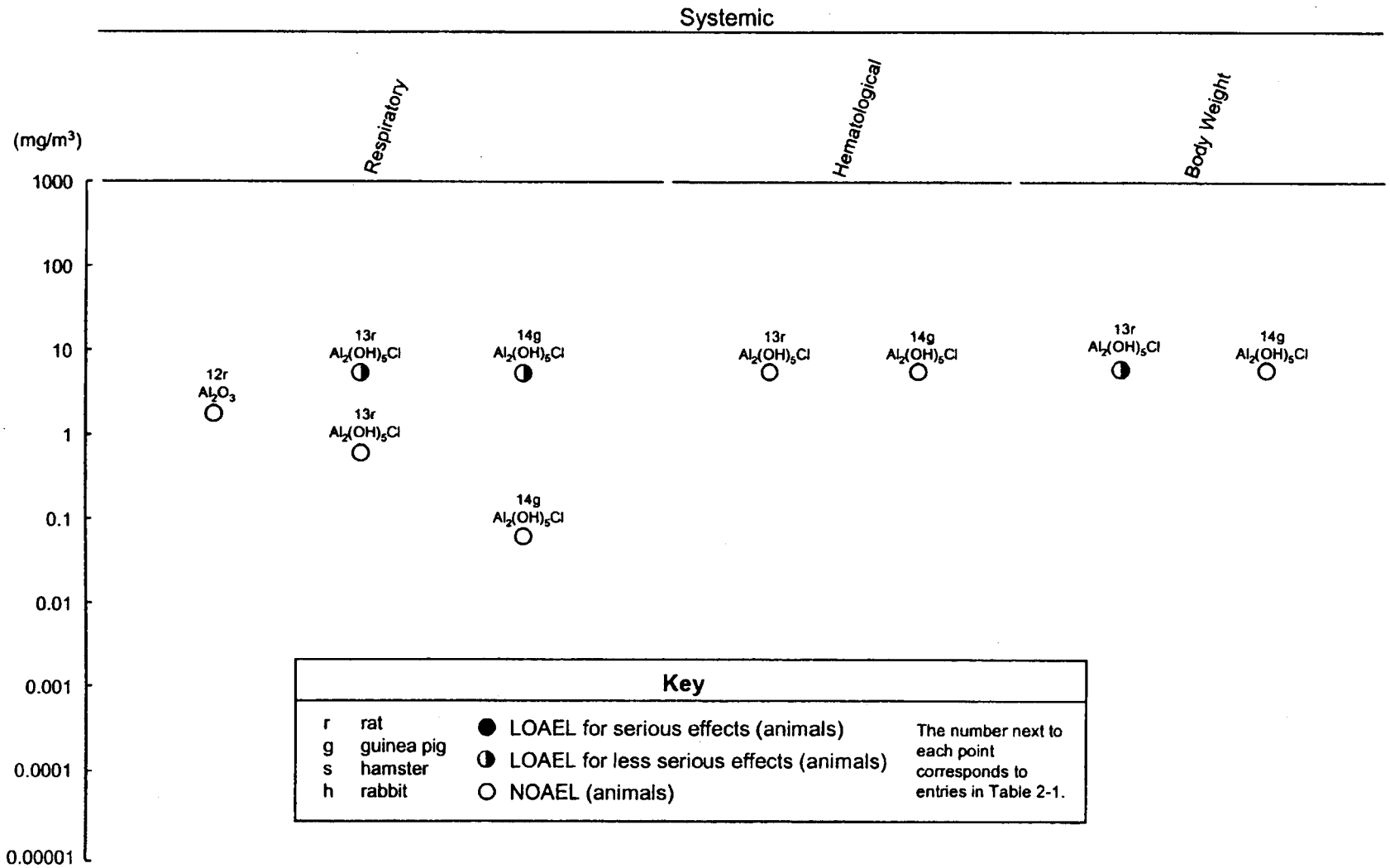


Figure 2-1. Levels of Significant Exposure to Aluminum - Inhalation (cont.)

Chronic (≥365 days)



pulmonary fibrosis were reported in German munition workers exposed to pyropowder. 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).

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 43 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 $\geq$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 $\geq$50 mg Al/m^3 and multifocal microgranulomas in the lungs and hilar lymph nodes at $\geq$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 was 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 5month 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).

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.

The highest NOAEL values and all reliable LOAEL values for respiratory effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

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. 196 1). 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-Peetersen et al. 1994).

No histological alterations changes 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). These NOAEL values are recorded in Table 2-l and plotted in Figure 2- 1.

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). These NOAEL values are recorded in Table 2- 1 and plotted in Figure 2-l.

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 7 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. 197 1).

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). These NOAEL values are recorded in Table 2-l and plotted in Figure 2-l.

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 by inhalation 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). These NOAEL values are recorded in Table 2-1 and plotted in Figure 2- 1.

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 7 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).

The highest NOAEL values and all reliable LOAEL values for hepatic effects in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2- 1.

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). One study did report an increase in urinary fluoride in male workers chronically exposed by inhalation to aluminum oxide, although control levels also increased slightly (Chan-Yeung et al. 1983). Workers in the aluminum reduction industry are exposed to fluoride as part of the reduction process (see Chapter 4).

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).

The highest NOAEL values and all reliable LOAEL values for renal effects in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2- 1.

Endocrine Effects. No studies were located regarding endocrine effects in humans following acuteor 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-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). These NOAEL values are recorded in Table 2-l and plotted in Figure 2-l.

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). These NOAEL values are recorded in Table 2- 1 and plotted in Figure 2- 1.

Ocular Effects. No studies were located regarding ocular effects in humans following acute- or intermediate-duration inhalation exposure to various forms of aluminum. Following the cessation of exposure, normal eye examination results were reported 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). These NOAEL values are recorded in Table 2-1 and plotted in Figure 2-l.

Body Weight Effects. 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 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 2-l and plotted in Figure 2-l.

Metabolic Effects. No studies were located regarding metabolic effects in humans following acuteor 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).

2.2.1.3 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. Sarcoid-like epitheloid granulomas were found in the lungs of a 32-year-old man chronically exposed by inhalation to metallic aluminum and aluminum dust (De Vuyst et al. 1987). These granulomas contained dust identified primarily as aluminum particles. Immunological testing failed to confirm sarcoidosis, but did find helper T-lymphocyte alveolitis and blastic transformation of peripheral blood lymphocytes in the presence of soluble aluminum compounds in vitro. Additional testing one year after termination of exposure indicated the man no longer had alveolitis.

Although 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.

The highest NOAEL values and all reliable LOAEL values for immunological/lymphoreticular effects in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2-l.

2.2.1.4 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 or symptoms of neurotoxicity in workers exposed to aluminum dust (potroom and foundry workers) (Bast-Peetersen et al. 1994; Dick et al. 1997; Hosovski et al. 1990; Simet al. 1997; White et al. 1992), in aluminum welders , (Hlnninen et al. 1994; Sjogren et al. 1996), or miners exposed to McIntyre powder (finely ground aluminum and aluminum oxide) (Rifat et al. 1990). Although no overt neurological effects were observed, subclinical effects have been reported in some of these studies. In the Hanninen et al. (1994) study of aluminum welders, no alterations in neurobehavioral performance tests were found, but significant correlations between urinary aluminum levels and memory test performance and between plasma aluminum levels and visual reaction time tests were found. Additionally, quantitative EEG changes, similar to those found in patients with aluminum encephalopathy, were also found in the welders. Hosovoski et al. (1994) and Sjogren et al. (1990) also found significant alterations in performance tests assessing reaction time, eye-hand coordination, memory, and/or motor skills in aluminum foundry workers and aluminum welders, respectively, and Rifat et al. (1990) found impaired performance on cognitive tests in miners exposed to McIntyre powder. Higher incidences of subjective neurological symptoms (e.g., incoordination, difficulty buttoning, depression, fatigue) were reported in two studies of aluminum potroom workers at an aluminum smelter (Sim et al. 1997; White et al. 1992) and in a study of aluminum welders (Sjiigren et al. 1990). Although Bast-Peetersen et al. (1994) did not find aluminum-related alterations in the incidence of reported neurological symptoms or neurobehavioral performance in potroom workers, they did find a higher incidence of subclinical tremors in the aluminum-exposed workers. In a retrospective study conducted by NIOSH, no alterations in reaction

time (Sim et al. 1997) or incidence of subclinical tremor (Dick et al. 1997) were found in aluminum potroom workers.

In general, these 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; Sjogren et al. 1996; White et al. 1992), but did not have earlier monitoring data when aluminum exposures were higher. The lack of adequate exposure monitoring data and the different types of aluminum exposure makes it difficult to compare these studies and draw conclusions regarding the neurotoxic potential of inhaled aluminum in workers.

A case control study by Salib and Hillier (1996) examined the possible relationship between the risk of Alzheimer's disease and occupational exposure to airborne aluminum. The occupation histories of patients with a clinical diagnosis of Alzheimer's disease (198 cases) were compared with two control groups: patients with dementia other than Alzheimer's disease (164 cases) and patients with diagnoses other than dementia. Occupational histories were obtained from the patients via a questionnaire. No significant association between occupational exposure to aluminum dust or fumes and the risk of Alzheimer's disease were found (the odds ratio for the comparison with all controls was 0.98, 95% confidence interval of 0.53-1.75).

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). These NOAEL values are recorded in Table 2- 1 and plotted in Figure 2- 1.

2.2.1.5 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 2-l and plotted in Figure 2-1.

2.2.1.6 Developmental Effects

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

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to various forms of aluminum Genotoxicity studies are discussed in Section 2.5.

2.2.1.8 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 5 aluminum reduction plants were assessed with respect to incidence of bladder cancer. The number of men working in the plants was 300-l ,200 except for 1 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, 3 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 less than 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 which focused on mortality from lung cancer in a group of 5,406 aluminum production workers (Gibbs and Horowitz 1979), a doseresponse 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 or more years experiences 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).

2.2.2 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, recently 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 12-7 1 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 150-8,300 ppm

for Purina Rodent 5001 Laboratory Chow (Fleming and Joshi 1987; 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 1988d) 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 2-2 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 2-2 and Figure 2-2. 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; Golub et al. 1989, 1992a, 1992b, 1994, 1995; Oteiza et al. 1993) and Domingo and coworkers (Colomina et al. 1992, 1994, 1998; Domingo et al. 1987a, 1987b, 1989, 1993; Gomez et al. 1986, 1991; Paternain et al. 1988). The Golub studies are additionally noteworthy because they tested aluminum lactate, which represents a bioavailable form of aluminum with an anion (lactate) that is a common human dietary constituent.

Although levels of human oral intake of aluminum are well-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 2.3.1.2, 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.

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

Key to[a] figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
ACUTE EXPOSURE							
Death							
1	Rat (Sprague-Dawley)	once (G)				261 (LD_{50})	Llobet et al. 1987 $Al(NO_3)_3$
2	Rat (Sprague-Dawley)	once (G)				370 (LD_{50})	Llobet et al. 1987 $AlCl_3$
3	Rat (Sprague-Dawley)	once (G)				162 (LD_{50})	Llobet et al. 1987 $AlBr_3$
4	Mouse (Swiss-Webster)	once (G)				286 (LD_{50})	Llobet et al. 1987 $Al(NO_3)_3$
5	Mouse (Swiss-Webster)	once (G)				222 (LD_{50})	Llobet et al. 1987 $AlCl_3$
6	Mouse (Swiss-Webster)	once (G)				164 (LD_{50})	Llobet et al. 1987 $AlBr_3$
7	Mouse (Dobra Voda)	once (G)				770 M (LD_{50})	Ondreicka et al. 1966 $AlCl_3$
8	Rabbit (New Zealand)	once (GW)				540 F (5/5 died)	Yokel and McNamara 1985 $C_9H_{15}AlO_9$

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

Key to[a] figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Developmental						
9	Mouse (Swiss)	Gd 6-15 (GW)		141			Domingo et al. 1989 AlH_3O_3
	INTERMEDIATE EXPOSURE						
	Death						
10	Mouse (Swiss-Webster)	Gd 1 - Gd 21 Gd 1 - PND 21 PND 1 - 21 (F)				250 F (death in 1/9 dams at weaning)	Golub et al. 1992a $C_9H_{15}AlO_6$
	Systemic						
11	Rat (Sprague-Dawley)	100 d (W)	Resp	284 F			Domingo et al. 1987b $Al(NO_3)_3$
			Cardio	284 F			
			Hemato	284 F			
			Hepatic	284 F			
			Bd Wt	284 F			
12	Rat (Sprague-Dawley)	1 mo (W)	Resp	133 F			Gomez et al. 1986 $Al(NO_3)_3$
			Cardio	133 F			
			Gastro	133 F			
			Hemato	133 F			
			Hepatic	79 F	133 F (hyperemia in the liver; periportal monocytic infiltrate in the liver)		
			Renal	133 F			
			Bd Wt	133 F			
13	Rat (Sprague-Dawley)	16 d (F)	Bd Wt	158 M			Greger and Donnaubauer 1986 AlH_3O_3

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

Key to[a] figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
14	Rat (Wistar)	10 weeks (F)	Musc/skel	100 M			Konishi et al. 1996 $C_9H_{15}AlO_9$
15	Mouse (Swiss-Webster)	Gd 1 - PND 21 (F)	Bd Wt	330 F			Donald et al. 1989 $C_9H_{15}AlO_9$
16	Mouse (Swiss-Webster)	6 wk (F)	Renal	130 F			Golub et al. 1989 $C_9H_{15}AlO_9$
17	Mouse (Swiss-Webster)	90d (F)	Bd Wt	195 F			Golub et al. 1992b $C_9H_{15}AlO_9$
18	Mouse (Swiss-Webster)	5 or 7 wk (F)	Hemato	195 F			Oteiza et al. 1993 $AlCl_3$
			Hepatic	195 F			
			Bd Wt	195 F			
19	Dog (Beagle)	26 wk (F)	Cardio	75			Pettersen et al. 1990 $NaAl_3H_{14}(PO_4)_8$
			Hemato	75			
			Renal	75			
			Endocr	75			

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

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Immunological/Lymphoreticular						
20	Mouse (Swiss-Webster)	Gd 0 - PND 180 (F)		1.2	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. 1993b $C_9H_{15}AlO_9$
21	Mouse (Swiss-Webster)	Gd 1 - PND 31 (F)			155 F (increased susceptibility to infection)		Yoshida et al. 1989 $C_9H_{15}AlO_9$
22	Mouse (Swiss-Webster)	6 wk (F)		195			Yoshida et al. 1989 $C_9H_{15}AlO_9$
	Neurological						
23	Rat (Sprague-Dawley)	6.5 months (W)		125			Domingo et al. 1996 $Al(NO_3)_3$
24	Mouse (Swiss-Webster)	Gd 1 - PND 21 (F)		330 F			Donald et al. 1989 $C_9H_{15}AlO_9$
25	Mouse (Swiss-Webster)	6 wk (F)		62[b] F	130 F (decreased total, vertical, and horizontal activity; decreased diurnal period; shortened activity periods)		Golub et al. 1989 $C_9H_{15}AlO_9$

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

Key to[a] figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
26	Mouse (Swiss-Webster)	Gd 1 - Gd 21 Gd 1 - PND 21 PND 1 - 21 (F)				250 F (maternal hindlimb splaying and dragging and seizures at weaning in 1/9 mice)	Golub et al. 1992a $C_9H_{15}AlO_9$
27	Mouse (Swiss-Webster)	90d (F)		4.9 F	195 F (decreased fore- and hindlimb grip strengths and startle response in weanlings)		Golub et al. 1992b $C_9H_{15}AlO_9$
28	Mouse (Swiss-Webster)	Gd 1-PND 170 (F)		7.5	155 (decreased fore- and hindlimb gripstrength and decreased air puff startle response)		Golub et al. 1995 $C_9H_{15}AlO_9$
29	Mouse (Swiss-Webster)	5 or 7 wk (F)		0.6 F	195 F (reduced forelimb and hindlimb grip strength)		Oteiza et al. 1993 $AlCl_3$
30	Dog (Beagle)	26 wk (F)		75			Pettersen et al. 1990 $NaAl_3H_{14}(PO_4)_8$
	Reproductive						
31	Rat (Sprague-Dawley)	116 d (GW)		52 F			Domingo et al. 1987c $Al(NO_3)_3$
32	Mouse (Swiss-Webster)	Gd 1 - PND 21 (F)		7.5 F	155 F (altered gestational length)		Donald et al. 1989 $C_9H_{15}AlO_9$
33	Mouse (Swiss-Webster)	Gd 1 - Gd 21 Gd 1 - PND 21 PND 1 - 21 (F)		250 F			Golub et al. 1992a $C_9H_{15}AlO_9$

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

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
34	Mouse (Dobra Voda)	180 d (W)		49.1			Ondreicka et al. 1966 $AlCl_3$
	Developmental						
35	Rat (Sprague-Dawley)	Gd 6-19 (F)		110			McCormack et al. 1979 $AlCl_3$
36	Mouse (Swiss-Webster)	Gd 1- PND 21 Gd 1- PND 45 (F)		7.5	155 (decreased forelimb and increased hindlimb grip strength and increased foot splaying in weanlings)		Donald et al. 1989 $C_9H_{15}AlO_9$
37	Mouse (Swiss-Webster)	Gd 1 - PND 35 (F)		330 M			Golub and Germann, 1998 $C_9H_{15}AlO_9$
38	Mouse (Swiss-Webster)	Gd1 - Gd21 Gd1 - PND21 PND1 - 21 (F)			250 (dec. pup weight, crown-rump length, forelimb grip strength in gestation -exposed group, incr. hindlimb grip & tail withdrawal times in gestation & lactation exposed groups, incr. negative geotaxis latency in lactation exposed groups)		Golub et al. 1992a $C_9H_{15}AlO_9$
39	Mouse	Gd 0 - PND 180 (F)		1.2	200 (19% incr. absolute spleen weights; depressed spleen cell concentrations of interleukin-2, interferon-g & tumor necrosis factor-a; deficiency of CD4+ cells in T-cell populations)		Golub et al. 1993b $C_9H_{15}AlO_9$

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

Key to[a] figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
40	Mouse (Swiss-Webster)	Gd 1-PND 170 (F)		7.5	155 (decreased fore- and hindlimb gripstrength and decreased air puff startle response)		Golub et al. 1995 $C_9H_{15}AlO_9$
41	Mouse (Swiss-Webster)	Gd 1-PND 21 (F)		7.5	155 F (decreased fore- and hindlimb grip strengths and startle response in weanlings)		Golub et al. 1995 $C_9H_{15}AlO_9$
42	Mouse (Swiss-Webster)	Gd 1 - PND 31 (F)			155 F (increased susceptibility to bacterial infection)		Yoshida et al. 1989 $C_9H_{15}AlO_9$

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

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	CHRONIC EXPOSURE						
	Systemic						
43	Rat (Long- Evans)	2.5 yr (W)	Resp	0.6			Schroeder and Mitchener 1975a $AlK(SO_4)_2.12\ H_2O$
			Cardio	0.6			
			Hemato	0.6			
			Hepatic	0.6			
			Renal	0.6			
			Bd Wt	0.6			
44	Mouse (Dobra Voda)	390 d (W)	Musc/skel	49			Ondreicka et al. 1966 $AlCl_3$
			Hepatic	49			
			Renal	49			
			Bd Wt	49			
45	Mouse (B6C3F1)	20 mo (F)	Resp	979			Oneda et al. 1994 $AlK(SO_4)_2.12\ H_2O$
			Cardio	979			
			Gastro	979			
			Hepatic	979			
			Renal	979			
			Bd Wt	979			

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

Key to[a] figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
46	Mouse (CD)	2 yr (W)	Resp	1.2			Schroeder and Mitchener 1975b $AlK(SO_4)_2 \cdot 12\ H_2O$
			Cardio	1.2			
			Hepatic	1.2			
			Renal	1.2			
			Bd Wt	1.2			
	Immunological/Lymphoreticular						
47	Rat (Long- Evans)	2.5 yr (W)		0.6			Schroeder and Mitchener 1975a $AlK(SO_4)_2 \cdot 12\ H_2O$
48	Mouse (Dobra Voda)	390 d (W)		49			Ondreicka et al. 1966 $AlCl_3$
49	Mouse (B6C3F1)	20 mo (F)		979			Oneda et al. 1994 $AlK(SO_4)_2 \cdot 12\ H_2O$
50	Mouse (CD)	2 yr (W)		1.2			Schroeder and Mitchener 1975b $AlK(SO_4)_2 \cdot 12\ H_2O$
	Neurological						
51	Mouse (B6C3F1)	20 mo (F)		979			Oneda et al. 1994 $AlK(SO_4)_2 \cdot 12\ H_2O$

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

Key to[a] figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Reproductive						
52	Mouse (Dobra Voda)	390 d (W)		49			Ondreicka et al. 1966 $AlCl_3$

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

[b]The intermediate duration oral MRL of 2.0 mg/kg/day was calculated by dividing 62 mg/kd/gay by an uncertainty factor of 30 (3 for extrapolation from animals to humans, and 10 for human variablility).

ad lib = ad libitum; AMP = adenosine monophosphate; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; (F) = food; (G) = gavage; Gastro = gastrointestinal; Gd = Gestation day; (GW) = gavage in water; Hemato = hematological; LD50 = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; MAP 2 = microtubule-associated protein 2; Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; PDN = post-natal day; Resp = respiratory; (W) = water; wk = week(s); x = times; yr = year

Figure 2-2. Levels of Significant Exposure to Aluminum - Oral

Acute (≤14 days)

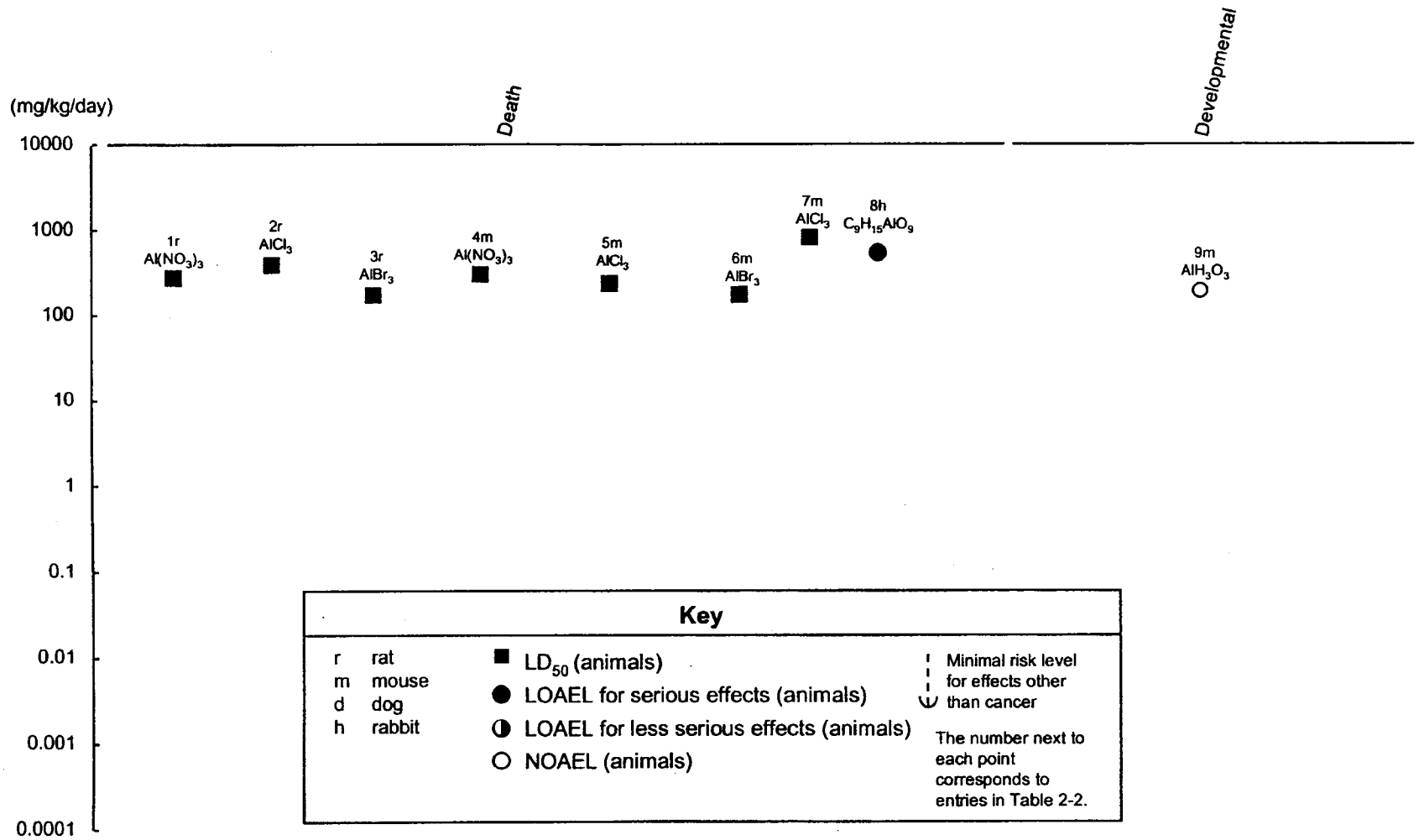


Figure 2-2. Levels of Significant Exposure to Aluminum - Oral (cont.)

Intermediate (15-364 days)

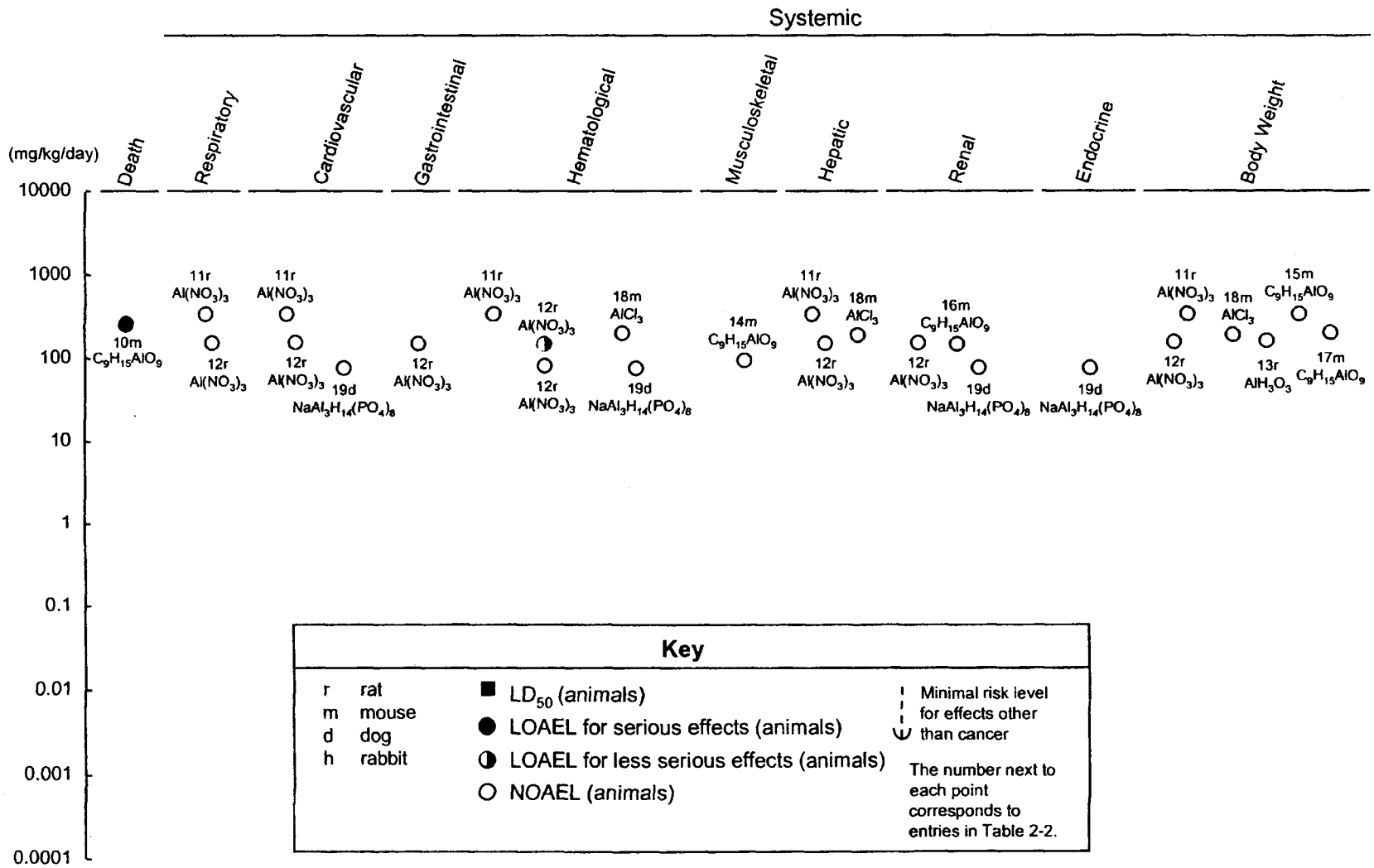


Figure 2-2. Levels of Significant Exposure to Aluminum - Oral (cont.)

Intermediate (15-364 days)

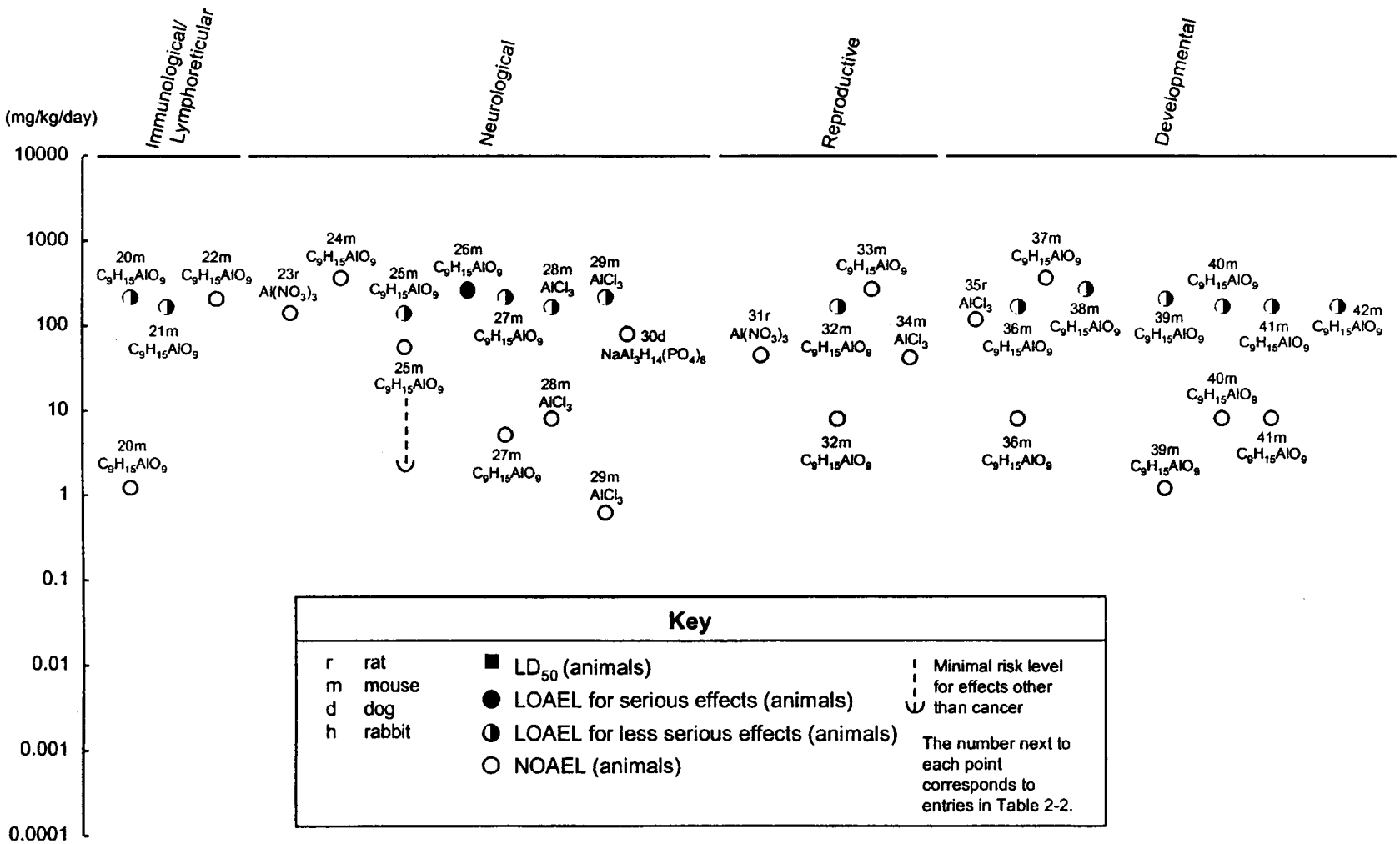


Figure 2-2. Levels of Significant Exposure to Aluminum - Oral (cont.)

Chronic (≥365 days)

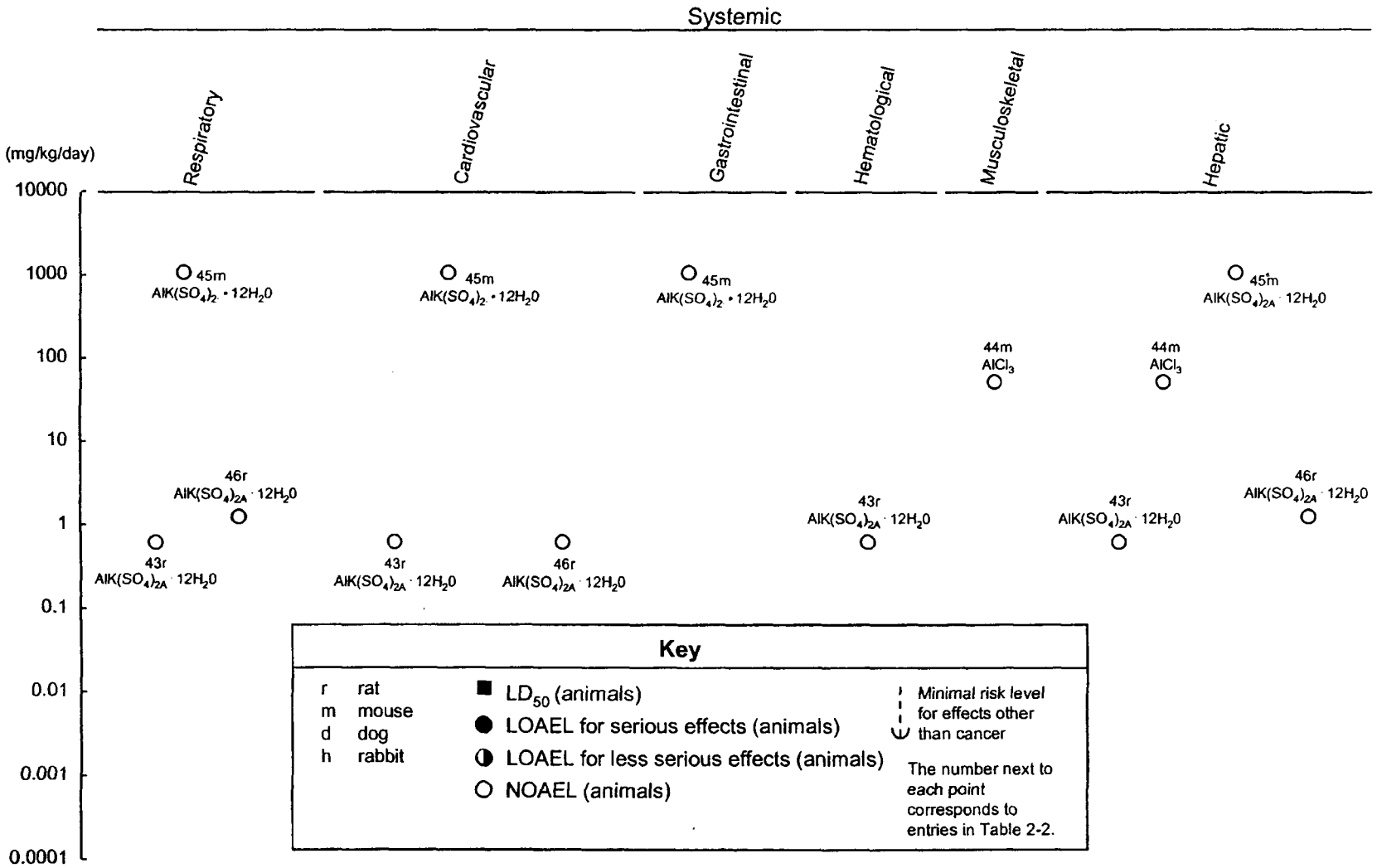
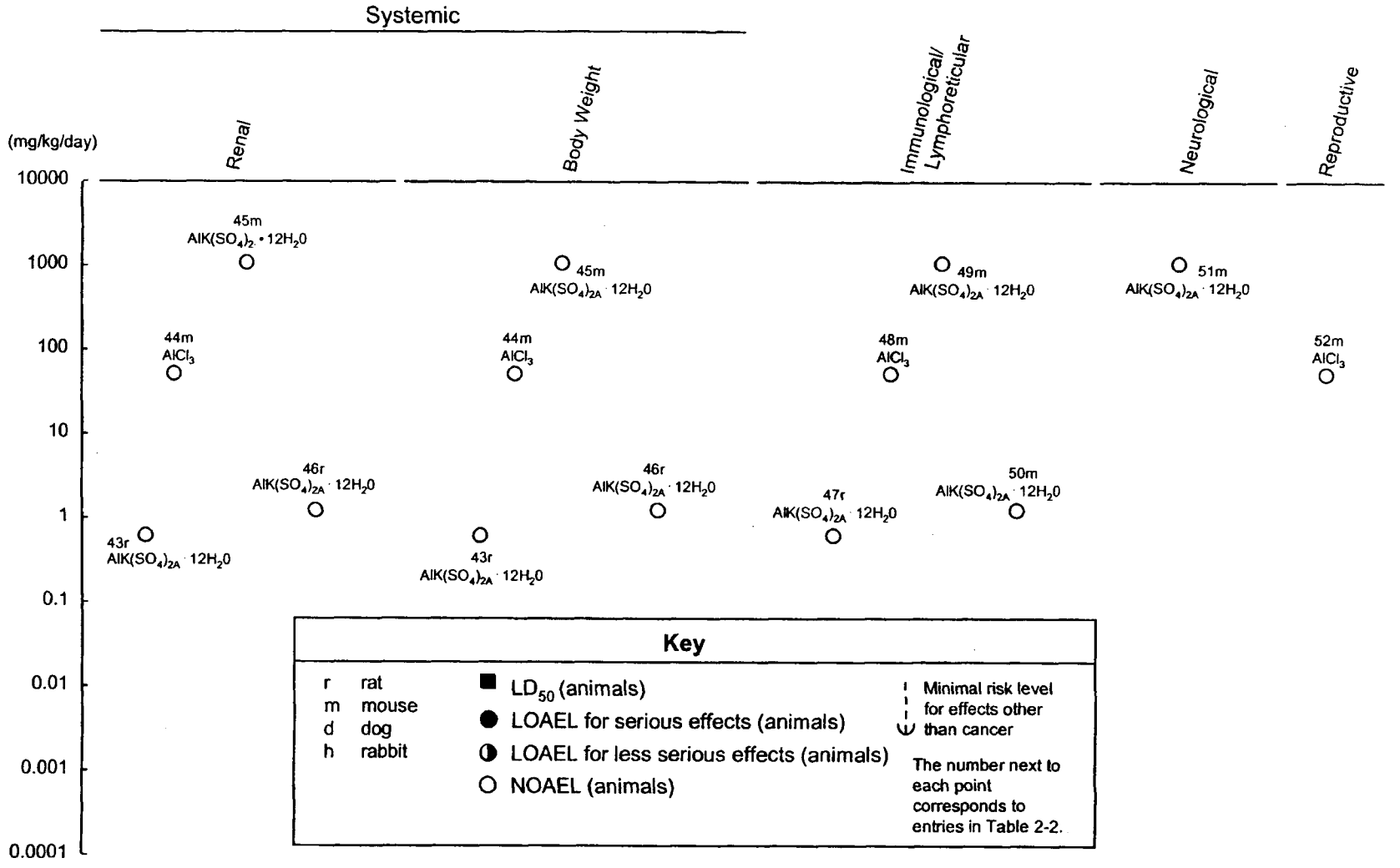


Figure 2-2. Levels of Significant Exposure to Aluminum - Oral (cont.)

Chronic (≥365 days)



2.2.2.1 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, but actual doses are unclear due to insufficient information on aluminum intake from the base diet. For the nitrate form, LD_{50} (lethal dose, 50% kill) 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). For aluminum bromide, LD_{50} values of 162 and 164 mg Al/kg have been reported in Sprague-Dawley rats and Swiss Webster mice, respectively (Llobet et al. 1987). 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 5 of 5 lactating female New Zealand rabbits (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 appears 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 9 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 (a common human food additive) and base levels of aluminum in the feed for 26 weeks (Pettersen et al. 1990). In chronic-duration studies, no consistent differences in mortality rate were observed between male and female Wistar rats (30/sex/group) exposed for 24 months to unspecified levels of aluminum phosphide/ammonium carbamate in the feed and rats fed control diets (Hackenberg 1972). All reliable LOAEL values for death in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 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 2-2 and plotted in Figure 2-2.

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 pathologic changes in the lungs of rats and mice. No organ weight or histological changes were observed in the lungs of groups of 7-10 male Sprague-Dawley rats given 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). No adverse organ weight or histological changes were found in the lungs of groups of 10 female Sprague-Dawley rats that ingested 133 or 284 mg Al/kg/day as aluminum nitrate in drinking water and base diet for 1 month or 100 days, respectively (Domingo et al. 1987b; Gomez et al. 1986). Similarly, in chronic-duration exposures, lung histology was normal in male and female Long Evans rats and Swiss mice given 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), male and female Wistar

rats fed a diet containing unspecified quantities of aluminum phosphide/ammonium carbamate for 24 months (Hackenberg 1972), male and female Dobra Voda mice given 19.3 mg Al/kg/day as aluminum chloride in drinking water and base diet for 390 days (Ondreicka et al. 1966) and in male and female B6C3Fl mice given 1979 mg Al/kg/day as aluminum potassium sulfate in the feed (base dietary aluminum not reported) for 20 months (Oneda et al. 1994). Although data on aluminum in the base diet used by Schroeder and Mitchener (1975a, 1975b) were not reported, the animals were exposed to a low-metal diet and metal-free environmental conditions.

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

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 male and female Beagle dogs (4-6/sex/dose) that consumed up to 75 (Pettersen et al. 1990) or 93 (Katz et al. 1984) mg Al/kg/day as sodium aluminum phosphate (a common human food additive) in the diet for 6 months; the doses in the Katz et al. (1984) study do not include aluminum in the base diet.

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 Wistar rats fed a diet containing an unspecified amount of aluminum phosphide/ammonium carbamate for 24 months

(Hackenberg 1972). Similarly, no histological changes were observed in the hearts of male and female Long Evans rats or Swiss mice (52 of each sex) 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 B6C3Fl mice (60 per sex) 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..

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

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 acuteduration 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 and female Beagle dogs that consumed 93 mg Al/kg/day as sodium aluminum phosphate (a human food additive) in the diet for 6 months (Katz et al. 1984); the dog dose does not include base dietary aluminum. Similarly, no histological changes were observed in the gastrointestinal tissues of male Wistar rats fed a diet containing an unspecified amount of aluminum phosphide/ammonium carbamate for 24 months

(Hackenberg 1972) or in male or female B6C3Fl mice that ingested 2979 mg Al/kg/day as aluminum potassium sulfate in the feed (base dietary aluminum not reported) for 20 months (Oneda et al. 1979).

The highest NOAEL values for gastrointestinal effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

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. No adverse hematological changes were observed in rats following a single oral dose of 50 mg Al/kg as aluminum chloride (Krasovskii et al. 1979). The method of oral exposure and level of aluminum in the base diet were not reported.

With intermediate-duration oral exposure to aluminum nitrate or aluminum chloride, no hematological changes have been observed. Female Sprague-Dawley rats given up to 133 or 284 mg Al/kg/day as aluminum nitrate in drinking water for up to 1 month (Gomez et al. 1986) or 100 days (Domingo et al. 1987b), respectively, had no changes in total protein, glucose, cholesterol, uric acid, urea, creatinine, GOT, GPT, hematocrit, or hemoglobin. Female Swiss Webster mice that consumed 195 mg Al/kg/day as aluminum chloride in the diet for 5 or 7 weeks had no change in hematocrit levels (Oteiza et al. 1993). Similarly, no changes in hematocrit, hemoglobin concentration, erythrocyte count, or leukocyte count were reported for male and female Beagle dogs that consumed up to 75 (Pettersen et al. 1990) or 93 (Katz et al. 1984) mg Al/kg/day as sodium aluminum phosphate (a common human food additive) in the diet for 6 months. Similarly, no hematological effects were observed in male and female Dobra Voda mice given 49 mg Al/kg/day as aluminum chloride in drinking water for 180 days (Ondreicka et al. 1966). The doses for all but one of the above studies (Katz et al. 1984) include aluminum in the base diet.

No changes in hematological parameters were observed in rats and mice following chronic-duration oral exposure. Erythrocyte count, total and differential leukocyte counts, packed cell volume, and hemoglobin concentration were unaffected in male Wistar rats fed a diet containing an unspecified amount of aluminum phosphide/ammonium carbamate for 24 months (Hackenberg 1972). No hematological effects were observed in male and female Long Evans rats given 0.6 mg Al/kg/day as aluminum sulfate in drinking water for 2.5 years (Schroeder and Mitchener 1975a) or male and female Dobra Voda mice given 49 mg Al/kg/day in drinking water and base diet for 390 days (Ondreicka et al.

1966). Data on base dietary aluminum were not reported by Schroeder and Mitchener (1975a), although the rats were fed a low-metal diet in metal-free environmental conditions.

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

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). Therefore, it is difficult to ascribe these effects to aluminum alone. 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 1993b) 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 Sections 2.5 and 2.9.

No studies were located regarding musculoskeletal effects of various forms of aluminum following acute-duration exposure in animals. 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 and base diet for 10 weeks (Konishi et al. 1996), femurs of male and female Wistar rats fed a diet containing unspecified amounts of aluminum phosphide/ammonium carbamate for 24 months

(Hackenberg 1972), or in the femurs of male and female Dobra Voda mice exposed to 49 mg Al/kg/day as aluminum chloride in drinking water and base diet for 390 days (Ondreicka et al. 1966).

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

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.

No studies were located regarding hepatic effects of various forms of aluminum following acute-duration exposure in animals. No organ weight or histological changes were observed in the livers of male Sprague-Dawley rats given 70 mg Al/kg/day as aluminum chloride in drinking water (aluminum in the base diet not reported) for 30,60, or 90 days (Dixon et al. 1979). Similarly, no hepatic histological changes were observed in male and female Dobra Voda mice given 49 mg Al/kg/day as aluminum chloride in drinking water and base diet for 180 days (Ondreicka et al. 1966).

Exposure to aluminum nitrate has been shown to cause minor hepatic effects. Hyperemia and periportal lymphomonocytic 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); however, these effects were not found at higher doses with longer exposures (Domingo et al. 1987b). No liver weight or histological changes occurred in female Sprague-Dawley rats given up to 284 mg Al/kg/day as aluminum nitrate in drinking water for 100 days (Domingo et al. 1987b). No histological changes were observed in 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). No liver weight changes were observed in female Swiss Webster mice that consumed 195 mg Al/kg/day as aluminum chloride in feed (Oteiza et al. 1993). Similarly, no organ weight or histological effects were observed in the livers of male and female Beagle dogs that consumed up to 93 mg Al/kg/day as sodium aluminum phosphate in the diet for 6 months (Katz et al. 1984). Mild hepatocyte vacuolation was found in high-dose males in groups of 4 male and 4 female Beagle dogs orally exposed to up to 80 mg Al/kg/day in the feed for 26 weeks (Pettersen et al. 1990), but the authors concluded the hepatic effects in the males resulted from a drastic reduction in food consumption. The

doses in all but two of the above studies (Dixon et al. 1979; Katz et al. 1984) include aluminum in the base diet.

In chronic-duration exposures, liver histology was normal in male and female Long Evans rats and Swiss mice given 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), male and female Wistar rats fed a diet containing unspecified quantities of aluminum phosphide/ammonium carbamate for 24 months (Hackenberg 1972), male and female Dobra Voda mice given 19.3 mg Al/kg/day as aluminum chloride in drinking water and base diet for 390 days (Ondreicka et al. 1966), and in male and female B6C3Fl mice given ≤ 979 mg Al/kg/day as aluminum potassium sulfate in the feed (base dietary aluminum not reported) for 20 months (Oneda et al. 1994). Although data on aluminum in the base diet used by Schroeder and Mitchener (1975a, 1975b) were not reported, the animals were exposed to a low-metal diet and metal-free environmental conditions.

Reliable NOAEL and LOAEL values for hepatic effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

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.

No studies were located regarding renal effects of various forms of aluminum following acute-duration exposure in animals. No adverse histological changes were found in the kidneys of male and female Dobra Voda mice given 49 mg Al/kg/day as aluminum chloride in drinking water and base diet for 180 days (Ondreicka et al. 1966). Normal histology was observed in the kidneys of female Sprague-Dawley rats given 133 mg Al/kg/day as aluminum nitrate in drinking water for 1 month (Gomez et al. 1986), and in male and female Beagle dogs that consumed up to 93 mg Al/kg/day as sodium aluminum phosphate in the diet for 6 months (Katz et al. 1984). However, mild tubular "glomerulanephritis" was observed in high-dose male Beagle dogs that consumed 75 mg Al/kg/day as sodium aluminum phosphate in the diet for 26 weeks (Pettersen et al. 1990). This effect is not considered to be adverse because it was

mild in severity, not accompanied by clinical evidence of kidney dysfunction, and was not observed in female dogs fed diets containing a comparable concentration of aluminum. The doses in all but one of the above studies (Katz et al. 1984) include aluminum in the base diet.

In chronic-duration exposures, kidney histology was normal in male and female Long Evans rats and Swiss mice given 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), male and female Wistar rats fed a diet containing unspecified quantities of aluminum phosphide/ ammonium carbamate for 24 months (Hackenberg 1972), male and female Dobra Voda mice given 19.3 mg Al/kg/day as aluminum chloride in drinking water and base diet for 390 days (Ondreicka et al. 1966), and in male and female B6C3Fl mice given ≤ 979 mg Al/kg/day as aluminum potassium sulfate in the feed (base dietary aluminum not reported) for 20 months (Oneda et al. 1994). Although data on aluminum in the base diet used by Schroeder and Mitchener (1975a, 1975b) were not reported, the animals were exposed to a low-metal diet and metal-free environmental conditions.

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

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 93 (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. These organs were also normal in male and female Wistar rats fed a diet containing unspecified amounts of aluminum phosphide/ ammonium carbamate for 24 months (Hackenberg 1972).

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

Dermal Effects. No studies were located regarding dermal effects of various forms of aluminum following intermediate- or chronic-duration 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. For more information on this study, see Gastrointestinal Effects, above.

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). No histological changes were observed in the skin of male and female Wistar rats fed a diet containing unspecified amounts of aluminum phosphide/ammonium carbamate for 24 months (Hackenberg 1972).

Ocular Effects. No studies were located regarding ocular effects of various forms of aluminum following acute-, intermediate-, or chronic-duration 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 93 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. Normal ocular histology was observed in male and female Wistar rats fed a diet containing unspecified amounts of aluminum phosphide/ ammonium carbamate for 24 months (Hackenberg 1972).

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

Reductions in body weight gain and food consumption were observed in male Wistar rats that ingested feed containing 273 mg Al/kg/day as aluminum sulfate and base dietary aluminum for 8 days (Ondreicka et al. 1966). These effects were not evident after 24 days of exposure, suggesting that they were transient. There were no body weight changes in female Wistar rats that consumed as much as 192 mg Al/kg as aluminum chloride in the feed (aluminum in the base diet not reported) on gestation days (Gd) 8-20 (Bernuzzi et al. 1986b), although a 19-20% decrease in maternal body weight gain

occurred in Sprague-Dawley rats exposed to 38-77 mg Al/kg/day as aluminum nitrate by gavage and base diet on Gd 6-14 (Paternain et al. 1988). Factors contributing to the occurrence of an effect in the Paternain et al. (1988) gestational exposure study could include increased absorption of aluminum due to the bolus method of treatment and increased bioavailability of aluminum nitrate compared to aluminum chloride (Yokel and McNamara 1988).

Effects on body weight have been infrequently and inconsistently observed in intermediate-duration oral exposure studies of aluminum in animals. For example, no changes in body weight were found in male Sprague-Dawley rats that ingested up to 158 mg Al/kg/day as aluminum hydroxide in the diet for 16 days (Greger and Donnaubauer 1986), male and female Long Evans rats administered to up to 104 mg Al/kg/day as aluminum chloride once daily by gavage for 90 days (Bilkei-Gorzo 1993), or female Sprague-Dawley rats that ingested 259 mg Al/kg/day as aluminum nitrate in drinking water for as long as 100 days (Domingo et al. 1987b; Gomez et al. 1986), although transient decreases in body weight occurred in male Sprague-Dawley rats given 346 mg Al/kg/day as aluminum sulfate in drinking water for 4 weeks (Connor et al. 1989). No changes in body weight were observed in female Swiss Webster mice that ingested 130 or 170 mg Al/kg/day as aluminum lactate in the diet for 6 weeks (Golub et al. 1989) or 90 days, respectively (Golub et al. 1992b), or female Swiss Webster mice that ingested 260 mg Al/kg/day as aluminum chloride in the diet for 5 or 7 weeks (Oteiza et al. 1993). Body weight gain was decreased approximately 20% 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 similarly designed different study (Donald et ai. 1989) by the same group of investigators; the effect on body weight appears to be related to a nutritional insufficiency in the semipurified diet used by Golub et al. (1987). The doses in all but one of the above studies (Bilkei-Gorzo 1993) include aluminum in the base diet.

No conclusive changes in body weight were observed in male and female Beagle dogs that consumed 88 mg Al/kg/day as sodium aluminum phosphate in the feed for 6 months (base dietary aluminum not included in the dose) (Katz et al. 1984). Another 6-month study of sodium aluminum phosphate in Beagles found a marked (not quantified), but transient, decrease in body weight gain associated with dietary exposure to 75 mg Al/kg/day (included base dietary aluminum) (Pettersen et al. 1990). The health significance of the effect is unclear because it only persisted for one and a half weeks, was attributed to concurrent palatability-related decreased food consumption, and did not occur in both sexes (only occurred in males).

No body weight effects were observed in rats or mice following chronic-duration exposure to aluminum compounds. The body weights of male and female Dobra Voda mice were similar to controls following exposure to 49 mg Al/kg/day as aluminum chloride in drinking water and base diet for 180 or 390 days (Ondreicka et al. 1966). No effect on body weight was seen in male and female Wistar rats fed a diet containing unspecified amounts of aluminum phosphide/ammonium carbamate for 24 months (Hackenberg 1972). The administration of 0.6 mg Al/kg/day as aluminum sulfate in drinking water to male and female Long Evans rats for 2.5 years also did not affect body weight (Schroeder and Mitchener 1975a). Data on base dietary aluminum were not reported by Schroeder and Mitchener (1975a), although the rats were fed a low-metal diet in metal-free environmental conditions.

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

Metabolic Effects. No studies were located regarding metabolic effects of various forms of aluminum in humans or animals.

2.2.2.3 Immunological and Lymphoreticular Effects

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

No studies were located regarding immunological effects of various forms of aluminum following acuteduration exposure in animals. An intermediate-duration study with female Sprague-Dawley rats found that 79 mg Al/kg/day as aluminum nitrate in drinking water caused hyperemia in the red pulp of the spleen when ingested for 1 month (Gomez et al. 1986). However, the significance of this finding is unclear because immune function was not evaluated, and 284 mg Al/kg/day as aluminum nitrate in drinking water for 100 days did not affect organ weight or cause histological changes in the spleens of female Sprague-Dawley rats (Domingo et al. 1987b). Additionally, no organ weight or histological changes in the spleen and/or thymus were observed in 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), male and female Dobra Voda mice given 49 mg Al/kg/day as aluminum chloride in drinking water for 180 or 390 days (Ondreicka et al. 1966), 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 Dixon et al. (1979) and Oneda et al. (1994) include aluminum in the base diet.

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-y and tumor necrosis factor-a, and a deficiency of CD4+ cells in T-cell populations were observed in Swiss Webster mice that were exposed to aluminum from conception through 6 months of age (Golub et al. 1993b). 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 that were 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 195 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.

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

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects of various forms of aluminum following intermediate-duration oral exposure in humans. Memory loss, fatigue, depression, behavioral changes, and learning impairment were reported in 5 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.

A large number of epidemiology and case-control studies have examined the potential association between oral aluminum exposure and Alzheimer's disease. A number of these studies have been criticized for flawed patient selection, poor comparability of exposed and control groups, poor exposure assessment, poor assessment of health outcomes, and weak statistical correlations (Nieboer et al. 1995; Schupf et al. 1989). Studies conducted by Martyn et al. (1989), McLachlan et al. (1996), and Michel et al. (1990) have found an association between oral exposure to aluminum and an increased risk of Alzheimer's disease. In a survey study conducted by Martyn et al. (1989), the incidence of Alzheimer's disease in individuals under the age of 70 was estimated from computerized tomographic (CT) records. The 1,203 subjects lived in 88 county districts within England and Wales. Data on aluminum concentrations in the municipal water over a lo-year period were obtained from water authorities and water companies. The subjects were classified as having probable Alzheimer's disease, possible Alzheimer's disease, other causes of dementia, or epilepsy. The relative risks of Alzheimer's disease were elevated in the subjects living in districts with aluminum water concentrations of ≈0.01 mg/L. However, the relative risk exceeded unity only in the subjects with aluminum water concentrations of >0.11 mg/L (relative risk of 1.5, 95% confidence interval of 1.1-2.2).

McLachlan et al. (1996) also found a significant association between Alzheimer's disease and aluminum drinking water concentrations of ≥0.10 mg/L. In this case-control study of residents in Ontario, Canada, the diagnosis of Alzheimer's was based on a clinical history of dementia and the histopathologic findings of widespread neuritic plaques with amyloid cores and neurofibrillary tangles in neocortical and subcortical structures. Aluminum concentrations in the municipal water supplies were compared between the 296 cases and the 295 control cases (125 cases had no histopathological alterations in the brain and 170 had other neurodegenerative diseases such as Huntington's disease, schizophrenia, and multiple sclerosis). The odds ratio for Alzheimer's disease at drinking water concentrations of ≥0.10 mg/L was 1.7 (95% confidence intervals of 1.2-2.6).

Unlike the Martyn et al. (1989) and McLachlan et al. (1996) studies, Michel et al. (1990) found increased risks of Alzheimer's disease in subjects living in areas with low aluminum concentrations in drinking water. This study examined 2,792 subjects at least 65 years of age living in South-Western France. Alzheimer's disease was clinically diagnosed. Aluminum concentrations in drinking water ranged from 0.01 to 0.16 mg/L for the 40 cases of probable Alzheimer's disease. The relative risks for probable Alzheimer's disease was 1.16 (significantly different from 1) for 0.01 mg/L and 4.52 for 0.1 mg/L.

In contrast, several studies did not find a significant association between aluminum exposure and the risk of Alzheimer's disease (Forster et al. 1995; Martyn et al. 1997; Wettstein et al. 1991). A case-control study by Forster et al. (1995) examined several risk factors, including aluminum exposure, in 109 patients under 65 years of age with presenile dementia of the Alzheimer's type and in 109 age and sex matched controls. Aluminum exposure was assessed using mean aluminum concentrations in drinking water in the place of residence 10 years before the onset of dementia and the mean aluminum concentrations in drinking water at birthplace (only analyzed in 80 pairs). The aluminum concentration in drinking water was not significantly related to risk of presenile dementia; it should be noted that at the higher aluminum concentrations, there were a small number of cases and controls (43 pairs with aluminum drinking water concentrations of >0.09 mg/L and 2 pairs with aluminum drinking water levels of >0.149 mg/L).

Similar to the Martyn et al. (1989) study, Martyn et al. (1997) used CT records to identify individuals with Alzheimer's disease; 106 cases were identified. Three sets of controls were used: patients with other types of dementia (99 cases), patients with brain cancer (226 cases), and patients with other neurologic disorders (441 cases). The subjects (or next of kin) were mailed questionnaires that asked for all addresses (with dates of residence), and the investigators used this information to gather quantitative data for aluminum concentrations in the municipal water for each address and period of residence. No significant associations were found between the risk of Alzheimer's disease (as compared to each control group) and aluminum levels in drinking water.

In the Wettstein et al. (1991) study, senile dementia was used as a surrogate for Alzheimer's disease because in the area examined, 73% of individuals with dementia show significant Alzheimer changes on autopsy. The subjects consisted of 400 and 405 residents living in two Swiss cities with low (0.004 mg/L) or high (0.098 mg/L) aluminum concentrations in drinking water. The subjects were between 81 and 85 years of age and lived in the area for at least 15 years. Senile dementia was assessed using the mnestic and naming subtest of the Mini Mental Status test (Zurich variant). Performance on mnestic and naming tests did not significantly differ between the high and low exposure groups. Thus, the study authors concluded that there was no relationship between aluminum concentrations in drinking water and the risk of Alzheimer's disease.

Although some of these studies suggest that there may be a relationship between high aluminum intake and Alzheimer's disease, the epidemiologic data do not establish a cause and effect relationship; the relationship between Alzheimer's disease and aluminum is discussed in more detail in Section 2.5.

Uremic persons represent a population at risk for aluminum-related dementia (Alfrey 1993b). 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 (1993b) 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 greater than 500 μg/L (normal levels are approximately 10 μg/L). 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 1993b; 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. For more information, see Sections 2.5 and 2.9.

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 2.2.2.6, 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 2.2.2, 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 2-2. Bioavailability is another issue complicating comparison of NOAELs and LOAELs because there can be a marked difference in absorption (i.e., actual doses) of aluminum depending on the form in which it is ingested. As discussed in Section 2.3.1.2, absorption of aluminum can be 10-fold higher for relatively bioavailable forms such as aluminum citrate compared to less available forms such as aluminum hydroxide.

A number of the studies of aluminum with adequately reported dietary information are intermediate-duration neurotoxicity and neurodevelopmental studies in Swiss-Webster mice that were performed by one group of investigators (Golub and coworkers) using 500 and/or 1,000 ppm concentrations of Al as aluminum lactate in a common semipurified diet formulation. Aluminum lactate was tested because it represents a bioavailable form of aluminum and lactate is a common human dietary constituent. Most of the studies by Golub and coworkers also used similar standardized observational end points and test batteries for assessing neurobehavioral function. The use of similar testing protocols, and the same semipurified diet with known aluminum content within the range of human diet content and minimal batch-to-batch variations, indicates that studies by Golub and coworkers (Donald et al. 1989; Golub et al. 1989, 1992a, 1992b; Oteiza et al. 1993) are the most reliable data set for comparing neurotoxicity effect levels. Although these studies all used the same dietary levels of aluminum, variations in daily aluminum intakes (mg Al/kg/day) from the 500 and 1,000 ppm Al diets occurred due to differences in food intake consequent to factors such as age of animal (e.g., higher in weanlings than adults) and time of exposure (e.g., higher during lactation than during pregnancy or in adults that are not pregnant or lactating). Information on concentrations of aluminum in the base diet is also available for a few other neurotoxicity studies (Domingo et al. 1987b, 1996; Gomez et al. 1986; Vamer et al. 1993, 1994, 1998); these studies used commercial rather than semi-purified diets, indicating that excess and variable amounts of essential and nonessential trace minerals and metal binding ligands were present that can alter aluminum uptake in comparison to semipurified or purified diets in which trace metal levels are precisely determined (Golub et al. 1992b).

Neuromotor, behavioral, and cognitive changes have been observed in oral studies of exposed female adult mice. Overall motor activity was 20% lower and activity periods were 35% shortened compared to controls in mice that ingested 130 mg Al/kg/day as aluminum lactate for 6 weeks (Golub et al. 1989). There were no effects on activity or any clinical signs at 62 mg Al/kg/day, indicating that this is a NOAEL for neurotoxicity. Comprehensive neurobehavioral testing of mice that were exposed to 195 mg Al/kg/day as dietary aluminum lactate for 90 days also found reduced motor activity, as well as decreased hindlimb grip strength, decreased startle responsiveness, and increased tissue levels of aluminum (brain and liver, but not bone), but no clinical signs of neurotoxicity (Golub et al. 1992b). Adult mice that consumed 195 mg Al/kg/day as aluminum chloride for 5-7 weeks in a diet that also contained 3.5% sodium citrate (Oteiza et al. 1993) showed neurotoxic effects similar to those observed by Golub et al. (1992b). The citrate is likely to have enhanced the responses in comparison to those found in the Golub et al. (1992b) study without citrate, because grip strength was reduced in forelimbs as well as hindlimbs, and aluminum levels were increased in bone as well as in central nervous system and liver tissue. Only single exposure levels were tested by Golub et al. (1992b) and Oteiza et al. (1993), precluding identification of NOAELs in these studies. Performance in a skilled motor coordination test (roto-rod treadmill) was impaired in mice that were reportedly exposed to a lower level of aluminum (1.1 mg Al/kg/day as aluminum chloride in drinking water) for 100 days (Sahin et al. 1995b), but the actual effect level (total dose) is unknown due to lack of data on levels of aluminum in the base diet. The NOAEL for neurotoxicity in mice of 62 mg Al/kg/day (Golub et al. 1989) is used to calculate an intermediate oral MRL of 2.0 mg Al/kg/day as described in the footnote to Table 2-2 and in Appendix A.

Marked signs of neurotoxicity, including ataxia, splaying and dragging of hindlimbs, and paralysis, occurred in maternal mice that were exposed to estimated doses of 184 mg Al/kg/day (Golub et al. 1987) or 250 mg Al/kg/day (Golub et al. 1992a) as aluminum lactate during gestation and lactation. The dissimilarity in the LOAELs for these effects is attributable to the composition of semipurified diet used by Golub et al. (1987) which differed from that used subsequently. In particular, the diet formulation was revised in the Donald et al. (1989) and later Golub studies 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 (Golub et al. 1987). 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 2-2.

Some information is available on oral neurotoxicity of aluminum in species other than mice. No effects on spontaneous motor activity (open-field) or passive avoidance operant training or performance (grid floor shock, light/dark shuttle box) were found in rats that were co-exposed to ≤ 125 mg Al/kg/day as aluminum nitrate and citric acid(< 355 mg/kg/day) in drinking water and the base diet for 6.5 months beginning at 21 days, 8 months, or 16 months of age (Domingo et al. 1996). Cognitive deficits and other changes, were found in other studies in rats as summarized below, but the effect levels in these studies cannot be assumed to be accurate due to insufficient information on base dietary aluminum. Because dietary aluminum is likely to have significantly contributed to total intake, the reported dosages may considerably underestimate actual doses. Maze-learning ability was decreased and brain aluminum levels were increased in rats that were treated for 90 days by gavage with 6 or 20 mg Al/kg/day as aluminum chloride, 104 mg Al/kg/day as aluminum hydroxide, or 35 mg Al/kg/day as aluminum hydroxide plus 30 mg/kg citric acid (Bilkei-Gorzo 1993). Altered general motor activity, as well as impaired motor coordination (roto-rod treadmill performance) and visual temporal acuity (increased critical flicker frequency), were observed in rats that were treated with 45 mg Al/kg/day of aluminum chloride for 28 days (Bowdler et al. 1979). Motor activity and acquisition of shuttle-box avoidance behavior were reduced in rats exposed to 86 mg Al/kg/day as aluminum chloride for 11 months (Commissaris et al. 1982), although there was no effect on retention or extinction of the learned behavior. Rats that were exposed to aluminum hydroxide in the diet at doses of 1,252 mg Al/kg/day as weanlings for 60 days or 83 1 mg Al/kg/day as adults for 30 days had no clear effects on open-field activity or performance on passive avoidance and visual discrimination-reversal learning tasks in rats (Thorne et al. 1986, 1987). Although there were no definite differences between exposed and control groups in any of the tests, some responses appeared to be correlated with increased brain aluminum content in the younger rats (e.g., reduced activity level and performance on the learning tasks), suggesting that the young animals were less affected than the adults.

Other intermediate-duration oral studies in rats evaluated effects of aluminum on brain chemistry as well as neurobehavioral performance. Rats that consumed 5 1 mg Al/kg/day as aluminum chloride in drinking water for 180 days had alterations in behavior (reduced spontaneous locomotor activity, impaired learning, extinction and relearning of an active avoidance task, impaired maze relearning ability) and brain chemistry (increased lipid peroxidation, decreased activity of Na^+-, K^+-, and Mg^{2+}-ATPases) (Lal et al. 1993). Ingestion of 490 mg Al/kg/day as aluminum sulfate in drinking water for 4-12 weeks caused reduced retention of a learned passive avoidance task and changes in brain chemistry (e.g., increased cyclic adenosine monophosphate levels, decreased concentrations of MAP-2 and other structural

proteins), although no effects on an active avoidance task, maze performance, or locomotor activity were observed (Connor et al. 1988, 1989; Jope and Johnson 1992). Injection of the aluminum chelator deferoxamine returned the passive avoidance performance of the aluminum-exposed rats to control levels in a dose-dependent manner, indicating that the behavioral impairment was a specific and reversible toxic effect that was not due to nonspecific mechanisms affecting general motor activity (Connor et al. 1989). Changes in brain biogenic amines (decreased dopamine and 5-hydroxytryptamine, increased norepinephrine) occurred in rats that were treated with 21.4 mg Al/kg/day as aluminum nitrate by gavage for 6 weeks, but behavioral performance was not evaluated (Flora et al. 1991). None of these studies included information on levels of base dietary aluminum.

No histopathological changes in the brain were found in rats that ingested drinking water providing 51 mg Al/kg/day as aluminum chloride for 180 days (Lal et al. 1993), ≤70 mg Al/kg/day as aluminum chloride for 90 days (Dixon et al. 1979), 133 mg Al/kg/day as aluminum nitrate for 1 month (Gomez et al. 1986) or 284 mg Al/kg/day as aluminum nitrate for 100 days (Domingo et al. 1987b), or in dogs that consumed ≤ 80 mg Al/kg/day as dietary sodium aluminum phosphate for 26 weeks (Pettersen et al. 1990). In the only one of these rat studies to also evaluate behavioral changes, Lal et al. (1993) found that 5 1 mg Al/kg/day for 180 days did cause reduced spontaneous locomotor activity and impaired learning responses in an active avoidance task. Histopathologic changes were observed in the brain of rats that were fed 92 mg Al/kg/day as aluminum chloride and a high level of citrate (598 mg/kg/day) for 6 months (Florence et al. 1994). These alterations were not specific to any brain region and included extensive cytoplasmic vacuolization in astrocytes, swelling of astrocytic processes, and neuronal vacuolization and nuclear inclusions. No "significant behavioral changes" were observed; however, neurobehavioral tests were not performed by Florence et al. (1994). Increased aluminum levels and histological alterations in the brain (particularly increased numbers of abnormal and damaged neurons and reductions in cell density in areas of the hippocampus and neocortex) also occurred in rats that received an estimated 12 mg Al/kg/day as aluminum fluoride in drinking water and base diet for 45-52 weeks (Varner et al. 1993, 1994, 1998); behavioral tests indicated possible olfactory impairment, but no motor functional changes or effects on spatial memory. Unusual exposure conditions preclude identifying relevant LOAELs for brain histopathology. In particular, the induction of brain lesions by Florence et al. (1994) is apparently due to greatly enhanced uptake of aluminum by the massive co-exposure to citrate compared to normal human citrate intake (62 mg/kg/day), because the purpose of the study was to develop an animal model of aluminum overload. Similarly, the brain alterations observed by Varner et al. (1993, 1994, 1998) likely resulted from enhanced availability of aluminum because the aluminum

fluoride in drinking water was prepared to form an optimum fluoroaluminum species capable of crossing the gut and vascular barriers. The doses for all but two of the above studies (Dixon et al. 1979; Lal et al. 1993) include aluminum in the base diet.

Information on chronic oral neurotoxicity of aluminum in animals is limited to a 20 month diet study in mice which found no histopathologic changes in the brain following ingestion of estimated doses as high as 979 mg Al/kg/day as dietary aluminum potassium sulfate (Oneda et al. 1994). These doses do not include aluminum in the base diet.

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 2.2.2.6, 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 2-2 and plotted in Figure 2-2.

2.2.2.5 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 BALBk mice treated with 41 mg Al/kg/day as aluminum chloride by gavage (aluminum in base diet not reported) on Gd 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 Gd 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 Gd 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 Gd 5-15 showed a transient irregularity of the oestrus 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 Gd 18, whereas 4 of 17 litters exposed to $\geq$ 155 mg Al/kg/day were born earlier or later (Gd 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 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 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 B6C3Fl mice that ingested ≤ 979 mg Al/kg/day as dietary aluminum potassium sulfate for 20 months (Oneida 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 2-2 and plotted in Figure 2-2.

2.2.2.6 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 3 infants with kidney failure who had been treated orally with more than 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).

Maternal and embryo/fetal effects of oral gestational exposure to aluminum have been studied in rats and mice. Information on total aluminum doses (experimental plus baseline dietary aluminum) is available for most of these studies (Colomina et al. 1992, 1994; Domingo et al. 1987a; Domingo et al. 1987a,

1989; Gomez et al. 1991; McCormack et al. 1979; Paternain et al. 1988). The total doses for all but McCormack et al. (1979) are not highly reliable because the base dietary intake is an assumed value based on a wide range of concentrations (60-280 ppm) reported for the same commercial diet (Panlab) in only three studies (Colornina et al. 1998; Domingo et al. 1987a, 1993), indicating the potential for large batch-to-batch variations. Rats that ingested up to 110 mg Al/kg/day in feed that contained added aluminum chloride on Gd 6, 9, 12, 15, and 18 did not experience maternal toxicity, embryo/fetal toxicity, teratogenicity, fetal growth retardation, or significantly increased fetal whole carcass concentrations of aluminum (McCormack et al. 1979). The 110 mg Al/kg/day dose is not a definite NOAEL because the intermittent daily exposure schedule could have missed a critical developmental time for inducing effects. Concurrent administration of parathyroid hormone by subcutaneous injection, which increased tissue levels of aluminum by presumably enhancing its absorption, increased the percentage of resorbed or dead fetuses. As summarized below, other studies in rats also indicate that aluminum was fetotoxic under conditions that enhanced its uptake (e.g., intake with citrate or nitrate, and/or as a bolus by gavage) .

No maternal toxicity or effects on embryo/fetal viability or fetal development occurred in rats that were exposed to 158 mg Al/kg body weight/day as aluminum hydroxide or aluminum citrate by gavage and commercial base diet on Gd 6-15 (Gomez et al. 1991). In contrast, effects in dams (reduced weight gain) and fetuses (reduced body weight and skeletal variations [increased delayed occipital and sternebrae ossification and increased absence of xiphoids]) were found in rats exposed to 158 mg Al/kg/day as aluminum hydroxide concurrently with citric acid at 62 mg/kg/day (Gomez et al. 1991). Similar effects (decreased maternal body weight and skeletal changes [delayed ossification, hypoplastic deformed ribs]) were induced in rats exposed to 38-77 mg Al/kg/day as aluminum nitrate by gavage and base diet on Gd 6-14 (Patemain et al. 1988). Additionally, similar exposure to 38-77 mg Al/kg/day as aluminum nitrate in a single generation reproduction study caused transient reduction in growth of rat offspring (Domingo et al. 1987c). Although a LOAEL of 38 mg Al/kg/day could be identified for developmental toxicity based on skeletal effects, the value is inappropriate for several reasons. This effect level may be unnaturally low and not relevant to human environmental exposure because the skeletal changes could be related to phosphate depletion caused by excess binding with aluminum in the maternal gut due to the bolus administration. Enhanced bioavailability is another possible reason for this low LOAEL because aluminum nitrate was shown to be twice as bioavailable as aluminum chloride in rats (Yokel and McNamara 1988) (see Section 2.3.1.2). Also, commercial diets contain excess and variable amounts of essential and nonessential trace minerals, and metal binding ligands were present that can alter aluminum

uptake in comparison to semipurified or purified diets in which trace metal levels are precisely determined (Golub et al. 1992b). Additionally, evidence for developmental growth effects (e.g., decreased fetal weight, delayed skeletal maturation) in animals exposed to high levels of nitrate (NRC 1995) suggests that the skeletal changes caused by aluminum nitrate may not be entirely attributable to aluminum; these effects are likely secondary to maternal or fetal methemoglobinemia rather than a direct effect of aluminum.

Gestational exposure studies in mice also indicate that compound bioavailability and the presence of dietary components that promote uptake are factors affecting the developmental toxicity of aluminum In a study designed to evaluate the influence of lactate on the developmental toxicity of aluminum mice were exposed to an estimated dose of 83 mg Al/kg/day as aluminum lactate, aluminum hydroxide, or aluminum hydroxide concurrent with lactic acid (570 mg/kg/day) by gavage and base diet on Gd 6-15 (Colomina et al. 1992). Effects observed in the aluminum lactate-treated mice included reduced maternal food consumption and body weight gain, reduced fetal body weight, and 13-15% increased incidences of cleft palate, dorsal hyperkyphosis (i.e., excessive flexion of spine), and delayed parietal ossification. No exposure-related developmental effects occurred in the fetuses that were exposed to aluminum hydroxide alone or combined with lactic acid. Other studies by the same group of investigators also found no developmental changes in mice that were exposed to $\leq$ 141 mg Al/kg/day as aluminum hydroxide (Domingo et al. 1989), or 129 mg Al/kg/day as aluminum hydroxide alone or combined with ascorbic acid (85 n&kg) (Colomina et al. 1994), by gavage and base diet on Gd 6-15. No developmental effects occurred in mice that were gavaged with $\leq$ 61 mg Al/kg/day as aluminum chloride on Gd 7-16 (Cranmer et al. 1986), but the actual dose of aluminum is not known due to lack of information on aluminum content in the base diet in this study.

Other studies in mice suggest that developmental exposure to aluminum may adversely affect the immune systems. As summarized in Section 2.2.2.3, increased susceptibility to bacterial infection and other immunologic alterations were found in gestationally- and neonatally-exposed young animals (Golub et al. 1993b; Yoshida et al. 1989).

Neurodevelopmental effects of aluminum have been investigated in a large number of oral studies in mice and rats, but determination of accurate effect levels in many of these studies is precluded by a lack of information'on aluminum content in the base diet. As discussed in Section 2.2.2.4, most of the neurodevelopmental studies of aluminum with adequately reported dietary information were performed

in mice by the same group of investigators (Golub and associates) who evaluated aluminum lactate in a common semipurified diet with known aluminum content using similar testing methods (Donald et al. 1989; Golub et al. 1992a, 1992b, 1994, 1995; Golub and Germann 1998). Aluminum lactate was tested because it represents a bioavailable form of aluminum and lactate is a common human dietary constituent. As discussed below, neurodevelopmental deficits have been observed in weanling and young mice and rats exposed during gestation, combined gestation and lactation, combined gestation and lactation followed by postweaning ingestion, or postweaning ingestion alone. The most frequently observed behavioral patterns are indicative of altered and delayed reflex and neuromotor development. Performance of learning and memory tasks by mice and rats have not been consistently shown to be disrupted by developmental oral aluminum exposure, although extensive cognitive testing has not been performed (Domingo 1995; Golub and Domingo 1996).

Effects indicative of altered neuromotor maturation occurred at estimated doses as low as 155 mg Al/kg/day in mice exposed to aluminum lactate in studies with adequate base dietary aluminum information (Donald et al. 1989; Golub et al. 1995). Lower doses of aluminum were not tested in these or other adequately reported studies in mice or rats. Effects observed at the 155 mg Al/kg/day LOAEL included increased fore- and hindlimb grip strengths, increased foot splay, and increased latency to remove tail from hot water in offspring that were exposed during gestation and lactation and tested as weanlings (Donald et al. 1989), and decreased grip strength and decreased air-puff startle response in offspring exposed during gestation and lactation, or from gestation through adulthood, and tested as adults (Golub et al. 1995). The pattern of effects (types and magnitude of responses) in mice exposed during development and tested as adults was similar to that in mice exposed subchronically for up to 90 days only as adults (Golub et al. 1992b; Oteiza et al. 1993) (see Section 2.2.2.4). This indicates that it is likely that the effects were induced during the preweaning period and not further intensified by continuing exposure, and that the differences in effects seen in the younger (weanling) mice after developmental exposure are due to age at evaluation rather than age at exposure (Golub et al. 1995). Findings in other mouse studies by Golub and coworkers using similar or higher estimated doses of aluminum lactate corroborate the neuromotor alterations summarized above, including increased grip strength, increased tail withdrawal time from hot water, and negative geotaxis latency (as well as decreased weight and crown-rump length) in weanlings following gestation and/or lactation exposure (Golub et al. 1992a), and reduced auditory startle responsiveness in pups exposed during gestation and lactation, or from gestation continuing into postweaning, and tested at 52 days of age (Golub et al. 1994). In contrast to impaired neuromotor responses, mice exposed to $\geq$155 mg Al/kg/day during

development and/or as adults showed enhanced performance during training and performance of foodmotivated operant learning tasks (Golub et al. 1995; Golub and Germann 1998).

Neurodevelopmental effects in oral studies of aluminum in rats are summarized below, but doses in these studies cannot be assumed to be accurate because they may considerably underestimate actual aluminum intake due to insufficient information on aluminum in base diets. Offspring of rats that were gestationally exposed to 73.1 mg Al/kg/day as aluminum chloride by gavage showed delays in pivoting and longer latencies and more rearings in an open field test (Misawa and Shigeta 1992). Effects observed in rat pups that were pre- or postnatally exposed to 100-400 mg Al/kg/day as aluminum chloride or lactate included delays in neuromotor maturation (e.g., impaired grasping and righting reflexes and locomotor coordination), reduced body weight, and/or increased mortality, although there was no effect on learning ability in offspring that were gestationally exposed to 400 mg Al/kg/day and tested on postnatal day 65 using operant conditioning (Bemuzzi et al. 1986b, 1989a, 1989b; Muller et al. 1990). Rats that were treated with 100 or 200 mg Al/kg/day as aluminum lactate on postnatal days 5-14 and tested at postnatal days 50 and 100 showed no alterations in learning ability based on tests of motivation (avoidance of an aversion light or alimentary motivation) and achievement (pressing on a lever or radial maze performance), although a small reduction in general activity was observed at 200 mg Al/kg/day (Cherroret et al. 1992). Weanling rats that were exposed to 83 1 mg Al/kg/day as aluminum hydroxide in the diet for 60 days had no effects on open field activity or performance in passive avoidance and radial maze learning tasks (Thome et al. 1987).

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

2.2.2.7 Genotoxic Effects

No studies were located regarding genetic effects of various forms of aluminum following oral exposure in humans or animals. Genotoxicity studies are discussed in Section 2.5.

2.2.2.8 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. Multiple tumors and lymphoma leukemia were significantly increased in the female mice. A doseresponse 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. Nevertheless, the authors did not consider aluminum potassium sulfate to be carcinogenic. 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 male or female B6C3Fl 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).

2.2.3 Dermal Exposure

2.2.3.1 Death

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

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, 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 2-3.

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 some types of aluminum-containing antiperspirants and develop skin rashes which may be aluminum-related. (Brusewitz 1984).

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, 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.

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological/lymphoreticular effects in humans after intermediateor 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 (Bijhler-Sommeregger and Lindemayr 1986; Veien et al. 1986). Dermal hypersensitivity to aluminum appears to be rare in humans.

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

Species (Strain)	Exposure/ Duration/ Frequency	System	NOAEL	LOAEL Less serious	LOAEL Serious	Reference Chemical Form
ACUTE EXPOSURE						
Systemic						
Mouse (TFI)	5 d 1x/d	Dermal	10% F			Lansdown 1973 AlH_3O_3
Mouse (TFI)	5 d 1x/d	Dermal	25% F			Lansdown 1973 $Al_2(OH)_5Cl$
Mouse (TFI)	5 d 1x/d	Dermal	10% F			Lansdown 1973 $Al(C_2H_2O_2)_3$
Mouse (TFI)	5 d 1x/d	Dermal	2.5% F	5% F (slight to moderate hyperplasia)	25% F (severe hyperplasia with focal ulceration)	Lansdown 1973 $AlCl_3$
Mouse (TFI)	5 d 1x/d	Dermal		10% F (epidermal damage; hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)		Lansdown 1973 $AlCl_3$
Mouse (TFI)	5 d 1x/d	Dermal	10% F			Lansdown 1973 $Al_2(SO_4)_3$
Mouse (TFI)	5 d 1x/d	Dermal		10% F (epidermal change: hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)		Lansdown 1973 $Al(NO_3)_3$

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

Species (Strain)	Exposure/ duration/ frequency	System	NOAEL	LOAEL Less serious	LOAEL Serious	Reference Chemical Form
Rabbit (New Zealand)	5 d 1x/d	Dermal	10%			Lansdown 1973 $Al(C_2H_2O_2)_3$
Rabbit (New Zealand)	5 d 1x/d	Dermal		10% (epidermal change: hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)		Lansdown 1973 $Al(NO_3)_3$
Rabbit (New Zealand)	5 d 1x/d	Dermal	10%			Lansdown 1973 $Al_2(SO_4)_3$
Rabbit (New Zealand)	5 d 1x/d	Dermal		10% (epidermal damage; hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)		Lansdown 1973 $AlCl_3$
Rabbit (New Zealand)	5 d 1x/d	Dermal	10%			Lansdown 1973 AlH_3O_3
Rabbit (New Zealand)	5 d 1x/d	Dermal	25%			Lansdown 1973 $Al_2(OH)_5Cl$
Pig (Large White)	5 d 1x/d	Dermal	10% F			Lansdown 1973 $Al(C_2H_2O_2)_3$

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

Species (Strain)	Exposure/ duration/ frequency	System	NOAEL	LOAEL Less serious	LOAEL Serious	Reference Chemical Form
Pig (Large White)	5 d 1x/d	Dermal		10% (epidermal change: hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)		Lansdown 1973 $Al(NO_3)_3$
Pig (Large White)	5 d 1x/d	Dermal	10%			Lansdown 1973 $Al_2(SO_4)_3$
Pig (Large White)	5 d 1x/d	Dermal		10% (epidermal damage; hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)		Lansdown 1973 $AlCl_3$
Pig (Large White)	5 d 1x/d	Dermal	10%			Lansdown 1973 AlH_3O_3
Pig (Large White)	5 d 1x/d	Dermal	25%			Lansdown 1973 $Al_2(OH)_5Cl$

d = day(s); F = female; LOAEL = lowest-observable-adverse-effect level; M = male; NOAEL = no-observable-adverse-effect level

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

2.2.3.4 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 were 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:

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

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

2.3 TOXICOKINETICS

Aluminum is poorly absorbed following either oral or inhalation exposure and is essentially not absorbed dermally. Occupational exposure to fine powders of aluminum metal has resulted in pulmonary effects as a result of particulate deposition in the lung and subsequent pulmonary fibrosis. Approximately 0.1% of ingested aluminum is usually absorbed, although absorption of more bioavailable forms can be on the order of 1%. The unabsorbed aluminum is excreted in the feces. The 10-fold range in absorption of aluminum is largely due to differences in bioavailability related to the form of ingested aluminum and the presence of dietary constituents which can complex with aluminum and 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 steady-state is maintained in most healthy adults, with aluminum body burdens neither increasing nor decreasing over time. 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 rise 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). "Free" aluminum ions (e.g., $Al(H_20)_6^{3+}$) 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 would not.

Toxicokinetic data for aluminum have been somewhat limited by a paucity of radioisotope tracer experiments, which have only recently been conducted with aluminum due to the lack of a suitable and convenient radioisotope. ^{28}Al can be produced, but it has a half-life of only 2.3 minutes (Ganrot 1986). Recently, ^{26}Al (half-life $7.2x10^5$ years) has been produced by accelerator mass spectrometry. Although ^{26}Al is not widely available to researchers, it has been used in a number of human and animal studies to

assess the toxicokinetic properties of aluminum (Day et al. 1991; Flarend et al. 1997; Hohl et al. 1994; Priest et al. 1995, 1996; Schiinholzer et al. 1997; Walton et al. 1995).

2.3.1 Absorption

2.3.1.1 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 (Gitehnan et al. 1995). Results of an autopsy on a stonemason 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 μg/L to 4-414 μg/L (Sjiigren 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; Sjiigren 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 (Sjogren et al. 1988).

The percentage of aluminum absorbed following inhalation exposure was not reported in the occupational toxicokinetic studies (Gitelman et al. 1995; Mussi et al. 1984; Pierre et al. 1995; Sjogren et al. 1985, 1988). 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. However, it is not known if a possible difference in particle size between the aluminum fumes and aluminum dust influenced absorption.

It is possible that systemic absorption of airborne aluminum occurs via the lungs, gastrointestinal tract after mucociliary clearance from the respiratory tract (ICRP 1994), or via the olfactory tract. 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 or serum were seen, indicating that lung retention rather than absorption was taking place (Steinhagen et al. 1978; Stone et al. 1979).

2.3.1.2 Oral Exposure

Human studies indicate that only a small percentage of aluminum that is normally ingested in the diet and drinking water is absorbed. Most estimates of average gastrointestinal absorption of aluminum under normal dietary conditions are in the range of 0.1-0.3%, although some human studies indicate that absorption of the more bioavailable forms, particularly complexes of aluminum with particular carboxylic acids, (e.g., aluminum citrate), may be on the order of 1% (Day et al. 1991; DeVoto and Yokel 1994; Ganrot 1986; Greger and Baier 1983b; Jones and Bennett 1986; Nieboer et al. 1995; Priest 1993; Priest et al. 1996). In a representative study by Greger and Baier (1983b), eight healthy people ingested a control diet (5 mg Al/day) or the same diet supplemented with aluminum lactate (120 mg Al/day) in alternating 20-day periods, with the subjects receiving sodium lactate instead of aluminum lactate during the control phases. Based on the fraction of aluminum intake excreted in the urine per day, gastrointestinal absorption was estimated to be 0.78% during the control periods and 0.09% during the test periods. Blood levels of aluminum increased slightly only during the test period and quickly returned to normal during the control period. The 5 and 125 mg Al/day doses (0.07 and 1.8 Al/kg/day assuming a body weight of 70 kg) are within the normal range of aluminum intake in the United States, although aluminum lactate may have a different bioavailability than the forms of aluminum typically found in the diet (e.g., additives such as sodium aluminum phosphate, aluminum sulfates, and aluminum silicates [see Section 5.4.41).

People on antacid therapy consume much higher amounts of aluminum than in the diet, commonly up to several grams of aluminum per day ingested as large bolus doses or as much as a half gram of aluminum

throughout the day as aluminum hydroxide (a relatively insoluble form of aluminum) (Reiber et al. 1995). Although aluminum intake during antacid treatment can be substantial (i.e., two to three orders of magnitude higher than normal intake), usually greater than 99% of the ingested aluminum is still recovered in the feces and blood aluminum levels still rarely rise more than 50% higher than the preantacid level (Gorsky et al. 1979; Kaehny et al. 1977; Reiber et al. 1995), indicating that aluminum uptake is mainly controlled by factors other than the amount of ingested aluminum. As discussed in Section 2.4.1, most ingested aluminum is unlikely to be absorbed as it is precipitated in the small intestine and excreted in the feces. However, even though only a small percentage of ingested aluminum is absorbed, significant body burdens could arise, especially in individuals with impaired renal function, because antacids are commonly used in large quantities over long periods of time.

The absorption of aluminum depends on its bioavailability in the aqueous and varying pH conditions of the gut. Aluminum bioavailability is mainly related to the form in which it is ingested and the presence of dietary constituents with which the metal cation can complex (see Section 2.4.1). 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; Partridge et al. 1989; Molitoris et al. 1989; Slanina et al. 1984, 1985, 1986; Testolin et al. 1996; Weberg and Berstad 1986). For example, the percentages 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.

Most of the estimates of aluminum uptake summarized above are based on the assumption that urinary excretion represents absorption, although a few values were determined using the anthropogenic radioactive isotope ^{26}Al in combination with a sophisticated analytical technique (accelerator mass

spectrometry) (Day et al. 1991; Priest et al. 1996; Sch□nholzer et al. 1997). Isotopic tracer techniques have been infrequently used in absorption studies of aluminum because ^{26}Al (the only isotope with a biologically usable half-life) is not readily available and inexpensive in the quantities necessary for radiochemical detection. Radiotracer studies are favorable because they facilitate accurate quantification of the very small percentages of ingested aluminum that are absorbed and provide a means to distinguish administered radioactive aluminum from stable endogenous aluminum and from aluminum contamination of samples (Priest 1993). A radiochemical determination of the likely range of aluminum bioavailabilities has only recently been performed. Priest et al. (1996) determined the fraction of aluminum taken up by two male volunteers following administration of a single dose of ^{26}Al-labeled aluminum citrate (aqueous solution) or aluminum hydroxide (colloidal suspension in water) directly to the stomach using a pediatric feeding tube; there was a 3-week interval between dosing. These forms of aluminum were used because it was suspected that they would be either relatively bioavailable (citrate) or relatively nonbioavailable (hydroxide). Based on analyses of ^{26}Al in the blood (collected at 1, 4, and 24 hours after dosing) and excreta (urine and feces were collected for 6 days), the absorbed fractions were determined to be 0.5% for aluminum citrate and 0.01% for aluminum hydroxide. Similar exposure to aluminum (^{26}Al) hydroxide simultaneously with trisodium citrate resulted in 0.14% absorption of aluminum; this exposure likely represents a more normal exposure scenario (e.g., following the ingestion of aluminum in orange juice) than ingestion of pure aluminum citrate. The uptake of aluminum citrate was about a factor of two lower than a value of 1% previously determined in a study of ^{26}Al-labeled aluminum citrate using one subject (Day et al. 1991). Due to the use of a considerably higher quantity of citrate by Day et al. (1991), the small number of subjects in both studies, and other factors that could contribute to inter-subject variability in absorption (e.g., presence of food in the gut), Priest et al. (1996) concluded that aluminum absorption must at least equal 1% under some circumstances and 0.5% is probably close to the maximum bioavailability in adults and older children under normal ingestion exposure conditions. Schoriholzer et al. (1997) also examined aluminum absorption following oral exposure to ^{26}Al. Wistar rats received a single gavage dose of aluminum hydroxide, aluminum citrate, aluminum citrate with added sodium citrate, or aluminum maltolate. Fractional intestinal absorptions of 0.1, 0.7, 5.1, and 0. 1%, respectively, were estimated.

The influence of some of the aforementioned factors on aluminum absorption is further illustrated by the findings of two animal studies which estimated bioavailability differences by comparing areas under plasma concentration-time curves (AUC) after oral and intravenous dosing (Yokel and McNamara 1988). Using a single oral dose of aluminum chloride, aluminum absorption was estimated to be 0.57% in

rabbits treated with 333 mg Al/kg (Yokel and McNamara 1988). Following a single maximum safe oral dose 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, aluminumabsorption was 0.57, 1.16, 2.18, and 0.63%, respectively (Yokel and McNamara 1988). 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). Nitrate, therefore, was the most bioavailable form of aluminum after citrate. However, although aluminum citrate was more bioavailable than aluminum nitrate as determined from AUC, aluminum from aluminum nitrate reached a higher peak concentration in blood.

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, ranging from approximately 0.1% for relatively nonbioavailable water insoluble forms such as aluminum hydroxide to relatively bioavailable soluble forms such aluminum citrate. 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. Aluminum lactate is often used in animal oral toxicity studies (Section 2.2.2) because it is intermediate in bioavailability between inorganic complexes (e.g., aluminum hydroxide and aluminum silicates) and aluminum complexed with organic acids (e.g., citrate), and does not introduce nonbiological anions at the same time. Due to the range of possible bioavailabilities, the amount of aluminum ingested does not provide a estimate of exposure without information on bioavailability of the form in which it is ingested.

2.3.1.3 Dermal Exposure

No studies were located regarding aluminum absorption in humans after dermal exposure to aluminum or its compounds. 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 (Reiber et al. 1995). The possibility that aluminum in antiperspirants may be absorbed directly through the skin has been suggested (Graves et al. 1990), but this hypothesis has not been clinically confirmed.

A study by Anane et al. (1995) provides evidence that aluminum is absorbed through the skin. Increased levels of aluminum were observed 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.

2.3.1.4 Other Routes of Exposure

Aluminum uptake occurred in patients with chronic renal failure during hemodialysis treatment (Alfrey 1993b; Berlyne et al. 1970). Aluminum in dialysate water passed through the dialysis membrane and entered directly into the blood, resulting in increased serum aluminum levels in patients after dialysis. This toxicity has been largely prevented by eliminating aluminum from the water used to prepare the dialysate (AAMI 1998), substituting calcium-containing phosphate-binding agents for those containing aluminum and avoidance of the concomitant ingestion of citrate- and aluminum-containing compounds (Alfrey 1993b).

2.3.2 Distribution

Aluminum occurs normally in the 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. 1972/73; Tipton and Cook 1963). Of the total body burden of aluminum about one-half is in the skeleton, and about one-fourth is in the lungs (Ganrot 1986). Most of the aluminum detected in lungs is probably due to 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.

The normal level of aluminum in adult human lungs is about 20 mg/kg wet weight (w/w) and increases with age due to buildup; 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. 1972/73; Tipton and Cook 1963). 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. 1972/73; Tipton and Cook 1963).

There is relatively good agreement in the published literature that 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).

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. 1972/73), adrenals (Stitch 1957; Tipton and Cook 1963), and parathyroid glands (Cann et al. 1979). There is evidence that with increasing age of humans, aluminum concentrations may increase in the lungs and brain tissue (Alfrey 1980; Crapper and DeBoni 1978; Markesbery et al. 1981; McDermott et al. 1979; Stitch 1957; Tipton and Shafer 1964).

2.3.2.1 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.

Following inhalation exposure, the lungs receive aluminum mostly as particles of poorly soluble compounds (Ganrot 1986). ICRP (1994) reports that 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 assumed to be taken up by alveolar macrophages through phagocytosis, then transported up the bronchial tract, and ultimately swallowed. The remainder of aluminum is probably taken up by macrophages in the lung tissue where it remains indefinitely. It has been observed that the lungs have the highest aluminum concentration compared to other organs, and that the pulmonary concentration of aluminum increases with age.

2.3.2.2 Oral Exposure

There are limited data on the distribution of aluminum in humans. Clearance of ^{26}Al from the blood was assessed in 2 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; Domingo et al. 1993; Gomez et al. 1997a, 1997b; Greger and Donnaubauer 1986; Julka et al. 1996; Santos et al. 1987; Walton et al. 1995; Yokel and McNamara 1985). 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. Animal evidence suggests that aluminum accumulates in the brain and is preferentially distributed to the hippocampus. Acute oral exposure of weanling rats to both 1,25-dihydroxyvitamin-D_3 and 160 mg Al/kg/day as either aluminum hydroxide or aluminum citrate has been associated with significantly elevated aluminum concentrations in the cerebral cortex and hippocampus (Santos et al. 1987). In treated animals, the hippocampus aluminum concentration was about 53 times higher than that observed in the control group and approximately 32 times higher than that found in other areas of the brain (cortex, cerebellum). The potential role of 1,25-dihydroxyvitamin-D_3 in this preferential accumulation was not determined; however, it was suggested that the preferential deposition of aluminum in the hippocampus may play an important pathogenic role in aluminumneurotoxicity (Santos et al. 1987). Using ^{26}Al, Walton et al. (1995) showed that a single low dose oral exposure to aluminum sulfate can result in a substantial increase in brain aluminum levels in rats. In 6 of the 8 exposed rats, brain aluminum levels were 10 to 300 times higher than control values (brain aluminum levels in the remaining 2 rats were similar to control levels).

Results of several studies with experimental animals indicate that administration of vitamin D and 1,25-dihydroxyvitamin-D_3 enhances the accumulation and retention of aluminum in tissues (e.g., bone, kidneys, muscle, and heart) following oral exposure to aluminum compounds (Anthony et al. 1986; Burnatowska-Hledin et al. 1986; Chan et al. 1998).

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.

In addition to distribution of aluminum to the brain (hippocampus), bone, muscle, and kidneys of orally exposed animals, there is limited animal evidence indicating that aluminum has the potential to cross the placenta and accumulate in the fetus and to be distributed to some extent to the milk of lactating mothers (Cranmer et al. 1986; Golub et al. 1996a; Yokel 1985; Yokel and McNamara 1985). Increased concentrations of aluminum were detected 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. 1996a). 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). However, 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).

Once into the blood, aluminum is believed to be present almost exclusively in the plasma where it is bound mainly to transferrin (Ganrot 1986; Martin 1986; Öman and Martin 1994); Ohman and Martin (1994) showed that 89% of the aluminum in serum is bound to transferrin. 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). 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. 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).

2.3.2.3 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.

2.3.2.4 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).

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). 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. 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, 42, 4.2, and 2.3 days in the spleen, liver, lungs, serum renal cortex, and renal medulla, respectively. The kidneys of treated rabbits also demonstrated a second half-time which exceeded 100 days.

Subcutaneous injection of rabbits with aluminum chloride daily for 28 days was associated with significant accumulation of aluminum 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 either 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. At blood aluminum concentrations of 2-4 mg/L, there was no increase in brain aluminum with any of the compounds evaluated.

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). Jntraperitoneal exposure of pregnant mice to aluminum chloride on Gd 7-l 6 has been associated with significantly increased concentrations of aluminum in both placental and fetal tissues (Cranmer et al. 1986). Both intravenous and subcutaneous exposure of lactating rabbits and mice to aluminum lactate has been associated with increased concentrations of aluminum in milk (Yokel and McNamara 1985; Golub et al. 1996). 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. Because of the limited gastrointestinal absorption of aluminum and the limited distribution of aluminum to milk, it was suggested that there would be little risk of aluminum toxicity in suckling offspring of nursing females exposed to aluminum

2.3.3 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 affnrity 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; Dryssen et al. 1987; Ganrot 1986; Karlik et al. 1980).

2.3.4 Elimination and Excretion

2.3.4.1 Inhalation Exposure

The kidney is the major route of excretion of absorbed aluminum after inhalation exposure in humans. Six volunteers had urinary levels of 14-414 μg/L aluminum compared to concentrations of < 3 μg/L prior to a l-day exposure to 0.3-10.2 mg Al/m^3 in welding fumes (Sj□gren 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 g-hour workshift compared to concentrations at the beginning of the day (Mussi et al. 1984). In another occupational study, workers exposed to 1.5 mg/m^3 for 0.3-21 years eliminated the highest levels of urinary aluminum concentrations (82 μg/L) immediately after exposure (Sjögren et al. 1988). After an exposure-free period of 16-37-days, levels decreased to a mean concentration of 29 μg/L. These studies indicate that urinary levels were related to exposure concentration; however, quantitative correlations, as well as elimination of aluminum in the feces, were not reported.

A relationship between the duration of aluminum exposure and urinary concentrations has been found in humans (Sjogren et al. 1985, 1988). Welders exposed to 0.2-5.3 mg/m^3 (8-hour workshift) for more than 10 years had a urinary aluminum half-time of at least 6 months compared to 9 days for individuals exposed for less than 1 year (Sjogren et al. 1988). The excretion half-time was 8 hours following a single exposure to aluminum welding fumes (Sjogren et al. 1985); a half-time of 7.5 hours was estimated in workers exposed to aluminum dust (Pierre et al. 1995). However, if urinary concentrations were measured after an exposure-free period, the level was related to total number of exposed years. Apparently, the longer the exposure, the greater the retention of aluminum in humans.

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

2.3.4.2 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 1983b; Kaehny et al. 1977; Reeker et al. 1977). 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 concentration being 495 μg/day during exposure (Reeker 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 rug Al/kg/day as aluminum lactate in addition to 0.07 mg Al/kg/day in basal diet for 20 days (Greger and Baier 1983b). 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 a 3-fold increase in urinary aluminum levels (Gorsky et al. 1979). However, elimination may have been affected by other complications (i.e., osteoporosis, alcoholism calcium intake) in these patients.

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 a lower glomerular filtration rate, 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. Sprague-Dawley 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 difference in the excretion rates most likely reflects differences in gastrointestinal absorption.

2.3.4.3 Dermal Exposure

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

2.3.4.4 Other Routes of Exposure

Human and animal parenteral exposure studies indicate that the major excretion route of aluminum is through the kidneys. In a subject administered a single intravenous dose of ^{26}Al citrate, 40 times more aluminum was excreted in the urine than in the feces (Priest et al. 1995). In dogs that were studied to evaluate the renal handling of aluminum the controls excreted 37% of the aluminum load, while dogs dialyzed with tap water containing aluminum eliminated only a small fraction of aluminum (Kovalchik et al. 1978). In both groups of dogs, urinary excretion was the major route of elimination of aluminum Bile excretion was >0. 1% of the aluminum load. When aluminum was administered via the external jugular vein, aluminum excretion was found to occur in the distal tubule of the kidney in pigs (Monteagudo et al. 1988). Yokel and McNamara (1985) did not find any age-related differences in the systemic clearance or half-time of aluminum in rabbits following parenteral administration of aluminum lactate.

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

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological

processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

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

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

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

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically-sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 2-3 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.

There were no PBPK models for aluminum located in the literature. However, physiologically and mechanistically based models have been developed using basic information for estimating the deposition and elimination of a range of compounds; one recent model is described in ICRP (1994). Although this model is not specific to aluminum it provides information that may be useful for risk assessment, tissue dosimetry, and species extrapolations.

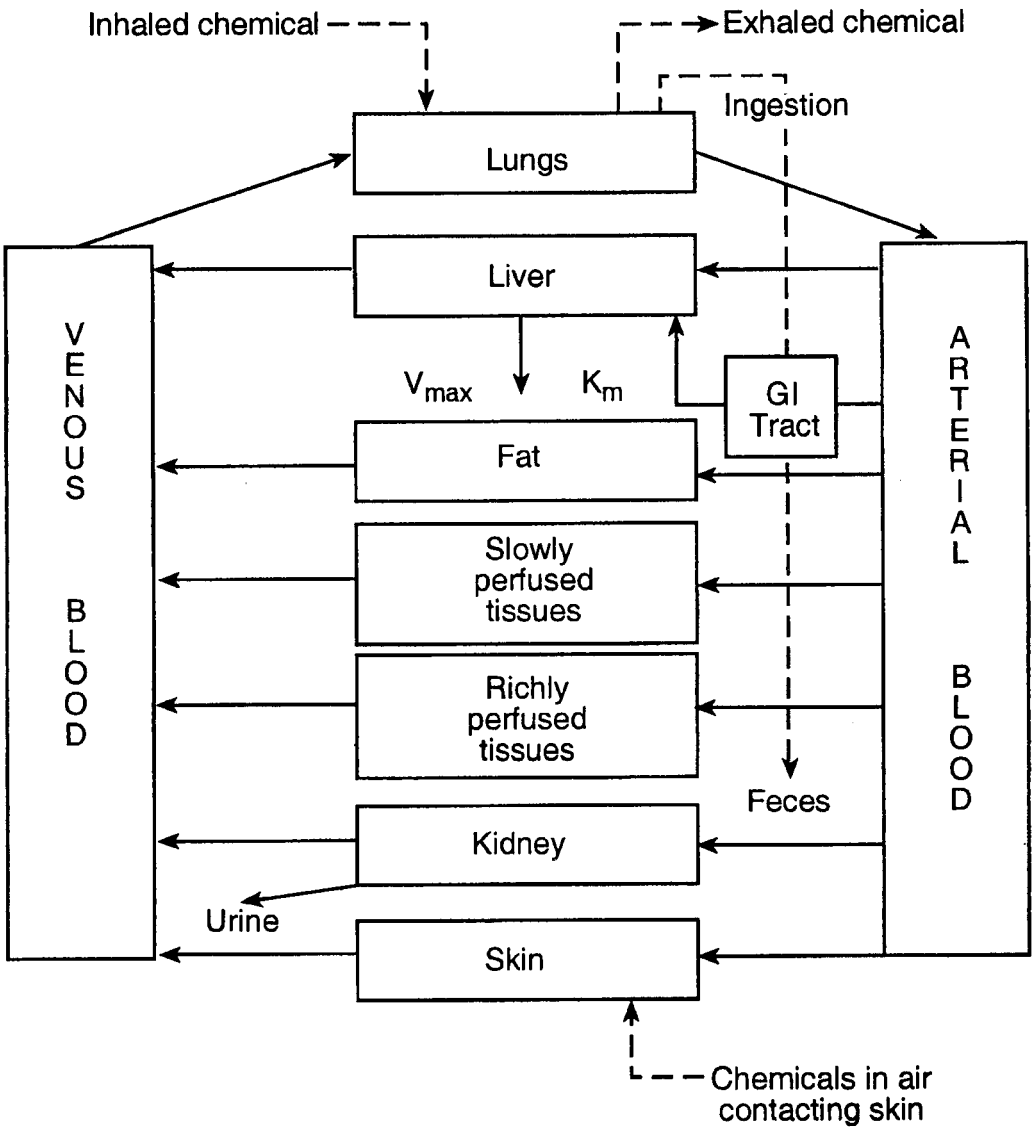
2.4 MECHANISMS OF ACTION

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 (Gannot 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; Dryssen 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.

2.4.1 Pharmacokinetic Mechanisms

Gastrointestinal absorption of aluminum is low, generally in the range of 0.1-1 % in humans as discussed in Section 2.3.1.2. Absorption of aluminum compounds is largely determined by its bioavailability in the aqueous conditions of the gut, which is mainly related to pH, the presence of complexing ligands with

Figure 2-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

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

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, $Al(H_20)_6^{+3}$, which is generally abbreviated Al^{+3} and referred to as "free" aluminum (Reiber et al. 1995). As pH increases, 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 ($[AI(OH)_3]$) an insoluble precipitate. 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 de solubilized aluminum is not complexed, is rapidly precipitated as insoluble (unabsorbable) aluminum hydroxide in the duodenum 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 et al. 1985a; Priest 1993; Rieber 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 1989), suggest that aluminum is mainly absorbed as neutral complexes by passive diffusion through paracellular 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 cellmediated 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 intercellular tight junctions (paracellular channels), possibly via disruption in calciumhomeostasis (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 into the blood stream or by macrophage phagocytosis (Priest 1993; Reiber et al. 1995).

2.4.2 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.

Lung Toxicity. There have been several cases of lung fibrosis in humans as the result of occupational exposure to aluminum dusts (Jordan 1961; Mitchell et al. 1961), and signs of lung damage have also been produced in rats, hamsters, and guinea pigs after exposure to several aluminum compounds (Drew et al. 1974; Finelli et al. 1981; Steinhagen et al. 1978; Thomson et al. 1986). 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 highly toxic dusts. The excessive levels of dust in the lung lead to excessive engulfment of particles by alveolar macrophages resulting in a progressive loss of alveolar macrophage mobility and an aggregation of alveolar macrophages (Morrow 1992). The relative or complete loss of alveolar macrophage mobility increases the likelihood of direct particle-epithelial cell interactions, often resulting in a prolonged inflammatory response, and interstitial localization of dust particles.

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 1993b). 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. Chelation therapy with deferoxamine and reducing oral aluminum exposure to the minimum practicable have been used'to successfully treat this condition. The pathogenesis and treatment of aluminum-related bone disease have been reviewed (Sherrard and Andress 1989).

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 (see Sections 2.2.2.4, 2.2.2.6, and 2.5). 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). 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 of general processes that are involved have been identified. Changes in cytoskeletal proteins, manifested as hyperphosphorylated neurofilamentous aggregates within the brain cells, 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 proteins 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 iufluence 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 (Jope and Johnson 1992).

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, cholinergic activity, signal transduction pathways, lipid peroxidation, and glucose metabolism as well as interfere with metabolism of essential trace elements (e.g., iron) because of similar coordination chemistries and consequent competitive interactions. Signal pathways are important in all cells and control differentiation and proliferation, neurotransmitter release,

and synaptic plasticity. Glucose metabolism may also be affected by aluminum due to specific inhibition of hexokinase and glucose-6-phosphate dehydrogenase (Erasmus et al. 1993; Strong et al. 1996).

Developmental Toxicity. Developmental toxicity of aluminum includes neurodevelopmental changes and skeletal effects in orally-exposed rodents (see Section 2.2.2.6). Neurobehavioral deficits have been observed in mice exposed via diet as adults, as well as in weanling and young developing animals exposed by gestation, combined gestation and lactation, combined gestation and lactation followed by postweaning ingestion, or postweaning ingestion alone (Donald et al. 1989; Golub and Germann 1998; Golub et al. 1987, 1992a, 1992b, 1994, 1995). The most frequently affected behaviors in mice exposed as adults, or exposed during development and tested as adults, included decreases in motor activity, grip strength, and startle responsiveness. The effects most commonly found in exposed weanlings and young mice included increases in grip strength and landing foot splay and decreased thermal sensitivity, indicating that the pattern of neurobehavioral impairment in developing animals was different from adults (i.e., the developmental syndrome did not included changes in spontaneous motor activity and startle responsiveness). It is not known whether the potential mechanisms of aluminum neurotoxicity identified in adults (see preceding section) parallel those active in the developing fetus and/or young animal. For example, aluminum competition for essential element uptake could be important during the development of the nervous system but less important for nervous system function in an adult animal (Strong et al. 1996).

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 relatively highly bioavailable (e.g., aluminum citrate or nitrate) and/or as bolus doses by gavage (Colomina et al. 1992; Gomez et al. 1991; Paternain et al. 1988). Given the relatively high bioavailability of the developmentally toxic forms of aluminum and bolus administration, it is possible that the skeletal changes are consequent to phosphate depletion caused by excess binding with aluminum in the maternal gut.

2.4.3 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 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.

2.5 RELEVANCE TO PUBLIC HEALTH

Overview. Aluminum is the third most common component of the earth's crust. Aluminum is a common trace element that has no known biological function. Exposure occurs primarily by ingestion. 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 compounds), and aluminum-containing medications (particularly antacid/antiulcer and buffered aspirin formulations) (Lione 1985b). Based on the FDA's 1993 Total Diet Study dietary exposure model and the 1987-1988 United States Department of Agriculture (USDA) Nationwide Food Consumption Survey, Pennington and Schoen (1995) estimated daily aluminum intakes of 0.10 mg Al/kg/day for 6- to 11-month-old infants, 0.30-0.35 mg Al/kg/day for 2- to 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- to 16-year-old males and females, and 0.10-0.12 mg Al/kg/day for adult (25- to 30- to 70+-year-old) males and females. These values are generally lower than the range of average intakes estimated in earlier reports (e.g., 0.2-0.6 mg Al/kg/day in adults) (Ganrot 1986; Greger 1985; Iyengar et al. 1987; Pennington 1987; Wilhelm et al. 1990), although Greger (1992) estimated that most adults consume from 0.01 to 0.1 mg Al/kg/day. Users of

aluminum-containing medications that are healthy (i.e., have normal renal function) can ingest much larger amounts of aluminum than in the diet, possibly as high as 12-7 1 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). Long-term use of many aluminum-containing medications (e.g., antacids for minor gastric distress, buffered aspirin for rheumatoid arthritis) appears to increase with age and is most common in elderly populations who simultaneously experience reduced renal function associated with advancing age (Lione 1985b). Aluminum antacids are also widely used to treat gastroesophageal reflux, esophagitis, and other peptic disorders in infants with normal renal function; pediatric doses appear to be similar to those recommended in adults (Tsou et al. 1991). Dosing and safety guidelines for aluminum antacids in infants have not been conclusively established (Tsou et al. 1991).

Gastrointestinal absorption of aluminum is low, generally in the range of 0.1-0.3% in humans, although absorption of particularly bioavailable forms such as aluminum citrate may be on the order of 1% (Day et al. 1991; DeVoto and Yokel 1994; Ganrot 1986; Greger and Baier 1983b; Jones and Bennett 1986; Nieboer et al. 1995; Priest 1993). Although large bolus doses of as much as half a gramof ahuninum throughout the day can be ingested during antacid therapy, absorption is still usually less than 1% of the intake amount (Gorsky et al. 1979; Kaehny et al. 1977; Reiber et al. 1995). Bioavailability of aluminum varies depending mainly on the chemical form of the ingested compound (i.e., type of anion) and, particularly, the kinds and amounts of ligands present in the stomach (i.e., dietary content) with which the metal can form absorbable aluminum species (DeVoto and Yokel 1994; Reiber et al. 1995). The acidic conditions of the stomach appear to ensure that the majority of consumed aluminum will be solubilized to Al^{+3} regardless of the chemical form or medium in which it is ingested. The solubilized aluminum competes for available ligands in the stomach but only a small portion of the Al^{+3} is complexed, causing it to remain soluble in the higher pH of the small intestine and therefore be available for uptake. Some of the solubilized Al^{+3} is likely to recomplex with the anion that was part of the aluminum compound originally ingested. The dietary ligands that seem to play the most important role in this process include resident carboxylic acids and common dietary constituents, particularly citric acid/citrate. Because the vast majority of the solubilized aluminum is not complexed, it is rapidly precipitated as insoluble unabsorbed aluminum hydroxide by the near-neutral intestinal pH conditions, and is ultimately excreted in the feces. Given the apparent 10-fold range in the gastrointestinal absorption of aluminum the amount of aluminum ingested does not necessarily provide an actual estimate of uptake without information on the bioavailability of the form in which it is ingested.

Little information is available on oral toxicity of aluminum in healthy people. 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-containing 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). 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 GRAS status of aluminum-containing food additives. Recent data, however, indicate 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 repeated antacid use, although studies or case reports investigating possible non-overt effects of aluminum-containing medications in healthy people, such as subtle neurotoxic changes, have not been performed. Several epidemiology and case-control studies have found associations between oral exposure to aluminum and an increased incidence of Alzheimer's disease, but none of the data conclusively establish a cause and effect relationship. The fact that Alzheimer's disease may largely be a genetic disorder further complicates the issue. Studies in rats and mice clearly show that oral exposure to relatively low doses of aluminum causes neurobehavioral effects in adult and developing animals, indicating that neurotoxicity is the critical end point of concern for aluminum. Issues relevant to children are explicitly discussed in Sections 2.6 Children's Susceptibility and 5.6 Exposures of Children.

Inhalation and dermal aluminum exposures are not associated with significant adverse health risks. Respiratory and neurological effects are the only consistent health effects from inhaled aluminum Respiratory effects, in particular fibrosis, have been observed in some workers exposed to aluminum dust containing nonpolar aliphatic lubricants; these lubricants are no longer used in the production process. Aluminum industry workers appear to be the only population at risk for the development of aluminum-related pulmonary toxicity. Poor industrial hygiene may increase the risk of lung toxicity in occupational exposures. Subtle neurological effects (e.g., altered performance on neurobehavioral tests, increased reporting of subjective symptoms) have also been observed in workers exposed to aluminum dust and aluminum fumes. Dermal aluminum application, such as an aluminum-containing antiperspirant, may cause rashes in some people.

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. Interpretation of the human data is complicated by the lack of exposure assessment and the potential for concomitant exposure to other toxic compounds. The most convincing evidence that aluminum exposure results in lung effects in humans comes from studies of workers exposed to fine aluminum dust (pyropowder) or alumina (aluminum hydroxide). Fibrosis has been observed in workers at facilities which used a nonpolar aliphatic oil lubricant to retard surface oxidation (Edling 1961; McLaughlin et al. 1962; Mitchell et al. 1961; Ueda et al. 1958); this type of lubricant is no longer used. Fibrosis was not observed when stearic acid was used as a lubricant (Crombie et al.' 1944; Meiklejohn and Posner 1957; Posner and Kennedy 1967). 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 highly toxic dusts. 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 neurobehavidral tests, increased reporting of subjective neurological symptoms, and altered EEGs (Bast-Peetersen et al. 1994; Hanninen et al. 1994; Hosovski et al. 1990; Rifat et al. 1990; Sjogren et al. 1996; White et al. 1992). Poor characterization of aluminum exposure 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. 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-contaminated dialysate, use of aluminum-containing phosphate binding agents, and possible increased gastrointestinal absorption. Although providing 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 and aluminum excretion is impaired by the poor renal function. No clinical studies on health effects of aluminum medicinals in people with normal renal function have been performed. 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 a loca action (phosphate depletion caused by binding of phosphate with aluminum in the stomach), and only suggest that typical antacid doses may not be safe for all people and indicate that non-overt effects of aluminum have not been adequately characterized in humans.

Derivation of an MRL(s) for aluminum based on animal studies is complicated by limitations in the database. Early animal studies often used injection routes to produce the pathology seen in humans, and there is no set of standard toxicology studies (e.g., subchronic, chronic, developmental, multigeneration) of aluminum; this is partly due to the GRAS status of aluminum food additives. Oral exposure studies in animals began to appear in the literature during the past 10-15 years, but these aluminum studies were designed to address basic science questions and not serve as a basis for risk evaluation. Additionally, information on aluminum content in the base diet is not reported in many of the studies. As discussed in the introduction to Section 2.2.2, 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, based on 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), estimated doses of 25 mg Al/kg/day (rats) and 68 mg Al/kg/day (mice), which represents

significant portions of lethal doses for these species, could be provided by diet alone. 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, are not suitable for comparing with effect levels from studies that used diets with known amounts of aluminum, and are inappropriate for MRL consideration. Concern for the adequacy of NOAEL and LOAEL values for aluminum is greatest for sensitive neurotoxic effects, which could occur in rodents at aluminum intake levels close to those provided by commercial diet alone.

No acute- or chronic-duration oral MRLs were derived for aluminum due to insufficient data on NOAELs and LOAELs for these exposure categories. This data insufficiency is due to an inadequate number of studies having sufficient dose information (most did not report the level of aluminum in the base diets) and/or information on sensitive toxicity end points. Acute oral studies of aluminum are essentially limited to lethality (LD_{50}) determinations and studies of growth and malformation end points in rats and mice. Developmental effects associated with acute (i.e., gestation-only) exposure to aluminum mainly include reduced fetal body weight and increased fetal skeletal variations (Bernuzzi et al. 1986b, 1989b; Colomina et al. 1992; Gomez et al. 1991; Misawa and Shigeta 1992). Information on chronic oral toxicity of aluminum is essentially limited to lifetime studies in rats and mice (Oneda et al. 1994; Schroeder and Mitchener 1975a, 1975b) that found no histopathological changes, but did not evaluate known or possible sensitive end points (e.g., neurotoxicity and skeletal effects).

*An MRL of 2.0 mg Al/kg/day has been derived for intermediate-duration oral exposure to aluminum and its compounds.

Comparison of effect levels in mice and rats from intermediate-duration studies with adequate dose information (i.e., doses that include aluminum in the base diet), and with no exposure to moieties which may greatly enhance bioavailability and/or contribute to toxicity (e.g., citrate and nitrate), indicate that neurotoxicity is the critical end point of concern for aluminum 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. Neurobehavioral impairments have been observed in animals orally-exposed for intermediate durations, as well as in weanlings and young animals exposed by gestation, combined gestation and lactation, combined gestation and lactation followed by postweaning ingestion, or postweaning ingestion alone. The lowest tested reliable neurotoxic doses (i.e., among those that include base dietary aluminum) are in

mice. The most frequently affected behaviors in mice exposed as adults, or exposed during development and tested as adults, included decreases in motor activity, grip strength, and startle responsiveness, and neurobehavioral effects most commonly found in exposed weanlings and young mice included increases in grip strength and landing foot splay and decreased thermal sensitivity, indicating that the spectrum of effects is different in adult and developing animals (Donald et al. 1989; Golub and Germann 1998; Golub et al. 1987, 1992a, 1992b, 1994, 1995). Neurobehavioral effects that have been associated with oral exposure to aluminum in rats include impairments in motor coordination and operant learning (Bernuzzi et al. 1989a; Bilkei-Gorzo 1993; Cherroret et al. 1992; Commissaris et al. 1982; Muller et al. 1990, 1993a; Thorne et al. 1986, 1987).

A LOAEL of 130 mg Al/kg/day is identified for decreased spontaneous motor activity in adult mice that were exposed to dietary aluminum lactate for 6 weeks (Golub et al. 1989). Overall activity was reduced about 20% compared to controls due to less frequent occurrence of the highest activity states, which usually occurred during the diurnal period of peak activity. The duration of peak activity periods was also reduced (about 35% compared to controls) and vertical movement (primarily rearing and feeding) was more affected than horizontal movement (primarily locomotion), but there was no shift in the diurnal activity cycle or any prolonged periods of inactivity. No effects on motor activity occurred at 62 mg Al/kg/day, indicating that this is the NOAEL. Mice that ingested doses higher than 130 mg Al/kg/day as aluminum chloride for 49 days or aluminum lactate for 90 days, and were tested using a standardized neurotoxicity screening battery, also showed decreased motor activity, as well as decreased grip strength and startle responsiveness (Golub et al. 1992b; Oteiza et al. 1993). Depressed motor activity has also been observed in exposed adult rats, suggesting that this effect is a consistent neurobehavioral outcome associated with ingested aluminum (Golub et al. 1992b).

Neurodevelopmental effects occurred at dose levels similar to the 130 mg Al/kg/day LOAEL for neurotoxicity in adult mice. A LOAEL of 155 mg Al/kg/day is identified for neurotoxicity in the offspring of mice exposed to dietary aluminum lactate during gestation and lactation, and tested as weanlings or adults (Donald et al. 1989; Golub et al. 1995). Lower dose levels were not tested in these studies, precluding determination of a NOAEL for neurodevelopmental toxicity. Effects observed at the 155 mg Al/kg/day neurodevelopmental LOAEL included increased fore- and hindlimb grip strengths, landing foot splay, and latency to remove tail from hot water in offspring tested as weanlings (Donald et al. 1989), and decreased grip strength, decreased air-puff startle response, and improved performance during operant training in offspring tested as adults (Golub et al. 1995).

Effects were reported at doses lower than the 130 mg Al/kg/day neurotoxicity LOAEL in several studies (Colomina et al. 1992; Domingo et al. 1987c; Florence et al. 1994; Paternain et al. 1988; Varner et al. 1993, 1994, 1998), but the LOAELs from these studies are inappropriate for MRL consideration. Colomina et al. (1992) found reduced fetal body weight and increased incidences of cleft palate and skeletal variations in fetuses of mice exposed to an estimated total dose of 83 mg Al/kg as aluminum lactate by gavage plus base dietary aluminum on Gd 6-15. Paternain et al. (1988) observed decreased maternal body weight and an increased incidence of skeletal variations, but no consistent effects on external or visceral malformations, in rats exposed to estimated total doses of 38-77 mg Al/kg/day as aluminum nitrate by gavage plus base dietary aluminum on Gd 6-14. Similar exposure to 38-77 mg Al/kg/day as aluminum nitrate in a single generation reproduction study caused transient reduction in growth of rat offspring (Domingo et al. 1987c). These studies are inappropriate for MRL consideration due to concern for the method of oral exposure since Savage does not realistically represent environmental aluminum intake. In particular, effect levels in the gavage studies may be unnaturally low compared to dietary exposure because the skeletal changes could be related to phosphate depletion caused by excess binding with aluminum in the maternal gut due to the bolus treatments. Additionally, the relatively low LOAELs in the Paternain et al. (1988) and Domingo et al. (1987c) studies may be related to the use of aluminum nitrate because data in rats indicate that aluminum from aluminum nitrate is twice as bioavailable as from aluminum chloride (Yokel and McNamara 1988) (see Section 2.3.1.2). Other studies found histopathologic changes in the brain of rats exposed by diet to 92 mg Al/kg/day as aluminum chloride in combination with an unnaturally high level of citrate for 6 months (Florence et al. 1994), or to 12 mg Al/kg/day as aluminum fluoride in drinking water and the base diet for 45-52 weeks (Varner et al. 1993, 1994, 1998). Unusual exposure conditions preclude identifying relevant LOAELs for brain histopathology from these studies. In particular, the effects appear to be due to greatly enhanced bioavailability because both studies were designed to maximize the uptake of aluminum (i.e., by the massive co-exposure to citrate, and the use of aluminum fluoride to form an optimum fluoroaluminum species capable of crossing the gut and blood-brain vascular barriers).

Considering the studies with adequate dose information and appropriate exposure conditions, including compound bioavailability, the 62 mg Al/kg/day NOAEL for neurotoxicity in adult mice (Golub et al. 1989) is the most suitable basis for calculating an intermediate MRL. This NOAEL was identified using aluminum lactate, a representative form of aluminum that is intermediate in bioavailability between inorganic complexes such as aluminum hydroxide and carboxylic acid complexes such as aluminum citrate. Using the 62 mg Al/kg/day NOAEL and an uncertainty factor of 30 (3 for extrapolation from

animals to humans and 10 for human variability), the MRL is calculated to be 2.0 mg Al/kg/day. An uncertainty factor of three was used for interspecies extrapolation because daily aluminum intake by humans in antacids is approximately 3-5 times lower than LD_{50} values for aluminum compounds in rats and mice, suggesting that humans are not more sensitive than rodents. The intermediate-duration MRL of 2.0 mg Al/kg/day is approximately 6-35 times lower than typical daily intake of aluminum from long-term use of antacids (12-7 1 mg Al/kg/day [Lione 1985b]), and approximately 20 times higher than recent estimates of adult dietary intake of aluminum (0.10-0.12 mg Al/kg/day [Pennington and Schoen 19951). Given the apparent lo-fold range in the gastrointestinal absorption of aluminum depending on compound, and considering that the bioavailability of aluminum in antacid preparations may be different than that of the aluminum lactate used in the Golub et al. (1989) study, information on the bioavailability of the form ingested should be considered in the use of the MRL. The MRL represents an estimate of daily human exposure that is likely to be without an appreciable risk of adverse health effects. It is not intended to support clean-up or other regulatory action, but to serve as a guideline for health assessors to consider when making recommendations to protect populations living in the vicinity of a hazardous waste site or substance emission.

Death. Aluminum is not thought to be life-threatening to healthy humans. Studies of people receiving extremely high doses of oral aluminum in antacids have not shown any human deaths from aluminum However, in the past, aluminum-related deaths have been reported for persons with renal disease dialyzed with aluminum-containing solutions, uremic patients exposed to dietary aluminum hydroxide to treat hyperphosphatemia and sodium citrate to correct metabolic acidosis (Kirschbaum and Schoolwerth 1989), and workers exposed by inhalation to fine powders of aluminum metal. Only very large doses (hundreds of mg/kg) of aluminum cause death in laboratory animals.

Systemic Effects

Respiratory Effects. There are numerous reports of respiratory effects in workers chronically exposed to airborne aluminum In many cases, the workers were also exposed to a number of other toxicants which may have been the causative agent. Pulmonary fibrosis has been observed in some groups workers exposed to fine aluminum dust (pyropowder) (Edling 1961; McLaughlin et al. 1962; Mitchell et al. 1961; Ueda et al. 1958). The pulmonary fibrosis has only been associated with pyropowders utilizing nonpolar aliphatic oil lubricants, such as mineral oil; exposure to pyropowder which used stearic acid as a

lubricant does not result in fibrosis (Crombie et al. 1944; Meiklejohn and Posner 1957; Posner and Kennedy 1967).

A number of respiratory effects have been observed in animals, including increases in the number of alveolar macrophages, and granulomatous foci in the lungs and peribronchial lymph nodes (Drew et al. 1974; Steinhagen et al. 1978). These respiratory effects are typically associated with inhalation of particulates and lung overload and may not be directly related to aluminum-induced toxicity to lung tissue.

Cardiovascular Effects. Altered heart rate has been observed in humans following oral exposure to aluminum phosphide (Chopra et al. 1986; Khosla et al. 1988); however, the cardiotoxicity probably resulted from exposure to phosphine gas, rapidly released from aluminum phosphide in the mouth and stomach, rather than the aluminum Oral exposure in rodents and dogs to other forms of aluminum has not been shown to affect heart weight or histology.

Gastrointestinal Effects. In humans, acute-duration oral exposure to unknown amounts of aluminum sulfate was reported to cause gastric distress (Ward 1989). Acute oral exposure to unknown amounts of aluminum phosphide produced vomiting and abdominal cramping (Chopra et al. 1986; Khosla et al. 1988).

Hematological Effects. Hematological effects have not been observed in humans or animals with normal renal function. However, microcytic, hypochromatic anemia has been observed in individuals with impaired renal function. The anemia is unresponsive to iron therapy. The severity of the anemia correlates with plasma and erythrocyte aluminum levels and can be reversed by terminating aluminum exposure and chelation therapy with DFO.

Musculoskeletal Effects. The occurrence of osteomalacia has been well-documented in uremic adults and children (Griswold et al. 1983; King et al. 1981; Mayor et al. 1985; Sherrard and Andress 1989; Wills and Savory 1989). The osteomalacia is directly related to the markedly increased aluminum levels in the bone. This type of aluminum-induced osteomalacia is not likely to occur in healthy individuals; in uremic patients, the impaired renal function and inefficient removal of aluminum during dialysis results in significantly increased aluminum body burdens. However, an osteomalacia associated with hypophosphatemia has been observed in otherwise healthy individuals following long-term use of

aluminum-containing antacids for the treatment of gastrointestinal disorders (Carmichael et al. 1984; Chines and Pacifici 1990; Pivnick et al. 1995; Woodson 1998). In these cases, the osteomalacia is not related to aluminum deposition in bone, rather the aluminum binds with dietary phosphorus in the gastrointestinal tract and prevents its absorption. 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). High levels of copper and lead were also present in drinking water; thus, it is difficult to ascribe this nonspecific symptom to aluminum exposure. No histological alterations in the have been observed in the tibia or femur of rats and mice orally exposed to aluminum for 10 to 24 months (Hackenberg 1972; Konishi et al. 1996; Ondreicka et al. 1966).

Hepatic Effects. Acute oral aluminum exposure is not hepatotoxic. Intermediate-duration oral exposure has generally been reported to be nonhepatotoxic, but relatively minor hepatotoxicity has been occasionally observed. Hyperemia and periportal lymphomonocytic 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). These effects were not observed at higher doses with longer exposures (Gomez et al. 1986).

Endocrine Effects. Little is known about the effects of aluminum on endocrine systems. The oral administration of sodium aluminum phosphate to male and female Beagle dogs for 6 months did not alter thyroid, adrenal, or pituitary gland weight or microanatomy (Katz et al. 1984; Pettersen et al. 1990). These organs were also normal in male and female Wistar rats fed a diet containing unspecified amounts of aluminum phosphide/ammonium carbamate for 24 months (Hackenberg 1972).

Renal Effects. 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; Koshla et al. 1988). The majority of animal studies indicate aluminum exposure does not affect renal weight or histology.

Dermal Effects. Skin rashes were commonly reported by 48 people who drank water containing unknown amounts of aluminum sulfate (Ward 1989). 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 some types of antiperspirants and develop skin rashes, which may be

caused by the aluminum (Brusewitz 1984). 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-O. 1 g) or aluminum nitrate (0.006-0.013 g) applied 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.

Ocular Effects. Limited information suggests aluminum does not cause ocular toxicity (Hackenberg 1972; Katz et al. 1984; Steinhagen et al. 1978).

Body Weight Effects. Aluminum-related effects on body weight are equivocal and, for *ad libitum* oral water exposure, may be related to the palatability of the test solution. Decreases in body weight gain have been observed in hamsters exposed to 3, 10, or 33 mg Al/m^3 as alchlor (Drew et al. 1974) and in rats exposed to 6.1 mg Al/m^3 as aluminum chlorhydrate for 24 months (Stone et al. 1979). However, other acute-, intermediate-, and chronic-duration studies did not find any significant alterations in rats or guinea pigs exposed to similar concentrations of aluminum chlorhydrate (Steinhagen et al. 1978; Stone et al. 1979) or 0.37-0.41 mg Al/m^3 as aluminum chloride or aluminum fluoride dust (Finelli et al. 198 1).

A 19% decrease in maternal body weight gain was observed in pregnant Sprague-Dawley rats given 38 mg Al/kg/day as aluminum nitrate via gavage on Gd 6-14 (Paternain et al. 1988). Decreased body weight was observed in male Wistar rats that consumed 273 mg Al/kg/day as aluminum sulfate in the diet for 8 days, but food consumption was also decreased in this study (Ondreicka et al. 1966). No body weight effects were observed in male or pregnant female Wistar rats acutely exposed to up to 192 mg Al/kg as aluminum chloride either in feed (Bernuzzi et al. 1986b) or drinking water (Ondreicka et al. 1966).

In general, no adverse body weight effects have been observed in rats, mice, or dogs following intermediate-duration oral administration of aluminum compounds (Domingo et al. 1987b; Donald et al. 1989; Golub et al. 1989; Gomez et al. 1986; Ondreicka et al. 1966). A 19% decrease in maternal body weight on postnatal day 20 was observed in Swiss Webster mice that consumed approximately 500-1,000 mg Al/kg/day as aluminum lactate in the diet throughout gestation and lactation (Golub et al. 1987), but this appears to be related to a nutritional insufficiency in the test diet. Transient body weight decreases were observed in male Sprague-Dawley rats given 346 mg Al/kg/day as aluminum sulfate in drinking water for 4 weeks (Connor et al. 1989).

No body weight effects were observed in rats or mice following chronic-duration exposure to aluminum compounds (Hackenberg 1972; Ondreicka et al. 1966; Oneda et al. 1994; Schroeder and Mitchener 1975a).

Male Long Evans rat pups administered aluminum hydroxide (14 mg Al/kg/day) in water for 60 days beginning on postnatal day 22 exhibited decreased body weights (Thorne et al. 1987). This was not related to a direct effect of aluminum, but to the palatability of the water. The effects on body weight during the initial rejection of the aluminum-treated water were so severe that body weights in the treated group never recovered to control levels. A palatability-related marked reduction in body weight was also observed in dogs exposed to aluminum potassium sulfate in the diet (Pettersen et al. 1990).

Metabolic Effects. No adverse effect on phosphate metabolism was identified in humans following intermediate-duration inhalation exposure to aluminum fumes or dust (Mussi et al. 1984).

Other Systemic Effects. Swiss Webster mice that consumed 130 mg Al/kg/day as aluminum lactate in the diet for 6 weeks had an increased incidence of fur loss (Golub et al. 1989); this effect was not repeated in later studies.

Immunological and Lymphoreticular Effects. 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 (Bohler-Sommeregger and Lindemayr 1986; Veien et al. 1986). Sarcoid-like epithelioid granulomas were found in the lungs of a 32-year-old man chronically exposed to metallic aluminum and aluminum dust (De Vuyst et al. 1987). Immunological testing failed to confirm sarcoidosis, but did find helper T-lymphocyte alveolitis and blastic transformation of peripheral blood lymphocytes in presence of the soluble aluminum compound. Additional testing one year after termination of exposure indicated the man no longer had alveolitis.

Granulomatous lesions have been observed in the hilar and peribronchial lymph nodes of animals exposed to aluminum powder (Thomson et al. 1986) or aluminum chlorhydrate (Steinhagen et al. 1978). Oral studies in mice found that developmental exposure to aluminum impaired the immune system in young animals (Golub et al. 1993b; Yoshida et al. 1989). These data suggest that immunotoxicity of aluminum may be a concern in some exposure scenarios.

Neurological Effects. Aluminum is generally considered to be a neurotoxic agent, and effects have been observed in humans and animals following inhalation-, oral-, and parenteral-exposure. A number of occupational studies have investigated the neurotoxic potential of airborne aluminum in chronically exposed workers; the workers were exposed to aluminum dust in the form of McIntyre powder, aluminum dust and fumes in potrooms, and aluminum fumes during welding. Collectively, these studies 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 (Hanninen et al. 1974; Hosovski et al. 1990; Rifat et al. 1990; Sim et al. 1997; Sjögren et al. 1996; White et al. 1992). With the exception of some isolated cases (for example, McLaughlin et al. 1962), inhalation exposure has not been associated with overt symptoms of neurotoxicity. A common limitation of the occupational exposure studies is that aluminum exposure has been well characterized. The available animal inhalation studies (Finelli et al. 1981; Steirihagen et al. 1978; Stone et al. 1979) are inadequate for assessing aluminum-induced neurotoxicity because the only neurological end points examined were brain weight and histology of the brain. The studies were not designed to assess subtle neurological alterations.

A possible relationship between aluminum and Alzheimer's disease was proposed over 30 years ago; this association is still highly controversial and there is little consensus regarding current evidence. As reviewed by Armstrong et al. (1996), the basis of this relationship was the finding of increased aluminum levels in the brains of individuals with Alzheimer's disease, neurofibrillary lesions in experimental animals, and the findings that aluminum interacts with various components of the pathological lesions in the brains of individuals with Alzheimer's disease. 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. There is some evidence to suggest that aluminum has an effect on production of the protein tau which is an important constituent of helical and straight filaments which comprise the neurofibrillary tangles, and that aluminum can influence amyloid precursor protein or promote the polymerization of the β-amyloid fragment. However, even if it could be established that aluminum was important in the production of the protein tau and/or β-amyloid, it would not necessarily indicate a primary role for aluminum in Alzheimer's disease pathology.

Individuals with Alzheimer's disease were reported to have more aluminum than usual in the neurofibrillary tangles in the hippocampus or cortical parts of their brains, but normal (as compared to control) levels of aluminum in hair, serum or spinal fluid (Shore and Wyatt 1983). This evidence suggests that Alzheimer's patients may have a reduced blood-brain barrier for aluminum; several investigators (Banks et al. 1988; Liss and Thorton 1986; Shore and Wyatt 1983) suggest that the altered blood-brain barrier in Alzheimer's disease may be a consequence and not the cause of the disease. More recent studies (Landsberg et al. 1992; Makjanic et al. 1998) utilizing nuclear microscopy without chemical staining techniques did not find increased aluminum levels in the pyramidal neurons in brain tissue or in plaque cores of patients with Alzheimer's disease. When conventional techniques for tissue preparation (fixation and osmication) and nuclear microscopy were used, elevated aluminum levels were detected, suggesting that the staining technique introduced contamination or produced elemental redistribution, and that aluminum is not associated with Alzheimer's disease (Makjanic et al. 1998).

Epidemiology and case-control studies that examined the possible relationship between Alzheimer's disease and aluminum report conflicting results. No increases in Alzheimer's disease-related deaths were observed in workers exposed to airborne aluminum (Salib and Hillier 1996). Some studies designed to show the possible relationship between oral exposure to aluminum and the incidence of Alzheimer's disease have found significant associations (Martyn et al. 1989; McLachlan et al. 1996; Michel et al. 1990), but other studies did not find a significant relationship (Forster et al. 1995; Martyn et al. 1997; Wettstein et al. 199 1). Forbes and McLachlan (1996) suggest that the relationship between aluminum and Alzheimer's disease is not linear, but rather forms a J- or U-shaped curve, and that the association may only exist at higher exposure levels (aluminum levels in water of $\geq$ 1 mg/L). However, individuals on renal dialysis who have received large amounts of aluminum orally or intravenously also can develop encephalopathy, but they do not develop the type of histopathology (tangles and plaques) associated with Alzheimer's disease (Hamdy 1990). There is no consensus on whether, collectively, the human studies provide sufficient evidence for suggesting an association between aluminum and Alzbeimer's disease; the human data do not establish cause and effect.

A sufficient animal model for human Alzheimer's disease has not been developed. Although animals, particularly rabbits, exposed to aluminum develop neurofibrillary tangles (Crapper-McLachlan and Farnell 1985b), the neurofibrillary tangles are both structurally and biochemically different from those associated with Alzheimer's disease (Perl and Brody 1980). Some recently developed animal models appear to mimic several aspects of the disease, such as co-injection of aluminum and paired helical

filaments into a rodent brain inducing the aggregation of other plaque and neurofibrillary tangles and injection of aluminum salts inducing the accumulation of neurofilaments in swollen parikarya and proximal axonal enlargements of certain neuronal populations in the brain and spinal cord (as discussed in Singer et al. 1997). Alzheimer's disease appears to be a heterogenous disease with numerous risk factors or etiologies including genetic and environmental factors (Gautrin and Gauthier 1989; King et al. 198 1; St. George-Hyslop 1995; Schellenberg 1995a, 1995b). Evidence is equivocal on the possible relationship between aluminum and Alzheimer's disease, and the animal data are inadequate to support a conclusion.

Amyotrophic lateral sclerosis (ALS) and Parkinsonism-dementia (PD) are neurodegenerative diseases which 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.

Whereas a causal role for aluminum in the etiology of Alzheimer's and other human neurodegenerative diseases has not been established, data on dialyzed patients provide convincing evidence that aluminum is the causative agent in "dialysis dementia". Dialysis dementia is a degenerative neurological syndrome, characterized by the gradual loss of motor, speech, and cognitive functions, that has developed in patients who received long term hemodialysis for chronic renal failure (Alfrey 1993b). It is caused by exposure to aluminum in dialysate and/or to high oral doses of aluminum used as phosphate binders to control hyperphosphatemia in uremic patients, has occurred in people with renal failure who were not dialyzed,

and has been observed in infants and young children as well as adults (Alfrey 1993b; Griswold et al. 1983).

The neurotoxic potential of aluminum is well-established in experimental animals. Neurodegenerative changes in the brain, manifested as intraneuronal hyperphosphorylated neurotilamentous 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 (Erasmus et al. 1993; Jope and Johnson 1992). Oral studies in rats and mice found no significant histopathological changes in the brain under typical exposure conditions (i.e., when bioavailability of aluminum was not intentionally maximized, such as by concurrent exposure to citrate) (Dixon et al. 1979; Domingo et al. 1987b; Florence et al. 1994; Gomez et al. 1986; Lal et al. 1993; Varner et al. 1993, 1994, 1998), although neuromotor, behavioral, and cognitive changes have been observed consistently in these species. Neurobehavioral deficits occurred in mice exposed via diet as adults, as well as in weanling and young developing annuals exposed by gestation, combined gestation and lactation, combined gestation and lactation followed by postweaning ingestion, or postweaning ingestion alone (Donald et al. 1989; Golub and Germann 1998; Golub et al. 1987, 1992a, 19928, 1994, 1995; Oteiza et al. 1993). The most frequently affected behaviors in mice exposed as adults, or exposed during development and tested as adults, included decreases in motor activity, grip strength, and startle responsiveness, The effects most commonly found in exposed weanlings and young mice included increases in grip strength and landing foot splay and decreased thermal sensitivity. The reason for the different effects on grip strength (decreased and increased) is unclear, but could be related to age of the animal at exposure and/or testing. Assessment of grip strength is a routine method for assessing neuromuscular function in rodents (Meyer et al. 1979). Orally-exposed rats have shown impairments in motor coordination and operant learning (Bernuzzi et al. 1989a; Bilkei-Gorzo 1993; Bowdler et al. 1979; Cherroret et al. 1992; Commissaris et al. 1982; Connor et al. 1988, 1989; Jope and Johnson 1992; Lal et al. 1993; Muller et al. 1990, 1993a; Thorne et al. 1986, 1987), while others have shown more rapid learning (Golub et al. 1998).

Considering the evidence for neurobehavioral effects of aluminum in humans exposed occupationally, and during dialysis therapy, and in animals exposed orally and by various unnatural routes of exposure, it is evident that neurotoxicity is an important effect of concern for aluminum Comparison of effect levels in mice and rats from intermediate-duration oral studies with adequate dose information (i.e., doses that include aluminum in the base diet), and exposure conditions that did not unnaturally enhance

bioavailability (e.g., without co-ingestion of high levels of citrate or exposure to highly bioavailable aluminum compounds), indicate that neurotoxicity is the most sensitive end point for aluminum. A LOAEL of 130 mg Al/kg/day was identified for decreased spontaneous motor activity in adult mice that were exposed to dietary aluminum lactate for 6 weeks (Golub et al. 1989). Observations of depressed motor activity in other studies of mice, as well as in rats, suggest that this effect is a consistent neurobehavioral outcome associated with ingested aluminum and an appropriate basis for human risk evaluation. The NOAEL for decreased spontaneous motor activity, 62 mg Al/kg/day, was used to derive the intermediate duration MRL for oral exposure to aluminum. The MRL is 6-35 times lower and ≈20 times higher than daily intake of aluminum from long-term antacid and dietary exposure, respectively (Lione 1985b; Pennington and Schoen 1995). Given the preponderance of evidence that aluminum is neurotoxic, considering that the gastrointestinal absorption of aluminum compounds may vary 10-fold and the bioavailability of aluminum in antacid preparations and human diet may be different than that of the aluminum lactate used in the MRL study, and recognizing that the neurotoxicity of aluminum-containing antacids and other medications has not been studied in people with normal renal function, there appears to be a potential for neurotoxic effects of aluminum in healthy individuals.

Reproductive Effects. There are no human studies that indicate that aluminum affects reproduction. Oral studies in male and female animals show some inconsistencies, as summarized below, but generally indicate that reproductive toxicity is not an effect of concern for aluminum-exposed people. An increased incidence of resorptions occurred in mice that were gestationally exposed to aluminum chloride by gavage (Crammer et al. 1986), but no reproductive effects were found in rats similarly exposed to aluminum chloride, hydroxide, or citrate (Gomez et al. 1991; Misawa and Shigeta 1992). The inconsistent findings in these acute-duration studies may reflect differences in susceptibility among different strains/species of animals or compound differences in toxicity or bioavailability. Offspring of rats that were gavaged with aluminum lactate during gestation had a transient irregularity of the oestrus cycle, but no other effects on end points of female reproductive system development (gonad weights, anogenital distance, time to puberty, duration of induced pseudopregnancy, or numbers of superovulated oocytes) were induced (Agarwal et al. 1996). An intermediate-duration study found no effects on fertility or other general reproductive indices in female rats that were exposed to aluminum nitrate by gavage from 14 days prior to mating (with treated males) through weaning of the offspring (Domingo et al. 1987c). Sperm count was reported to be decreased in male rats exposed to aluminum chloride for 6-12 months (Krasovskii et al. 1979), but reproductive function was not evaluated, and no adverse reproductive effects were seen in male rats, as assessed by plasma gonadotropin levels, histopathological

evaluation and serial matings, following exposure to aluminum chloride in the drinking water for up to 90 days (Dixon et al. 1979). No organ weight or histological changes were observed in the gonads of male and female Beagle dogs that were exposed to sodium aluminum phosphate in the diet for 6 months (Katz et al. 1984; Pettersen et al. 1990).

Developmental Effects. Studies in human infants indicate that only certain children are affected by aluminum. Excessive aluminum accumulation and encephalopathy may occur in premature infants with reduced renal function given dialysis with aluminum-containing intravenous fluid (Polinsky and Gruskin 1984; Sedman et al. 1985). Bone disease has also been reported in infants with renal failure who were treated orally with aluminum hydroxide (Andreoli et al. 1984).

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). Given the relatively high bioavailability of the developmentally toxic forms of aluminum and bolus administration, it is possible that the skeletal changes are consequent to phosphate depletion caused by excess binding with aluminum in the maternal gut. Neurobehavioral deficits have been observed in oral studies with 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 (Donald et al. 1989; Golub and Germann 1998; Golub et al. 1987, 1992a, 1992b, 1994, 1995; Muller et al. 1990). The most frequently affected behaviors in exposed weanlings and young animals included increases in grip strength and landing foot splay, decreased thermal sensitivity, and negative geotaxis. The effects most commonly found in mice exposed during development and tested as adults, or tested only as adults, included decreases in motor activity, grip strength, and startle responsiveness, indicating that the pattern of neurobehavioral impairment in developing animals was different from adults. Studies using intraperitoneal injections in rats (Benett et al. 1973, intravenous injections in mice (Wide 1984), and subcutaneous injections in rabbits (Yokel 1985, 1987) similarly found that aluminum can cause delays in neurobehavioral and skeletal development in pups. Teratogenic changes have not been associated with gestational exposure to aluminum

There is sufficient evidence from oral studies in animals to conclude that aluminum is potentially developmentally toxic in humans, especially under conditions in which aluminum is particularly bioavailable or in which renal dysfunction facilitates aluminum accumulation. There is concern for neurodevelopmental effects because aluminum-exposed animals appear to be more sensitive to these effects than skeletal changes, especially under natural (i.e., nonbolus) oral exposure conditions. Since it is well-documented that gastrointestinal absorption of aluminum may be significantly enhanced by certain normal dietary constituents such as citrate, the available developmental toxicity data suggest that it would be prudent to avoid excess intake of aluminum-containing compounds during gestation and lactation.

Genotoxic Effects. Some of the neurotoxic effects of aluminum can be partially explained by its genotoxic and subcellular effects on DNA in neurons and other cells demonstrated *in vitro*. These effects have been summarized (Crapper-McLachlan 1989; Crapper-McLachlan and Farnell 1985b). They include nuclear effects such as binding to DNA phosphates and bases, increasing histone-DNA binding, altering sister chromatid exchange, and decreasing cell division. Cytoplasmic effects include conformational changes in calmodulin and increasing intracellular calcium; although these effects may not specifically be caused by interactions with DNA, they will signiftcantly affect neuronal functions. Since aluminum accumulates in DNA structures in the cell nucleus, it may alter protein-DNA interactions. This is particularly important for the calcium-binding protein, calmodulin. This can affect the calcium-modulated second messenger system which is activated by neurotransmitters. Interference with DNA and protein synthesis may also be part of the mechanism that is involved in the creation of the neural filaments that compose the neurofibrillary tangles seen in Alzheimer's patients (Bertholf 1987).

Data from *in vivo* (intraperitoneal) exposures of mice to aluminum chloride also indicate that this compound is clastogenic. Mice were injected intraperitoneally with 0.01, 0.05, or 0.1 molar aluminum chloride, and bone marrow cells were examined for chromosomal aberrations. There was a significant increase in chromatid-type aberrations over the controls, and these occurred in a nonrandom distribution over the chromosome complement (Manna and Das 1972). No dose-response relationship could be demonstrated, although the highest dose of aluminum chloride did produce the greatest number of aberrations. These data are supported by *in vitro* studies that show that aluminum chloride causes cross-linking of chromosomal proteins and DNA in ascites hepatoma cells from Sprague-Dawley rats (Wedrychowski et al. 1986). Cross-linking agents frequently produce clastogenic effects due, presumably, to conformational distortions that prohibit proper DNA replication. Micromolar aluminum

levels have also been shown to reduce ^{3}H-thymidine incorporation in a transformed cell line (UMR 106-01), which indicates that aluminum may impede cell cycle progression (Blair et al. 1989). Generalizations to normal, untransformed cells, however, cannot be made.

There are also data that indicate that aluminum does not directly interact with DNA in mutagenicity tests. These data come from negative transformation assays in Syrian hamster cells (DiPaolo and Casto 1979), negative ret (recombination repair) assays in *Bacillus subtilis* (Kanematsu et al. 1980), and negative *Ames* assays in *Salmonella typhimurium* (Marzin and Phi 1985). These data are summarized in Table 2-4.

Cancer. Aluminum is not known to cause cancer in humans. Some workers in the aluminum industry have had a higher-than-expected cancer mortality rate, but this is probably due to the other potent carcinogens to which they are exposed, such as PAHs and tobacco smoke (Milham 1979; Mur et al. 1987; Rockette and Arena 1983; Theriault et al. 1984a).

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 due to the presence of known carcinogens (e.g., PAHs) in the workplace and is not due to aluminum or its compounds.

Available cancer studies of aluminum in animals do not indicate that aluminum is carcinogenic (Hackenberg 1972; Oneda et al. 1994; Pigott et al. 1981; Schroeder and Mitchener 1975a, 1975b).

2.6 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 due to maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Table 2-4. Genotoxicity of Aluminum *In Vitro*

Species (test system)	End point	Results[a]	Reference
Salmonella typhimurium	Gene mutation	–	Marzin and Phi 1985
Bacillus subtilis	Rec assay	–	Kanematsu et al. 1980
Rat osteoblasts	Thymidine incorporation	+	Blair et al. 1989
Syrian hamster embryo cells	Transformation assay	–	DiPaolo and Casto 1979
Rat ascites hepatoma cells	DNA cross-linking	+	Wedrychowski et al. 1986

[a]– = negative result; + = positive result

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 5.6 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 and 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 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 the newborn who has a low glomerular filtration rate and has 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 while others may decrease susceptibility to the same chemical. For example, the fact that infants breathe more air per

kilogram of body weight than adults may be somewhat counterbalanced by their alveoli being less developed, so there is a disproportionately smaller surface area for 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 (Griswold et al. 1983; Andreoli et al. 1984). 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. Another subpopulation of children that may be particularly sensitive to the toxicity of aluminum is preterm infants. The observed elevated plasma aluminum levels are probably due to the limited renal capacity of preterm infants to excrete aluminum (Tsou et al. 1991). Bougle et al. (199 1) 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 were also found. Growth failure, hypotonia, muscle weakness, and craniosynotosis have been observed 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).

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 (Donald et al. 1989; Golub and Germann 1998; 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. Although Thorne et al. (1986, 1987) did not find a significant relationship between aluminum exposure and open field activity or performance on learning tasks, they did find a correlation between activity and performance and brain aluminum content, which suggested that younger animals (weanling rats exposed for 60 days to dietary aluminum) were less affected than the adults (exposed to dietary aluminum for 30 days). Skeletal variations such as delayed ossification have also been observed in oral developmental toxicity studies (Colornina et al. 1992; Gomez et al. 1991; Paternain et al. 1988).

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 aluminumlactate, but was not seen in neonatal or adult rabbits (Yokel 1987).

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). There is also evidence that oral or parenteral exposure to aluminum can result in elevated levels in breast milk (Yokel and McNamara 1985). 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).

A recent 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.

2.7 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 (NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to aluminum are discussed in Section2.7.1.

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 2.7.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organisms 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 2.9, Populations That Are Unusually Susceptible.

2.7.1 Biomarkers Used to Identify or Quantify Exposure to Aluminum

Aluminum can be measured in the blood, urine, and feces (see Chapter 6 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.

2.7.2 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.

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

2.8 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 1993b; 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 2.3.1.2 and 2.4.1, 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). Similarly, aluminum oxide powders were administered via inhalation to miners as a means of prophylaxis against silicosis (Rifat et al. 1990; S tokinger 198 1); the effectiveness of this treatment is uncertain, but no lung damage or other ill effects have been observed. Aluminum hydroxide, commonly found in antacids, can decrease the intestinal absorption of fluoride and phosphorus in humans (Carmichael et al. 1984; Chines and Pacitici 1990; Pivnick et al. 1995; Spencer et al. 1980; Woodson 1998).

As discussed in Section 2.4.1, there are some data that suggest that aluminum absorption can be enhanced by parathyroid hormone and vitamin D, but the data are inconclusive.

There are some data showing age-related effects of the dietary concentration of aluminum on the retention and localization of the essential elements copper, iron, zinc, calcium magnesium and manganese (Sanchez et al. 1997). 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. In older animals, there was an increase of calcium magnesium manganese, and zinc in the testes and spleen. However, the significance, if any, of these changes is not clear.

2.9 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 may result in reduced detoxification or excretion of aluminum or compromised function of target organs affected by aluminum. Populations who are at greater risk due to their unusually high exposure to aluminum are discussed in Section 5.7, Populations With Potentially High Exposure.

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). Pre-term infants may also be particularly sensitive to the toxicity of aluminum due to reduced renal capacity (Tsou et al. 1991)

2.10 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.

Ellenhorn, MS, Barceloux, DG. 1988. Medical toxicology diagnosis and treatment of human poisoning. New York, NY (Elsevier). 1009-1011.

Haddad, CM, Winchester, JF. 1990. Clinical Management of poisoning and drug overdose. 2nd ed. Philadelphia, PA (WB Saunders) 1029.

2.10.1 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.

2.10.2 Reducing Body Burden

In persons with normal renal function, the body burden can be reduced simply by limiting exposure. Avoidance of aluminum-containing products is also recommended for patients with renal failure; in particular, use of nonaluminum containing phosphate binding gels, avoidance of co-administration of aluminum compounds and citrate compounds, and use of aluminum free dialysate and parenteral solutions. Administration of a chelator such as desferrioxamine (DFO) may also help reduce aluminum body burden. DFO is a chelating agent that reduces the ability of metals to bind to biological tissues. 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 and Winchester 1990). DFO is also used in dialyzed uremic patients for the treatment of neurological, hematopoietic, and skeletal toxicity. 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.

2.10.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanism of action for aluminum toxicity is not known; thus there are no known ways of interfering with its mechanism of action.

2.11 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.

2.11.1 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 2-4. 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* (ATSDR 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. 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.

Figure 2-4. Existing Information on Health Effects of Aluminum and Compounds

	Death	Systemic: Acute	Systemic: Intermediate	Systemic: Chronic	Systemic: Immunologic/Lymphoretic	Systemic: Neurologic	Systemic: Reproductive	Systemic: Developmental	Systemic: Genotoxic	Cancer
Inhalation	●			●		●				●
Oral	●	●	●	●		●				
Dermal		●	●		●					

Human

	Death	Systemic: Acute	Systemic: Intermediate	Systemic: Chronic	Systemic: Immunologic/Lymphoretic	Systemic: Neurologic	Systemic: Reproductive	Systemic: Developmental	Systemic: Genotoxic	Cancer
Inhalation		●	●	●						●
Oral	●	●	●	●	●	●	●	●		●
Dermal		●								

Animal

● Existing Studies

Effects following oral exposure to several aluminum salts are available for adults and newborn animals. One acute dermal study is available.

2.11.2 Identification of Data Needs: Children's Susceptibility

Several animal studies have examined potential age-related differences in the distribution, neurotoxicity, skeletal toxicity, and interactions of aluminum. However, conflicting results have been found and the database is not adequate to assess whether these differences are due to the animal species tested, the aluminum compound used, or the route of exposure. 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. Multiple species studies 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.

2.11.3 Identification of Data Needs

Acute-Duration Exposure. Excluding developmental and neurological toxicity, there are few data regarding the acute effects of aluminum exposure. A series of animal inhalation studies suggest that the lung may be a sensitive target for toxicity (Drew et al. 1974). The observed effects are similar to those which 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. The acute systemic toxicity of orally administered aluminum has not been well investigated, and systemic targets of toxicity have not been established. Data were insufficient to derive an acute-duration oral MRL. This is due to lack of data on sensitive toxicity end points and a lack of studies with sufficient dose information (aluminum levels in the base diet were not reported). However, further studies using this time-frame would not be particularly helpful in defining the human risk potential at hazardous waste sites since, if toxicity were to develop in the brain or bone, it would be after a very large cumulative exposure, which would take a long time, considering the poor absorption of aluminum.

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). 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 itialation MRL was not derived for aluminum. The central nervous system is the most sensitive target for intermediate-duration oral exposure to aluminum, and the MRL is based on a neurotoxic effect (reduced spontaneous motor activity) in mice (Golub et al. 1989). As discussed in the Data Needs section on Neurotoxicity, additional studies could confirm that motor activity is the most sensitive and appropriate neurotoxic end point for risk evaluation of aluminum, because no other neurotoxicity end points were tested in the MRL study. Nonneurotoxicity studies using this time-frame would not be particularly helpful in defining the human risk potential of aluminum at hazardous waste sites.

Chronic-Duration Exposure and Cancer. Aluminum has been implicated in causing neurological (Banks et al. 1988; Liss and Thorton 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. Pulmonary fibrosis has been associated with exposure to finely ground aluminum pyropowders which used nonpolar aliphatic oil lubricants (Edling 1961; McLaughlin et al. 1962; Mitchell et al. 1961; Ueda et al. 1958). 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 (Hanninen et al. 1974; Hosovski et al. 1990; Rifat et al. 1990; Sim et al. 1997; Sjijgren et al. 1996; White et al. 1992). Inhalation animal studies have focused on the pulmonary toxicity of aluminum (Stone et al. 1979). Data were considered inadequate for derivation of a chronic-duration inhalation MRL. Occupational exposure studies did not adequately characterize exposure and the animal studies did not examine sensitive end points of pulmonary toxicity. Several studies have examined the systemic toxicity of aluminum following chronic oral exposure (Oneda et al. 1994; Ondreicka et al. 1966; Schroeder and Mitchener 1975a). A chronic-duration oral MRL was not derived because the chronic-duration oral studies did not evaluate known or possible sensitive end points (e.g., neurotoxicity and skeletal effects). Chronic-duration animal studies are needed to identify target organs and to assess the human risk to chronic, increased, and greater-than-average aluminum exposures.

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). 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.

Genotoxicity. Animal data are available that indicate that aluminum may interact with neuronal DNA to alter gene expression and protein formation (Bertholf 1987; Crapper-McLachlan 1989; Crapper-McLachlan and Farnell 1985b). It is possible that this is a mechanism by which aluminum might exert its effects in the brains of patients with Alzheimer's disease. Further information on the mechanisms of aluminums effects on neurons would be helpful in determining whether aluminum has effects on gene expression that can adversely affect the human brain.

There are no human data to indicate that aluminum acts to cause cancer by genotoxic mechanisms. There are data from intraperitoneal exposures of mice to aluminum chloride that indicate that this compound is clastogenic (Manna and Das 1972). Although many carcinogens are also clastogens, there is no one-to-one relationship between these effects. Further genotoxicity studies, particularly *in vivo* exposures, would be useful for determining if clastogenic effects occur in additional species and at lower doses. In view of the negative carcinogenicity data for aluminum the significance of the clastogenic effects in one experiment is unclear.

Reproductive Toxicity. There are no human studies that indicate that aluminum affects reproduction. Animal studies in rats, mice, and dogs have shown that aluminum apparently does not affect reproduction. Finally, pharmacokinetic data do not indicate that the reproductive organs are target organs (Dixon et al. 1979; Ondreicka et al. 1966). Further studies in this area do no: appear to be necessary.

Developmental Toxicity. 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. 1993b

Yoshida et al. 1989). 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 (Donald et al. 1989; Golub and Germann 1998; Golub et al. 1987, 1992a, 1992b, 1994, 1995; 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 systems 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) LOAEZL 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 et al. 1992a, 1992b, 1994, 1995; Golub and Germann 1998). 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 who have received aluminum-containing vaccines (Bohler-Sommeregger and Lindemayr 1986; Veien et al. 1986). 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), although there is some evidence that developmental exposure to aluminum can affect the immune system in young mice (Golub et al. 1993b 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. Any 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. 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 (Hanninen et al. 1994; Hosovski et al. 1990; Rifat et al. 1990; Sim et al. 1997; Sjogren et al. 1996; White et al. 1992). There are several studies that have found an association between aluminum concentrations in drinking water and the risk for Alzheimer's disease (Martyn et al. 1989; McLachlan et al. 1996; Michel et al. 1990). However, 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 aluminums role in the Alzheimer's disease process. Apart from whether or not aluminum is involved in the development of Alzheimer's disease, there is the question of whetheror not it exacerbates the symptoms of the disease. Additional analytical studies are needed to identify the extent to which aluminum may incorporate into portions of the brain and, in particular, the neurofibrillary tangles associated with Alzheimer's disease, but those procedures, solutions, and equipment should strictly prevent unintended aluminum contamination of the tissues to be valid (Makjanic et al. 1998).

The neurotoxicity of aluminum is well-documented in animals and has been manifested following various routes of exposure, including neuromotor, behavioral, and cognitive changes in orally-exposed adult rats and mice (Bilkei-Gorzo 1993; Bowdler et al. 1979; Commissaris et al. 1982; Connor et al. 1988; Dixon et al. 1979; Domingo et al. 1987b; Florence et al. 1994; Golub et al. 1989, 1992b, 1995; Gomez et al. 1986; Jope and Johnson 1992; Lal et al. 1993; Oteiza et al. 1993; Thorne et al. 1986; Varner et al. 1993, 1994, 1998). Research issues related to neurodevelopmental effects of aluminum are discussed in the Data Needs section on Developmental Toxicity. Some of that discussion also pertains to the neurotoxicity database in adult animals, particularly the need for additional information on bioavailability of different forms and ingested amounts of aluminum to better assess its neurotoxic potential, as well as more low-dose studies in which levels of aluminum in the base diet are adequately characterized. Additional low-dose neurotoxicity data are desirable because the NOAEL for the effect on which the MRL is based (reduced spontaneous motor activity) is uncorroborated, in part due to a lack of total dose information in most existing low-dose studies (i.e., experimental doses were often reported with no data on aluminum in the base diet). Additional studies could also confirm that motor activity is the most sensitive and appropriate neurotoxic end point for risk evaluation of aluminum because other no other neurotoxicity end points were tested in the MRL study (Golub et al. 1989).

Numerous mechanistic studies of aluminum neurotoxicity have been performed, but the main sites of action have not been discerned as discussed in Section 2.4.2 and by Strong et al. (1996). Additional studies could help identify a single unifying mechanism that can explain and reconcile the wide variety of pathological, neurochemical, and behavioral effects of aluminum induced by oral exposure and in various model systems (e.g., intracerebral and intracisternal administration), but these kinds of studies are unlikely to better characterize neurotoxicity NOAELs and LOAELs relevant to MRL assessment. The relationship between aluminum exposure and neurotoxicity is an active area of research.

Epidemiological and Human Dosimetry Studies. Some studies have been conducted in the workplace on people who have been exposed by the inhalation route, but the exposure levels have not been well quantified. People with chronic renal failure may be at higher risk for developing aluminum-related neurological disorders (Alfrey 1993b). A number of studies have examined the possible association between Alzheimer's disease and aluminum exposure in air (Salib and Hillier 1996), drinking water (Forster et al. 1995; Martyn et al. 1989, 1997; McLachlan et al. 1996; Michel et al. 1990; Wettstein et al. 1991), and use of aluminum-containing antiperspirants/deodorants (Graves et al. 1990). These studies have found 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. Results from these studies could also be used to identify what are potentially unhealthy exposure levels for individuals living near hazardous waste sites.

Biomarkers of Exposure and Effect. Reliable methods for determining tissue and plasma levels of aluminum exist. The nlechanism 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 serum (Alfrey et al. 1980; Arieff et al. 1979; Ganrot 1986), urine (Gorsky et al. 1979; Greger and Baier 1983b; Kaehny et al. 1977; Mussi et al. 1984; Reeker et al. 1977; Sjögren et al. 1985, 1988), and feces (Greger and Baier 1983b), 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. Because of the great human variability in aluminum tissue and plasma levels following exposure, it is doubtful if additional studies will provide better models of aluminum exposure.

Effect. The mechanisms of action for aluminum toxicity is not known. Aluninum has a number of subcellular effects, such as affecting cation protein interactions or microtubule structure and effects on cellular signaling mechanisms, which can be observed *in vitro.* Further information would be useful in indicating whether these subcellular effects lead to disease processes. 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 0.1-0.3% in humans, although absorption of particularly bioavailable forms such as aluminum citrate can be on the order of 1% (Day et al. 1991; DeVoto and Yokel 1994; Ganrot 1986; Greger and Baier 1983b; Jones and Bennett 1986; Nieboer et al. 1995; Priest 1993). 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). Although the range of fractional absorption is low compared to many other chemicals, aluminum uptake can significantly increase following oral exposure depending on conditions, including long-term ingestion, the presence of certain dietary components (e.g., citrate), and when large quantities are ingested (e.g., during use of antacids). The apparent lo-fold range in aluminum absorption has not been systematically documented using a variety of aluminum compounds and the most suitable analytical techniques. Few estimates of aluminum absorption have been determined using isotopic tracer techniques because ^{26}Al (the only isotope with a biologically usable half-time) is not readily available, is expensive in the quantities necessary for radiochemical detection, and requires the use of a sophisticated analytical technique (accelerator mass spectrometry) (Day et al. 1991; Priest et al. 1996). 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). Only one ^{26}Al study (Priest et al. 1996) has assessed bioavailability using different forms of aluminum and this study is limited by testing of only two compounds (aluminum citrate and aluminum hydroxide), a minimal number (two) of human subjects, and lack of data on effects of diet on absorption (e.g., comparison of empty versus full stomach conditions). 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.

Oral bioavailability of aluminum compounds appears to generally parallel water solubility, but current knowledge does not allow a straight extrapolation from solubility in water to bioavailability. Studies of aluminum speciation in the stomach and intestines, including mathematical modeling, would be useful because they could enable such an extrapolation by helping to resolve the critical role of speciation in making aluminum available to uptake mechanisms.

Adequate data are available on the retention of aluminum following various durations of exposure. Metabolism of the element does not occur (Ganrot 1986), and excretion routes are known (Gorsky et al. 1979; Greger and Baier 1983b; Kaehny et al. 1977; Reeker 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. Although the interpretation of the human data is limited by poor exposure characterization, the occupational exposure studies suggest that neurotoxicity is also a sensitive end point following inhalation exposure (Htinninen et al. 1974; Hosovski et al. 1990; Rifat et al. 1990; Sim et al. 1997; Sjögren et al. 1996; White et al. 1992). The toxicokinetic properties of aluminumhave been extensively studied in human and animals. The results of these studies suggest that the absorption, distribution, and excretion properties of aluminum are similar across species.

Methods for Reducing Toxic Effects. The mechanism of absorption and distribution of aluminum have not been established. Studies which 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; however, the clinical

usefulness of DFO is limited by a variety of toxic effects. Studies which 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.

2.11.4 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 2-5 (FEDRIP 1998).

Table 2-5. Ongoing Studies for Aluminum Toxicity

Investigator	Study Topic	Institution	Sponsor
Swyt CR	Aluminum in Alzheimer's Disease	NCRR, NIH	National Center for Research Resources
Sakhaee K	Aluminum absorption - effects of calcium citrate on aluminum-containing antacids	University of Texas SW Med. Center	National Center for Research Resources
Bondy SC	Aluminum ion-induced interactions and neurological disease	University of California Irvine	National Institute of Environmental Health Science
Banks WA	Aluminum blood-brain barrier permeability	Department of Veterans Affairs Medical Center	USA
Berlyne GM	Aluminum handling in kidney and gut	Department of Veterans Affairs Medical Center	USA
NA	Aluminum in brain diseases	Atom Sciences Inc.	HHS
Dunn MA	Effects of dietary aluminum on vitamin D-dependent calcium absorption	University of Hawaii	U.S. Dept. Of Agriculture Competitive Research Grant Office
Fanti P	Effects of aluminum on bone cells in culture	Dept. of Veterans Affairs Medical Center	Dept of Veterans Affairs Research and Development
Castro CE Johnson NE	Interactive effects of dietary aluminum and zinc deficiency on nuclear chromatin structure and function	University of Hawaii	U.S. Dept. Of Agriculture Cooperative State Res. Ser.
Melethil SK	Mechanism of blood-brain transport of aluminum in rats	University of Missouri Kansas	National Institute of Environmental Health Sciences
Yokel R	Bioavailability of ^{26}Al from drinking water	University of Kentucky Medical Center	EPA
Golub MS	Mouse model for chronic oral aluminum toxicity	University of California Davis	National Institute of Environmental Health Sciences

Table 2-5. Ongoing Studies for Aluminum Toxicity *(continued)*

Investigator	Study Topic	Institution	Sponsor
Coburn JW	Studies of aluminum absorption in man	Department of Veterans Affairs Medical Center	USA

NA = not available

Source: FEDRIP 1998

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Aluminum appears in the second row of Group III of the periodic table. It generally has two oxidation states: Al(O) and Al(+3). Because of its high reactivity, aluminum is not found as the free metal in nature. Information regarding the chemical identity of aluminum and compounds is located in Table 3- 1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of aluminum is located in Table 3-2. In addition to the compounds listed in Table 3-2, aluminum in the form or alumina (Al_2O_3), combined with silica and other chemical compounds is a major component of clay minerals (Dombrowski 1993; Sennett 1993). The large number of types of clays and the variability in their composition make it impossible to include in this document.

Table 3-1. Chemical Identity of Aluminum and Compounds[a]

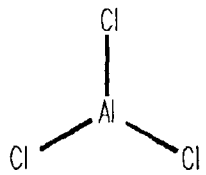
Characteristic	Information	Information	Information
Chemical name	Aluminum	Aluminum chloride	Aluminum chlorhydrate[b]
Synonym(s)	Aluminum; alumina fibre; metana; aluminum bronze; aluminum dehydrated; aluminum flake; aluminum powder	Aluminum trichloride; trichloroaluminum[c]; aluminum chloride (1:3)	Aluminum chlorohydroxide; aluminum hydroxychloride[d]; aluminum chloride, basic; aluminum chloride hydroxide; polyaluminum chloride
Registered trade name(s)	Aluminum-27; Jisc 3108/3110; Metana; Noral Aluminum; Pap-1	Pearsall	Astringen; Chlorhydrol; Locron[d]
Chemical formula	Al[d]	$AlCl_3$[d]	$AlClH_5O_5$ or $Al_2(OH)_5Cl{\bullet}2H_2O$[d] or $(Al(OH)_2Cl)_x$ or $Al_6(OH)_{15}Cl_3$; $[Al_2(OH)_5Cl]_x$ [e]
Chemical structure	Al		Not available

Table 3-1. Chemical Identity of Aluminum and Compounds[a] *(continued)*

Characteristic	Information	Information	Information
Chemical name	Aluminum	Aluminum chloride	Aluminum chlorhydrate[b]
Identification numbers:			
CAS registry	7429-90-5[d]	7446-70-0[d]	1327-41-9[d]; 11097-68-0; 84861-98-3[f]
NIOSH RTECS	BD330000	BD0525000	BD0549500[f]; BD0550000[g]
EPA hazardous waste	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMCO shipping	UN 1309; UN 1383; UN 1396; IMO 4.1; IMO 4.2; IMO 4.3	UN 1726; UN 2581; IMO 8.0	No data
HSDB	507	607	No data
NCI	No data	No data	No data

Table 3-1. Chemical Identity of Aluminum and Compounds[a] *(continued)*

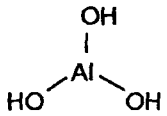
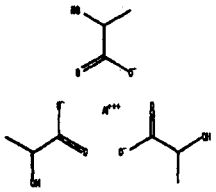
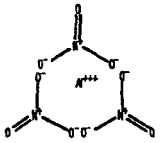
Characteristic	Information	Information	Information
Chemical name	Aluminum hydroxide	Aluminum lactate	Aluminum nitrate
Synonym(s)	α-Alumina trihydrate; alumina hydrate; alumina hydrated; aluminum oxide trihydrate; aluminum oxide hydrate; aluminum (III) hydroxide; hydrated alumina; hydrated aluminum oxide[a]; aluminum hydrate; aluminum trihydrate; hydrated alumina[d]	Aluctyl; aluminum, tris (2-hydroxypropanoato-O^1,O^2)[f]; propanoic acid, 2-hydroxy-, aluminum complex; aluminum tris (.alpha.-hydroxypropionate)	Aluminum trinitrate; aluminum (III) nitrate (1:3); nitric acid, aluminum salt; nitric acid, aluminum (3+) salt
Registered trade name(s)	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	No data	No data
Chemical formula	AlH_3O_3 or $Al(OH)_3$[d]; $AL_2O_3.3H_2O$[e]	$C_9H_{15}AlO_9$[d]	AlN_3O_9[d]; $AlN_3O_9 \cdot 9H_2O$[e]
Chemical structure			

Table 3-1. Chemical Identity of Aluminum and Compounds[a] *(continued)*

Characteristic	Information	Information	Information
Chemical name	Aluminum hydroxide	Aluminum lactate	Aluminum nitrate
Identification numbers:			
CAS registry	21645-51-2[d]	18917-91-4[d]	13473-90-0[d]
NIOSH RTECS	BD0940000	BD2214000[f]	BD1040000
EPA hazardous waste	No data	No data	No data
OHM/TADS	7216580	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	UN 1438; IMO 5.1
HSDB	575	No data	574
NCI	No data	No data	No data

Table 3-1. Chemical Identity of Aluminum and Compounds[a] *(continued)*

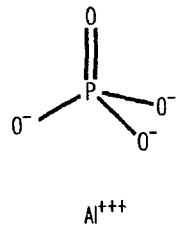
Characteristic	Information	Information	Information
Chemical name	Aluminum oxide[h]	Aluminum phosphate	Aluminum phosphide
Synonym(s)	Activated aluminum oxide; α-aluminum, α aluminum oxide; alumina; aluminum sesquioxide; aluminum trioxide; β-aluminum oxide; γ-alumina; γ-aluminum oxide[f]	Aluminum orthophosphate[d]; phosphoric acid; aluminum salt (1:1); aluminum phosphate tribasic[c]	Aluminum monophosphide; Quick-Phos; Quick-Fume[c]; AlP; Celphos; Detia; Phostoxin[d]
Registered trade name(s)	Almite; Alon; Aloxite; Alumite; Alundum; Campalox; Dispol Alumina; Exolon XW 60; Faserton; Hypalox II; Ludox CL; Martoxin; Microgrit WCA; Poraminar[f]	Alaphos (ingredient); Ukocid (ingredient); Phosphaljel (ingredient); Phosphalugel (ingredient); Phosphalutab (ingredient)	Celphos; Delicia; Delicia Gastoxin; Detia GAS EX-B/EX-T; Phostoxin; Detia phospine pellets[i]
Chemical formula	Al_2O_3[d]	$AlPO_4$[d]	AlP[d]
Chemical structure	Not available		

Table 3-1. Chemical Identity of Aluminum and Compounds[a] *(continued)*

Characteristic	Information	Information	Information
Chemical name	Aluminum oxide[h]	Aluminum phosphate	Aluminum phosphide
Identification numbers:			
CAS registry	1344-28-1[d]	7784-30-7[d]	20859-73-8[d]
NIOSH RTECS	BD1200000	No data	BD1400000
EPA hazardous waste	No data	No data	P006
OHM/TADS	No data	No data	8500249[i]
DOT/UN/NA/IMCO shipping	No data	No data	UN 1397; UN 3048; IMO 4.3; IMO 6.1
HSDB	506	No data	6035
NCI	No data	No data	No data

Table 3-1. Chemical Identity of Aluminum and Compounds[a] *(continued)*

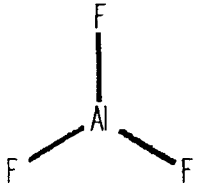
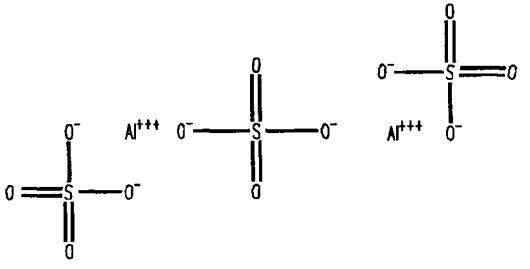
Characteristic	Information	Information
Chemical name	Aluminum fluoride	Aluminum sulfate
Synonym(s)	Aluminum trifluoride[d]; aluminum fluoride monohydrate[c]; Aluminum fluorure (French)	Alum; peral alum; pickle alum; cake alum; filter alum; papermakers' alum; patent alum[e]; aluminum sulfate (2:3); aluminum trisulfate; dialuminum sulfate; dialuminum trisulfate; sulfuric acid, aluminum salt (3:2)
Registered trade name(s)	No data	cake alum; patent alum[e]
Chemical formula	AlF_3[d]	$Al_2(SO_4)_3$[d]
Chemical structure		

Table 3-1. Chemical Identity of Aluminum and Compounds[a] *(continued)*

Characteristic	Information	Information
Chemical name	Aluminum fluoride	Aluminum sulfate
Identification numbers:		
CAS registry	7784-18-1[d]	10043-01-3[d]
NIOSH RTECS	BD0725000	BD1700000
EPA hazardous waste	No data	No data
OHM/TADS	7216579	7216581
DOT/UN/NA/IMCO shipping	No data	NA 9078; NA 1760
HSDB	600	5067
NCI	No data	No data

Table 3-1. Chemical Identity of Aluminum and Compounds[a] *(continued)*

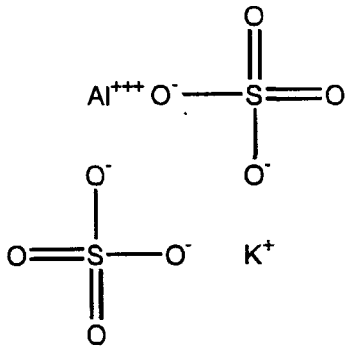
Characteristic	Information	Information	Information
Chemical name	Aluminum carbonate	Aluminum potassium sulfate	Alchlor
Synonym(s)	No data	Sulfuric acid, aluminum potassium salt (2:1:1)[i]	No data
Registered trade name(s)	No data	No data	No data
Chemical formula	$Al_2O_3 \cdot CO_2$; normal aluminum carbonate $Al_2(CO_3)_3$ is not known as an individual compound[e]	$AlKO_8S_2$[j]	$Al_2(OH)_5Cl \cdot nH_2O \cdot mC_2H_6O_2$; $Al_2(OH)_5Cl \cdot nH_2O \cdot mC_3H_8O_2$; $Al_2(OH)_4Cl_2 \cdot nH_2O \cdot mC_2H_6O_2$; $Al_2(OH)_4Cl_2 \cdot nH_2O \cdot mC_3H_8O_2$[k]
Chemical structure	No data		No data
Identification numbers:	No data	No data	No data
CAS registry	No data	10043-67-1	No data
NIOSH RTECS	No data	No data	No data
EPA hazardous waste	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data

Table 3-1. Chemical Identity of Aluminum and Compounds[a] *(continued)*

Characteristic	Information	Information	Information
Chemical name	Aluminum carbonate	Aluminum potassium sulfate	Alchlor
HSDB	No data	No data	No data
NCI	No data	No data	No data

[a]All information obtained from HSDB 1995, except where noted.
[b]Aluminum chlorhydrate is the common name for several different compounds, all containing aluminum, chloride, and hydroxyl ions; therefore, there are several chemical formulas and CAS numbers.
[c]Chemfinder 1997
[d]Budavari et al. 1989
[e]Lewis 1993
[f]RTECS 1989
[g]Sax and Lewis 1989
[h]According to Cotton and Wilkinson (1988), the structure of Al_2O_3 involves complicated crystalline, three dimensional arrays, which are prohibitively difficult to represent here. Anhydrous Al_2O_3 comes in α and γ forms. In α Al_2O_3, the oxide ions form a hexagonal close-packed array and the aluminum ions are distributed symmetrically among the octahedral interstices. The γ Al_2O_3 structure is sometimes regarded as a "defect" spinel structure; that is, as having the structure of spinel with a default of cations.
[i]OHM/TADS 1989
[j]Budavari et al. 1996
[k]Kroschwitz 1993

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

Table 3-2. Physical and Chemical Properties of Aluminum and Compounds

Property	Information		
	Aluminum	Aluminum chloride	Aluminum chlorohydrate
Molecular weight	26.98	133.34	174.46
Color	Tin-white, with bluish tint[a]	White when pure, ordinarily gray or yellow-to-greenish[a]	Glassy[a]
Physical state	Malleable, ductile metal[a]; crystalline solid[b]	White or yellowish crystals[b]	Solid[a]
Melting point	660 °C[a]	Volatilizes without melting[a]; 190 °C at 2.5 atm[b]; 381 °F (194 °C) at 5.2 atm[c]	No data
Boiling point	2,327 °C[a]; 2,450 °C[b]; 4,473 °F (2,467°C)[c]	182.7 °C at 752 mmHg[d]; sublimes readily at 178 °C[b]; sublimes at 358 °F (181 °C)[c]	No data
Density at 25 °C	2.70[a]	2.44[b]	No data
Odor	Metallic odor when dust is inhaled[c]	Strong odor of HCL[a]	No data
Odor threshold:			
Water	No data	1.5 ppm (HCL)[e]	No data
Air	No data	No data	No data
Solubility:			
Water at 25 °C	Insoluble[f]; rapidly oxidized by H_2O at 180 °C[b]	Reacts explosively with water evolving HCL gas[b]	Dissolves in H_2O, forming slightly turbid colloidal solutions (up to 55% w/w)[a]
Organic solvents	Soluble in alkalies, acids[g]	Freely soluble in benzophenone, C_6H_6, nitrobenzene, CCl_4, $CHCl_3$[a]; soluble in alcohol and ether[h]	No data

Table 3-2. Physical and Chemical Properties of Aluminum and Compounds *(continued)*

Property	Information		
	Aluminum	Aluminum chloride	Aluminum chlorohydrate
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
Vapor pressure	1 mmHg at 1,284 °C[d]	1 mmHg at 100 °C[d]	No data
Henry's law constant at 24.8 °C	No data	No data	No data
Autoignition temperature	1,400 °F (760 °C)[c]	Not flammable[i]	No data
Flashpoint	645 °C[f]	Not combustible[c]	No data
Flammability limits in air	Flammable solid if finely divided, easily ignited[c]	Not flammable[i]	No data
Conversion factors	No data	No data	No data
Explosive limits	No data	Combines with water with explosive violence and the liberation of much heat[a]	No data

Table 3-2. Physical and Chemical Properties of Aluminum and Compounds *(continued)*

Property	Information		
	Aluminum hydroxide	Aluminum lactate	Aluminum nitrate
Molecular weight	77.99[a]	294.18[a]	213.00[a]; 375.13 (-9 H_2O)[g]
Color	White[a]	Colorless[b]; white-yellowish	White[b]
Physical state	Bulky, amorphous powder[a]	Powder[b]	Nonahydrate, deliquescent crystals[a]
Melting point	300 °C[d]	No data	73 °C[a]
Boiling point	No data	No data	Decomposes at 135 °C[a]
Density at 25 °C	2.42[b]	No data	1.72 (-9H_2O)[g]
Odor	No data	No data	Odorless[i]
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water at 25 °C	Practically insoluble, forms gels on prolonged contact with H_2O [a]	Freely soluble in water[a]	Very soluble in water[a]; 63.7 g/100 cc at 25 °C
Organic solvents	Soluble in alkaline aqueous solutions or in HCL, H_2SO_4 [a]	No data	Very slightly soluble in acetone; almost insoluble in ethyl acetate and pyridine[a]
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
Vapor pressure at 25 °C	No data	No data	No data

Table 3-2. Physical and Chemical Properties of Aluminum and Compounds *(continued)*

Property	Information		
	Aluminum hydroxide	Aluminum lactate	Aluminum nitrate
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	Not flammable[i]
Flammability limits in air	No data	No data	Not flammable[i]
Conversion factors:			
ppm (v/v) to mg/m^3 in air at 25 °C	No data	No data	No data
mg/m^3 to ppm (v/v) in air at 25 °C	No data	No data	No data
Explosive limits	No data	No data	Not flammable[i]

Table 3-2. Physical and Chemical Properties of Aluminum and Compounds *(continued)*

Property	Information		
	Aluminum oxide	Aluminum phosphate	Aluminum phosphide
Molecular weight	101.94[a]	121.95[a]	57.96[a]
Color	White[a]	White[a]	Dark gray or dark yellow[a]
Physical state	Crystalline powder[a]	Infusible powder[a]; crystals[b]	Crystals[a]
Melting point	≈2,000 °C[a]; 2030 °C[b]; 2054 °C[g]	>1,460 °C[a]	Does not melt or decompose thermally at temps up to 1,000 °C[a]
Boiling point	≈3,000 °C[g]	No data	No data
Density at:	3.4–4.0[b]	2.57[b]	2.40[a]
at 15 °C	No data	No data	2.85[a]
at 20 °C	4.0[a]	No data	No data
at 23 °C	No data	2.56[a]	No data
at 25 °C	3.97[g]	No data	No data
Odor	No data	No data	Garlic odor[d]
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water at 25 °C	Practically insoluble in water[a]; soluble in cold water 0.000098 g/100 cc[d]	Insoluble[b]	Decomposes[a]
Organic solvents	Slowly soluble in aqueous alkaline solutions; practically insoluble in nonpolar organic solvents[a]	Very slightly soluble in conc HCL and HNO_3[a]	No data

Table 3-2. Physical and Chemical Properties of Aluminum and Compounds *(continued)*

Property	Information		
	Aluminum oxide	Aluminum phosphate	Aluminum phosphide
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
Vapor pressure at 25 °C	1 mmHg at 2158 °C[d]	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	Non combustible[b]	No data	No data
Flammability limits in air	No data	No data	Reacts with moisture to give phosphine a flammable gas[j]
Conversion factors:			
ppm (v/v) to mg/m^3 in air at 25 °C	No data	No data	No data
mg/m^3 to ppm (v/v) in air at 25 °C	No data	No data	No data
Explosive limits	No data	No data	No data

Table 3-2. Physical and Chemical Properties of Aluminum and Compounds *(continued)*

Property	Information	
	Aluminum fluoride	Aluminum sulfate
Molecular weight	83.98[a]	342.14[a]
Color	White[b]; colorless, triclinic[d]	White, lustrous[b]
Physical state	Hexagonal crystals[a]	Crystals, pieces, granules or powder[a]
Melting point	1,291 °C[d]; sublimes (760 mmHg) at 1,272 °C[a]	Decomposes at 770 °C[b]; decomposes at 1,040 °C[g]
Boiling point	1,276 °C (sublimation point)[g]	No data
Density at 25 °C	2.88[d]	2.71[b]
Odor	No data	Odorless[d]
Odor threshold:		
Water	No data	No data
Air	No data	No data
Solubility:		
Water at 25 °C	0.559 g/100 mL at 25 °C[a]	Soluble in 1 part H_2O[a]
Organic solvents	Sparingly soluble in acids and alkalies[a]; insoluble in alcohol and acetone	Soluble in dilute acids[d]; practically insoluble in alcohol[a]
Partition coefficients:		
Log K_{ow}	No data	No data
Log K_{oc}	No data	No data
Vapor pressure at 25 °C	1 mmHg at 1,238 °C[d]	Essentially zero[d]
Henry's law constant	No data	No data
Autoignition temperature	Not flammable[l]	No data
Flashpoint	Not flammable[l]	Not flammable[l]

Table 3-2. Physical and Chemical Properties of Aluminum and Compounds *(continued)*

Property	Information	
	Aluminum fluoride	Aluminum sulfate
Flammability limits in air	Not flammable[i]	Not flammable[i]
Conversion factors:		
ppm (v/v) to mg/m^3 in air at 25 °C	No data	No data
mg/m^3 to ppm (v/v) in air at 25 °C	No data	No data
Explosive limits	Produces strong explosion on impact when mixed with sodium[d]	No data

Table 3-2. Physical and Chemical Properties of Aluminum and Compounds *(continued)*

Property	Information		
	Aluminum carbonate	Aluminum potassium sulfate	Alchlor
Molecular weight	145.97[b]	258.21[k]	No data
Color	White[b]	White[k]	No data
Physical state	Lumps or powder[b]	Powder[k]	No data
Melting point	No data	No data	No data
Boiling point	No data	No data	No data
Density at 25 °C	No data	No data	No data
Odor	No data	No data	No data
Odor threshold:	No data	No data	No data
Water			
Air			
Solubility:			
Water at 25 °C	Insoluble[b]	50 g/L[k]	No data
Organic solvents	Dissolves in hot hydrochloric or sulfuric acid[b]	Insoluble in alcohol[k]	No data
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
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

Table 3-2. Physical and Chemical Properties of Aluminum and Compounds *(continued)*

	Information		
Property	Aluminum carbonate	Aluminum potassium sulfate	Alchlor
Flammability limits in air	No data	No data	No data
Conversion factors	No data	No data	No data
Explosive limits	No data	No data	No data

[a]Budavari et al. 1989
[b]Lewis 1993
[c]NFPA 1994
[d]HSDB 1995
[e]Weast et al. 1989
[f]Chemfinder 1997
[g]Lide 1997
[h]Sax and Lewis 1987
[i]Weiss 1986
[j]OHM/TADS 1989
[k]Budavari et al. 1996

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

4.1 PRODUCTION

Aluminum is the most abundant metallic element in the earth's crust, comprising approximately 8% of the crust (Brusewitz 1984). Aluminum does not occur naturally in the metallic, elemental state, but rather occurs in combination with oxygen, silicon, fluorine, and other elements (Browning 1969; Dinman 1983; IARC 1984; NRC 1982). The most important raw material for the production of aluminum is bauxite, which contains 40-60% alumina (aluminum oxide) (Dinman 1983; IARC 1984). 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).

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-Heroult process to produce aluminum and casting of aluminuminto ingots (Browning 1969; Dinman 1983; IARC 1984).

In the first step (Bayer process), bauxite (Al2O3•H2O) 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-Heroult process), alumina is reduced to aluminum metal by an electrolytic process involving carbon electrodes and cryolite flux ($3NaF•AlF_3$). 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 Soderberg 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-Heroult electrolytic reduction process may be refined to a maximum purity of 99.9% by the Badeau low-temperature electrolytic process (HSDB 1995). 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.

The use of electrodes in aluminum reduction operations is associated with the generation of several types of wastes (Dinman 1983; IARC 1984). In aluminum reduction facilities using the prebake process, PAHs are generated. In aluminum reduction operations using the Soderberg cell process, considerable amounts of volatiles from coal tar pitch, petroleum coke, and pitch, including PAHs, are generated.

In 1997, domestic primary aluminum production totaled just over 3.6 million metric tons (7.9 billion pounds. Thirteen companies operated 22 primary aluminum reduction plants, and 1 plant remained closed. Montana, Oregon, and Washington accounted for 38% of the production; Kentucky, North Carolina, South Carolina, and Tennessee, 21%; and other States, 41%. Aluminum recovered in 1997 from purchased scrap was almost 3.5 million metric tons (7.7 billion pounds), of which 50% came from new (manufacturing) scrap and 50% from old scrap (discarded aluminum products) (USGS 1997a, 1998, 1999).

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 is described in the following section.

Aluminum chloride is produced by a reaction of bauxite with coke and chlorine at about 875 °C (HSDB 1995; Sax and Lewis 1987).

Aluminum fluoride is made by heating ammonium hexafluoroaluminate to red heat in a stream of nitrogen; by the action of fluorine or hydrogen fluoride gas on aluminum trihydrate at high temperatures, followed by calcining the hydrate formed; by fusing cryohte or sodium fluoride with aluminum sulfate; or by a reaction of fluosilicic acid on aluminum hydrate (HSDB 1995).

Aluminum hydroxide is produced from bauxite. The ore is dissolved in a solution of sodium hydroxide, and aluminum hydroxide is precipitated from the sodium aluminate solution by neutralization (as with carbon dioxide) or by autoprecipitation (Bayer process) (HSDB 1995; Sax and Lewis 1987).

Aluminum nitrate is formed by dissolving aluminum or aluminum hydroxide in dilute nitric acid and allowing the resulting solution to crystallize (HSDB 1995).

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) (HSDB 1995).

Aluminum phosphide is made from red phosphorus and aluminum powder (Budavari et al. 1989).

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 (HSDB 1995).

Aluminum production in the United States in 1973 amounted to 4.5 million tons (9 billion pounds), representing an increase of 10% over that produced in 1972 (Stokinger 1981). In 1982, the United States produced 3.3 million tons (6.6 billion pounds). More recently, aluminum production has declined slightly from 1991 through 1996 (USGS 1996, 1997a). Annual primary production of aluminum in thousand metric tons was 4,121 (9.1 billion pounds), 4,042 (8.9 pounds), 3,695 (8.1 billion pounds), 3,299 (7.3 billion pounds), 3,375 (7.4 billion pounds), 3,577 (7.9 billion pounds), 3,603 (7.9 billion pounds), 3,700 (8.1 billion pounds) in 1991, 1992, 1993, 1994, 1995, 1996, 1997, and 1998, respectively (USGS 1996, 1997a, 1998,1999). During this same period, secondary recovery of aluminumfromnew or old scrap aluminum increased slightly. The volume of secondary recovery of aluminum (from old and new scrap) in thousand metric tons was 2,290 (5 billion pounds), 2,760 (6.1 billion pounds), 2,940 (6.5 billion pounds), 3,090 (6.8 billion pounds), 3,190 (7 billion pounds), 3,310 (7.3 billion pounds), and 3,690 (8.1 billion pounds) in 1991, 1992, 1993, 1994, 1995, 1996, and 1997 respectively (USGS 1996, 1997b). Primary aluminum was produced in 43 countries worldwide in 1996 (USGS 1997b). The United States was the largest single producer with 17% of the total world production, followed by Russia with 14%, and Canada with 11% (USGS 1997b).

Table 4-1 lists the facilities in each state that manufacture or process aluminum the intended use, and the range of maximum amounts of aluminum that are stored on site. The data listed in Table 4-1 is derived from the Toxics Release Inventory (TR196 1998). Only certain types of facilities were required to report (EPA 1995e). Therefore, this is not an exhaustive list.

With respect to aluminum compounds, annual production capacity for aluminum chloride (anhydrous) in thousand metric tons was 34 (75 million pounds), 37 (82 million pounds), 46 (101 million pounds),

Table 4-1. Facilities That Manufacture or Process Aluminum and Its Compounds

State[a]	Number of facilities	Range of maximum amounts on site[b] (in pounds)	Activities and uses[c]
AL	8	1,000–999,999	1, 5, 7, 8, 9, 11, 12
AR	10	0–999,999	1, 5, 6, 8, 9
AZ	1	1,000–9,999	1, 5, 7
CA	13	0–9,999,999	1, 3, 4, 5, 8, 9, 13
CT	2	0–99,999	1, 5, 8, 9, 12
GA	3	1,000–99,999	1, 5, 6
IA	7	1,000–9,999,999	1, 5, 7, 8, 9
IL	27	0–9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13
IN	25	0–9,999,999	1, 3, 4, 5, 7, 8, 9, 10, 12, 13
KS	2	1,000–99,999	8, 12
KY	10	0–9,999,999	1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 13
LA	1	100,000–9,999,999	7
MA	3	1,000–99,999	2, 3, 4, 8
MD	3	1,000–999,999	1, 5, 9
ME	1	10,000–99,999	9
MI	12	1,000–999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11
MN	5	1,000–999,999	1, 5, 7, 8, 9, 11, 12
MO	9	1,000–999,999	1, 3, 4, 5, 7, 8, 9, 10, 13
MS	1	100,000–999,999	11, 12
NC	7	0–99,999	1, 5, 7, 9, 10
NJ	5	1,000–9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 11
NY	4	10,000–99,999	1, 2, 3, 4, 5, 8, 9, 10
OH	34	100–9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
OK	4	1,000–999,999	1, 5, 6, 8, 10
OR	4	1,000–9,999,999	10, 12, 13
PA	24	100–9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13
SC	4	0–99,999	1, 2, 3, 5, 7, 10, 13
TN	16	1,000–49,999,999	1, 2, 3, 4, 5, 6, 7, 9, 10
TX	7	1,000–999,999	1, 3, 4, 5, 7, 8, 9, 12
UT	3	10,000–9,999,999	8, 9, 12
VA	3	0–9,999	1, 5, 12
WA	2	10,000–99,999	1, 6, 8, 9
WI	13	100–999,999	1, 5, 8, 9
WV	2	1,000–9,999,999	7, 9

Source: TRI96 1998

[a]Post office state abbreviations used
[b]Range represents maximum 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

51 (112 million pounds), and 54 (119 million pounds) in 1988, 1990, 1992, 1994, and 1995, respectively (SRI 1988,1990, 1992,1994,1995).

Annual production capacity for aluminum oxide (alumina, calcined, reduction grade) in thousand metric tons was 4,896 (10.8 billion pounds), 5,245 (11.6 billion pounds), 4,980 (11 billion pounds), 4,980 (11 billion pounds), and 5,035 (11.1 billion pounds) in 1988, 1990, 1992, 1994, and 1995, respectively (SRI 1988, 1990, 1992, 1994, 1995). Table 4-2 lists the facilities in each state that manufacture or process aluminum oxide, the intended use, and the range of maximum amounts of aluminum oxide that are stored on site. The data listed in Table 4-2 is derived from the Toxics Release Inventory (TR196 1998). Only certain types of facilities were required to report (EPA 1995e). Therefore, this is not an exhaustive list. Small quantities of highly purified aluminum oxide are now produced for use in systems that measure doses of ionizing radiation (McKeever et al. 1995).

Aluminum sulfate was ranked 43rd among the top 50 chemicals produced in the United States in both 1993 and 1994 (Kirschner 1995). Annual U.S. production of aluminum sulfate has remained relatively constant from 1984 to (Kirschner 1995). Annual production (in thousand metric tons) was 1,129 (2.5 billion pounds), 1,268 (2.8 billion pounds), 1,222 (2.7 billion pounds), 1,227 (2.7 billion pounds), 1,237 (2.7 billion pounds), 1,243 (2.7 billion pounds), 1,227 (2.7 billion pounds), 1,185 (2.6 billion pounds), 1,047 (2.3 billion pounds), 1,050 (2.4 billion pounds), and 1,149 (2.5 billion pounds), in 1984, 1985, 1986, 1987, 1988, 1989, 1990, 1991, 1992, 1993, and 1994, respectively (Kirschner 1995).

4.2 IMPORT/EXPORT

Limited data are available regarding the import and export of aluminum by the United States. A total of 1,484 million pounds and 1,000 million pounds of aluminum were imported by the United States in 1972 and 1975, respectively (HSDB 1995). More recently, import volumes (in thousand metric tons) were 1,490 (3.3 billion pounds), 1,730 (3.8 billion pounds) 2,540 (5.6 billion pounds), 3,380 (7.4 billion pounds), 2,970 (6.5 billion pounds), 2,810 (6.2 billion pounds), and 3,100 (6.8 billion pounds) from 1991, 1992, 1993, 1994, 1995, 1996, and 1997, respectively (USGS 1996, 1997a). U.S. imports for consumption decreased in 1995, reversing an upward trend that began in 1992. Although imports of semifabricated materials and scrap increased in 1995, crude metal and alloy imports decreased significantly compared to those in 1994 (USGS 1996, 1997a).

Table 4-2. Facilities That Manufacture or Process Aluminum Oxide

State[a]	Number of facilities	Range of maximum amounts on site[b] (in pounds)	Activities and uses[c]
CA	3	10,000–999,999	2, 4, 7, 8, 12, 13
CT	1	10,000–99,999	12
GA	2	1,000–999,999	2, 3, 4, 9
IA	2	1,000–9,999	12
IL	1	1,000–9,999	12
IN	5	1,000–999,999	9, 12, 13
KY	2	1,000–99,999	8, 12
MI	2	1,000–99,999,999	9, 12
MN	1	1,000–9,999	2, 3, 12
MS	1	1,000–9,999	13
NC	1	1,000–9,999	12
NY	3	10,000–9,999,999	2, 4, 10, 12
OH	7	1,000–99,999	5, 9, 10, 12, 13
PA	2	0–999,999	9, 12
TN	2	10,000–999,999	8, 9
TX	2	10,000–99,999	8, 11
VA	1	10,000–99,999	12
WI	5	1,000–99,999	8, 9, 12

Source: TRI96 1998

[a]Post office state abbreviations used
[b]Range represents maximum 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

A total of 527 million pounds and 747 million pounds of aluminum were exported by the United States in 1972 and 1975, respectively. More recently, total exports of aluminum from the United States continued to increase in 1995, reaching their highest level since 1991 (USGS 1996, 1997a). Export volumes in thousand metric tons were 1,760 (3.9 billion pounds), 1,450 (3.2 billion pounds), 1,210 (2.7 billion pounds), 1,370 (3.0 billion pounds), 1,610 (3.5 billion pounds), 1,500 (3.3 billion pounds), and 1,600 (3.5 billion pounds) (January through November total) from 1991, 1992, 1993, 1994, 1995, 1996, and 1997, respectively (USGS 1996, 1997a).

4.3 USE

Aluminum metal and compounds have a wide variety of uses (Anusavice 1985; Browning 1969; Budavari et al. 1989; Frank and Haupin 1985; Hawley 1977; HSDB 1995; Locock 1971; Staley and Haupin 1992; Stokinger 1981; Venugopal and Lucky 1978). Most primary aluminum is used for metallurgical purposes; 85-90% of these uses are in the production of aluminum-based alloy castings and wrought aluminum products. Pure aluminum is soft and lacks strength. By forming alloys, one can increase the strength, hardness and add other useful properties to the metal while building on the inherent properties of aluminum of low density, high electrical and thermal conductivity, high reflectivity, and corrosion resistance. In speaking of the uses of metallic aluminum one is therefore referring to the uses of aluminum and its alloys.

The major uses of aluminum and its alloys are in packaging, building and construction, transportation, and electrical applications. Over 95% of beer and carbonated drinks are packaged in two-piece aluminum cans. Aluminum sheet and foil, are used in pie plates, frozen food trays and other packaging applications. In construction, aluminum is used for siding and roofing, doors, and windows. Aluminum is used in the bodies, trim and mechanical parts of cars, trucks, airplanes, ships, and boats, as well as other transportation-related structures and products such as bridges and highway signs. Electrical applications include overhead transmission lines, cable sheathing, and wiring. Other applications of aluminum include die-cast auto parts, corrosion-resistant chemical equipment, cooking utensils, decorations, fencing, sporting equipment, toys, lawn furniture, jewelry, paint, and in dental alloys for crowns and dentures. Other uses include absorbing occluded gases in the manufacture of steel; testing for gold, arsenic, and mercury; precipitating copper, as a reducer for determining nitrates and nitrites; in coagulating colloidal solutions of arsenic or antimony; in explosives; and in flashes for photography. Aluminum powder is used in paints, protective coatings, and fireworks.

The transportation and container and packaging industries remained the dominant domestic markets for aluminum products in 1997. The transportation industry accounted for an estimated 34% of domestic consumption; containers and packaging, 25%; building and construction, 15%; electrical and consumer durables, 8% each; and other uses (including machinery and equipment), 10% (USGS 1997a).

Aluminum compounds and materials also have a wide range of uses summarized below (Anusavice 1985; Browning 1969; Budavari et al. 1989; Hawley 1977; Locock 1971; Sax and Lewis 1987; Stokinger 1981; Venugopal and Lucky 1978). Naturally occurring aluminum-containing minerals, such as bentonite and zeolite, are used in water purification, sugar refining, and in the brewing and paper industries.

Aluminum chloride 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 (HSDB 1995). 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 (Budavari et al. 1989).

Aluminum chlorohydrate is the active ingredient in many antiperspirants and deodorants (Budavari et al. 1989; Hawley 1977; Sax and Lewis 1987).

Aluminum hydroxide is used in stomach antacids (including Maaloxe, Mylantae, and Delcide), as a desiccant powder; in antiperspirants and dentifrices; in packaging materials; as a chemical intermediate; as a filler in plastics, rubber, cosmetics, and paper; as a soft abrasive for brass and plastics; as a glass additive to increase mechanical strength and resistance to thermal shock, weathering, and chemicals; and in ceramics (HSDB 1995). Aluminum hydroxide is also used pharmaceutically to lower the plasma phosphorus levels of patients with renal failure (Budavari et al. 1989; Sax and Lewis 1987).

Aluminum nitrate is used in antiperspirants, for tanning leather, as a corrosion inhibitor, in the preparation of insulating papers, on transformer core laminates, in incandescent filaments, and in cathode ray tube heating elements (HSDB 1995).

Ahuninum oxide is used in the production of aluminum; manufacture of abrasives, refractories, 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 1995). A recent 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 over-the-counter stomach antacids (Budavari et al. 1989; Sax and Lewis 1987).

Aluminum phosphide is used as an insecticidal grain fumigant (Budavari et al. 1989).

Aluminum sulfate is used primarily for water purification systems and sewage treatment systems as a flocculent, in the paper and pulp industry, in fireproofing and waterproofing cloth, clarifying oils and fats, waterproofing concrete, in antiperspirants, in tanning leather, as a mordant in dyeing, in agricultural pesticides, as an intermediate in the manufacture of other chemicals, as a soil conditioner to increase acidity for plants (e.g., rhododendrons, azaleas, camellias, and blueberries), and in cosmetics and soap. A saturated solution of aluminum sulfate is employed as a mild caustic. Solutions containing 5-10% aluminum sulfate have been used as local applications to ulcers and to arrest foul discharges from mucous surfaces. Aluminum sulfate is also used in the preparation of aluminum acetate ear drops (HSDB 1995). With respect to use application, about 65% of the aluminum sulfate produced is used for water and sewage treatment (HSDB 1995).

Little information was located regarding the amounts of aluminum or aluminum compounds used by various industries or in various products.

4.4 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 7.

According to the Toxic Chemical Release Inventory, in 1996, an estimated 12,754 pounds of aluminum (fume or dust) were released by manufacturing and processing facilities to publicly owned-treatment works (POTWs) and an estimated 30,93 1,000 pounds were transferred off-site (TR196 1998). In addition, an estimated 1,328 pounds of aluminum oxide also were released by manufacturing and processing facilities to POTWs and an estimated 9527,000 pounds of aluminum oxide were transferred off-site (TR196 1998). The TRI data should be used with caution because only certain types of facilities are required to report (EPA 1995e). This is not a exhaustive list.

Aluminum recovered from purchased scrap increased to approximately 3.2 million tons (6.4 billion pounds) in 1995. Fifty-three percent of this recovered metal came from new (manufacturing) scrap and 47% from old scrap (discarded aluminum products). The recycling rate for used aluminum beverage can scrap decreased slightly from 65.4% in 1994 to 62.2% in 1995. During 1995, 62.7 billion used aluminum beverage cans were recycled in the United States. Aluminum beverage cans produced domestically in 1995 had an average of 51.3% post-consumer recycled content, the highest percentage of recycled content of all recyclable packaging materials (USGS 1996).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Aluminum, a silver-white, malleable, and ductile metal, is the most abundant metallic element in the lithosphere, comprising about 8% of the earth's crust. It is never found free in nature, but occurs combined with other elements, most commonly as aluminosilicates, oxides, and hydroxides in rock, minerals, clays, and soil. It is also present in air, water, and many foods. Bauxite, a weathered rock consisting primarily of aluminum hydroxide minerals, is the primary ore used in aluminum production. 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 earths crust, natural weathering processes far exceed the contribution of releases to air, water, and land associated with human activities.

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.

Aluminum is not bioaccumulated to a significant extent. Notable exceptions include some herbs and the tea plant, which can accumulate aluminum to 3,000-4,000 ppm and to 10,000 ppm respectively. 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. Similarly, because of its toxicity to many aquatic organisms, including fish, aluminum does not bioconcentrate in aquatic organisms to any significant degree. In order to bioaccumulate in the food chain, a substance cannot be acutely toxic to links in the chain; otherwise, the bioaccumulation stops.

Background levels of aluminum in rural air typically range from 0.005 to 0.18 ng/m^3, whereas levels in urban and industrial areas can be considerably higher, ranging from 0.4 to 10 ng/m^3. Concentrations of aluminum are highly variable in drinking water, ranging from <1 ppb to 1,029 ppb (Schenck et al. 1989). The use of alum (aluminum sulfate) as a flocculent in water treatment facilities is the usual cause of

higher levels of aluminum in finished drinking water. The median level of aluminum in drinking water not receiving coagulation treatment is 0.043 mg/L, while that receiving coagulation treatment is 0.224 mgL Dissolved aluminum levels 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, levels in most surface water are very low. Aluminum is the third most common element in soil. Its concentration ranges widely from about 0.07% by weight (700 ppm) to 10% (100,000 ppm) with a typical concentration of about 7.1% (7 1,000 ppm).

Daily exposure to aluminum is inevitable due to its abundance and ubiquitous occurrence in nature and its diverse use by man. The general population is exposed to aluminum through consumption of food (including infant formula) and drinking water and through inhalation of airborne dust particulates, as well as through the use of such consumer items as antiperspirants, cosmetics, internal analgesics (buffered aspirins), anti-ulcerative medications, antidiarrheals, and antacids which contain aluminum compounds. The intake of aluminum from food and drinking water is very low, especially compared with that consumed by people taking aluminum-containing medicinal preparations, such as antacids. 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.

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, buffered analgesics, antidiarrheal medications, or vitamins and food supplements may also be exposed to high levels of aluminum.

According to the Toxic Chemical Release Inventory, in 1996, total releases of aluminum to the environment (including air, water, and soil) from 264 large processing facilities were 5,605,000 pounds (TR196 1998). In addition, in 1996, total releases of aluminum oxide to the environment (including air, water, and soil) from 41 large processing facilities were 466,000 pounds (TR196 1998). Tables 5-l and 5-2 list amounts released from these facilities grouped by state. The TRI data should be used with

Table 5-1. Releases to the Environment from Facilities that Manufacture or Process Aluminum and Its Compounds

		Total of reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Land	Underground injection	Total environment[d]	POTW transfer	Off-site waste transfer
AL	8	53,599	1,000	500	0	55,099	250	32,705
AR	10	77,326	5,800	255	0	83,381	5	57,868
AZ	1	255	0	0	0	255	0	250
CA	12	304,213	755	11,272	0	316,240	255	117,377
CT	1	380	0	0	0	380	0	920
GA	3	13,675	0	34,000	0	47,675	750	555,600
IA	7	3,242	250	17,820	0	21,312	250	312,809
IL	26	138,826	0	930,704	0	1,069,530	5	698,069
IN	24	195,904	20	30,250	0	226,174	264	2,592,215
KS	1	0	0	0	0	0	0	7,585
KY	10	285,965	516	1,218,950	0	1,505,431	371	509,755
LA	1	13	0	0	0	13	0	0
MA	3	260	0	0	0	260	0	930
MD	3	21,250	10	1,075	0	22,335	0	78,145
ME	1	12	0	0	0	12	0	13,580
MI	12	39,772	260	9,733	0	49,765	2,510	1,689,621
MN	5	17,637	6	0	0	17,643	0	293,302
MO	9	105,731	250	26,258	0	132,239	250	2,856,335
MS	1	24,750	0	750	0	25,500	6,500	11,000
NC	7	31,318	0	2,100	0	33,418	0	225,924
NJ	4	4,959	0	0	0	4,959	0	1,312
NY	4	1,522	0	0	0	1,522	0	56,000
OH	32	134,953	1,293	0	0	136,246	0	2,075,492

Table 5-1. Releases to the Environment from Facilities that Manufacture or Process Aluminum and Its Compounds *(continued)*

		Total of reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Land	Underground injection	Total environment[d]	POTW transfer	Off-site waste transfer
OK	4	7,857	0	0	0	7,857	0	597,816
OR	4	3,063	0	0	0	3,063	0	3,591,260
PA	22	36,102	35,778	633	0	72,513	250	829,067
SC	3	8,429	0	0	0	8,429	0	1,925,544
TN	16	33,378	68	1,587,770	0	1,621,216	6	6,397,157
TX	7	57,993	94	0	0	58,087	0	28,106
UT	3	11,635	0	0	0	11,635	0	45,400
VA	3	15,352	94	0	0	15,446	0	184,870
WA	2	482	0	0	0	482	0	260,002
WI	13	52,714	0	837	0	53,551	1,088	4,884,488
WV	2	700	2,795	0	0	3,495	0	5
Totals	**264**	**1,683,267**	**48,989**	**3,872,907**	**0**	**5,605,163**	**12,754**	**30,930,509**

Source: TRI96 1998

[a]Data in TRI are reported amounts released by each facility
[b]Post office state abbreviations used
[c]The sum of fugitive and stack releases are included in releases to air by a given facility
[d]The sum of all releases of the chemical to air, land, and water, and underground injection wells
POTW = publicly-owned treatment works

Table 5-2. Releases to the Environment from Facilities that Manufacture or Process Aluminum Oxide

		Total of reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Land	Underground injection	Total environment[d]	POTW[e] transfer	Off-site waste transfer
CA	2	692	0	0	0	692	0	98,279
CT	1	5	5	0	0	10	250	12,363
GA	2	750	250	45,000	0	46,000	0	64,300
IA	2	12,250	0	0	0	12,250	0	56,160
IL	1	0	0	0	0	0	250	41,200
IN	5	51,306	250	17,000	0	68,556	0	220,946
KY	2	5	0	0	0	5	323	11,133
MI	2	0	0	295,360	0	295,360	250	250
MN	1	255	0	0	0	255	0	0
MS	1	0	0	0	0	0	0	14,470
NC	1	0	0	0	0	0	0	64,980
NY	3	750	0	0	0	750	250	179,312
OH	7	24,214	0	0	0	24,214	0	414,294
PA	2	147	0	0	0	147	0	160,160
TN	2	0	0	0	0	0	5	56,036
TX	3	15,232	0	290	0	15,522	0	6,300
VA	1	0	0	0	0	0	0	36,000
WI	5	1,785	0	0	0	1,785	0	8,090,960
Totals	**43**	**107,391**	**505**	**357,650**	**0**	**465,546**	**1,328**	**9,527,143**

Source: TRI96 1998

[a]Data in TRI are reported amounts released by each facility
[b]Post office state abbreviations used
[c]The sum of fugitive and stack releases are included in releases to air by a given facility
[d]The sum of all releases of the chemical to air, land, and water, and underground injection wells
[e]POTW = publicly-owned treatment works

caution because only certain types of facilities are required to report (EPA 1995e). This is not an exhaustive list.

Aluminum has been identified in at least 427 of 1,428 hazardous wastes sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 1996). However, the number of sites evaluated for aluminum is not known. The frequency of these sites within the United States can be seen in Figure 5-l. Of these sites, 425 are located in the United States and 2 are located in the Commonwealth of Puerto Rico (not shown).

5.2 RELEASES TO THE ENVIRONMENT

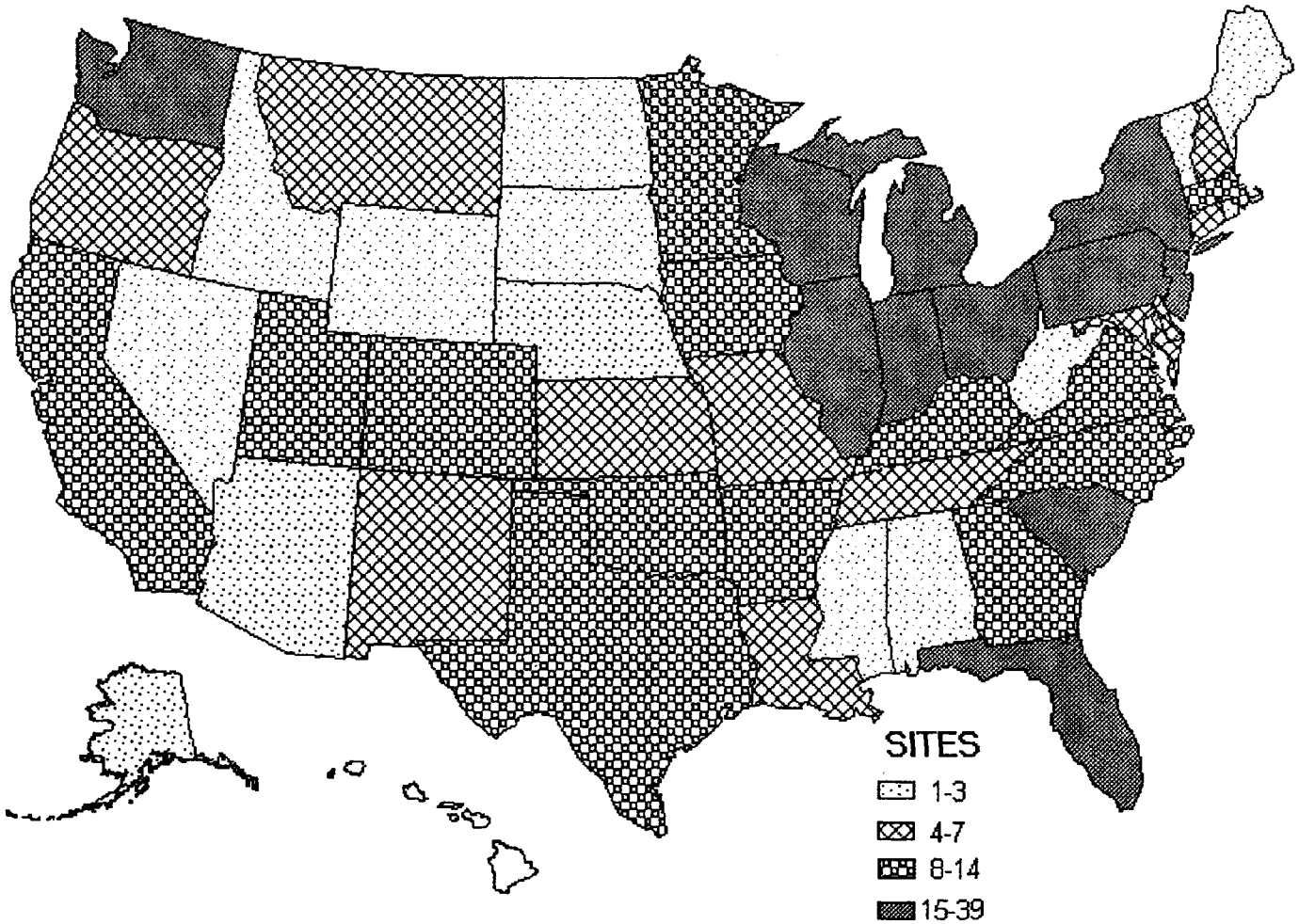
Aluminum is released to the environment by both natural processes and anthropogenic sources. Because of its prominence as a major constituent of the earth's crust, natural processes far exceed the contribution of anthropogenic releases to the environmental distribution of aluminum (Lantzy and MacKenzie 1979). Anthropogenic releases are primarily to the atmosphere.

According to the Toxic Chemical Release Inventory, in 1996, a reported total of 5,605,000 pounds of aluminum were released to the environment (air, water, and soil) from 264 large processing facilities (TR196 1998). In addition, 466,000 pounds of aluminum oxide were released to the environment (air, water, soil) from 41 large processing facilities (TR196 1998). Tables 5-1 and 5-2 list amounts released from these facilities. An additional reported 12,754 pounds of aluminum were released by manufacturing and processing facilities to POTWs and a reported 30,93 1,000 pounds were transferred off-site (TR196 1998). A reported 1,328 pounds of aluminum oxide also were released by manufacturing and processin& facilities to POTWs and an estimated 9,527,000 pounds of aluminum oxide were transferred off-site (TR196 1998). The TRI data should be used with caution because only certain types of facilities are required to report (EPA 1995e). This is not an exhaustive list.

5.2.1 Air

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, a significant amount of aluminum-containing dust is generated by volcanic activity. Human activities, such as mining

Figure 5-1. Frequency of NPL Sites with Aluminum Contamination



Derived from HazDat 1998

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).

According to the Toxic Chemical Release Inventory, in 1996, the estimated releases of aluminum of 1,683,000 pounds to the air from 264 large processing facilities accounted for about 30% of total environmental releases (TR196 1998). Also, in 1996, the reported releases of aluminum oxide of 107,000 pounds to the air from 41 large processing facilities accounted for 23% of total environmental releases for this aluminum compound (TR196 1998). Tables 5-1 and 5-2 list amounts released from these facilities for aluminum and aluminum oxide respectively. The TRI data should be used with caution because only certain types of facilities are required to report (EPA 1995e). This is not an exhaustive list.

Aluminum has been identified in air samples collected at 9 of the 427 NPL hazardous waste sites where it has been detected in some environmental media (HazDat 1996).

5.2.2 Water

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 Campell 1991; Rosseland et al. 1990).

Aluminum levels 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 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 (Malmberg 1985; Miller et al. 1984; Qureshi and Sung 1984). 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).

According to the Toxic Chemical Release Inventory, in 1996, the reported releases of 48,989 pounds of aluminum to water from 264 large processing facilities accounted for 0.9% of the total environmental releases (TR196 1998). An additional 12,754 pounds of aluminum were released indirectly to POTWs and some of this mass ultimately may have been released to surface waters. Also, in 1996, the reported releases of 505 pounds of aluminum oxide to water from 43 large processing facilities accounted for 0.1% of the total environmental releases (TR196 1998). An additional 1,328 pounds were released indirectly to POTWs and some of this mass ultimately may have been released to surface waters. Tables 5-1 and 5-2 list amounts released from these facilities for aluminum and aluminum oxide, respectively. The TRI data should be used with caution because only certain types of facilities are required to report (EPA 1995e). This is not an exhaustive list.

Aluminum has been identified in surface water, leachate, and groundwater samples collected at 227,54, and 336 of the 427 NPL hazardous waste sites, respectively, where it has been detected in some environmental media (HazDat 1996).

5.2.3 Soil

Aluminum is the third most abundant element in the soil, constituting about 8% of the minerals (Rosseland et al. 1990). This element can be released naturally by the weathering of aluminumcontaining 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 (Gabler and Stroll 1983; Krishnaswamy 1984).

According to the Toxic Chemical Release Inventory, in 1996, reported releases of 3873,000 pounds of aluminum to soil from 264 large processing facilities accounted for 69% of total environmental releases of aluminum (TR196 1998). Also, in 1996, reported releases of 358,000 pounds of aluminum oxide to soil from 43 large processing facilities accounted for 77% of total environmental releases (TR196 1998). No aluminum or aluminum oxide was released via underground injection in 1996. Tables 5-1 and 5-2 list amounts released from these facilities for aluminum and aluminum oxide, respectively. The TRI data should be used with caution because only certain types of facilities are required to report (EPA 1995e). This is not a exhaustive list.

Aluminum has been identified in soil and sediment samples collected at 203 and 151 of the 427 NPL hazardous waste sites, respectively, where it has been detected in some environmental media (HazDat 1996).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Aluminum occurs widely in nature in silicates such as micas and feldspars, complexed with sodium and fluorine as cryolite, and in bauxite rock, which is composed of hydrous aluminum oxides, aluminum hydroxides, and impurities such as free silica (Cotton and Wilkinson 1988). Because of its reactivity, aluminum is not found as a free metal in nature (Bodek et al. 1988). Aluminum exhibits only one oxidation state (+3) in its compounds and its 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 the chemical properties of the element itself and the characteristics of the environmental matrix that affect 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 $Al\text{-}SO_4$ and $A1^{3+}$ 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 or 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 ($Al(SO_4)(OH)\bullet H_2O$) 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). This is most likely due to the higher solubility of aluminum nitrate than aluminum sulfate. 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 alkahnized 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 recent study, the wet and dry deposition of aluminum was measured biweekly for one 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).

The mobilization of aluminum by acid rain results in more aluminum being available for plant uptake (Brusewitz 1984). 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). Because the tea plant, *Symplocos spicata,* is able to grow in very acidic soils, where aluminum is readily available for uptake by the roots, high concentrations of aluminum may be found in the leaves which serve as a sink for the aluminum (Lewis 1989). 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 (Baes et al. 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 $(kg\text{-}day)^{-1}$ for uptake into milk and 0.0015 $(kg\text{-}day)^{-1}$ for uptake into beef tissue have been reported (Baes et al. 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). Then Cleveland et al. (1991) reported that the estimated steady-state bioconcentration factors (BCF) values for aluminum in brook trout, (which were inversely related to pH), were 215 at pH 5.3, 123 at pH 6.1, and 36 at pH 7.2. The maximumBCFs were 232 at pH 5.3, 153 at pH 6.1, and 46 at pH 7.2. 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 gillassociated 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. Most recently, Buckler et al. (1995) reported concentrations of aluminum in whole-body tissue of the Atlantic sahnon 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 levels 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. A BCF value of 0.13-0.5 in the whole-body was 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 (ppm) dry weight (d/w) in crayfish from roadside ditches ranged from 1.75-6.39 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 d/w) 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 sulphureu)* at low pH (4.5). The nymphs were exposed at 2 concentrations (0.2 and 2 mg inorganic aluminum per liter) and for 2 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 2 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 (*Ficedulu 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 dulecarlica* from the River Lestijoki in Western Finland. The concentrations of aluminum in the water were low (87-196 μg/L [ppb]) due to the high pH values; however, the concentrations in the young terminal shoots of *F. dulecarlica* appeared to be quite high (303-1 ,852 1-1 μ/g [ppm] 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 3 acidified (pH≈ 5) and 3 nonacidified (pH≈ 6.5) constructed wetlands. They found that the metal content of *Sparganium americanum* (bur-reed) was only slightly affected by acidification.

5.3.2 Transformation and Degradation

Because aluminum is an element, its atoms do not degrade in the environment. In addition, aluminum compounds occur in only one oxidation state, Al(+3). Aluminum can complex with electron-rich species that occur in the environment. The forms of aluminum encountered in a natural system are determined by the strength of the attraction between the positively charged aluminum and the anionic or negatively charged ligands, and the preponderance and types of ligands that are present. These factors will be influenced by pH.

5.3.2.1 Air

Aluminum-containing particulate matter in the atmosphere is mainly derived from soil and industrial processes where crustal material (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. Should aluminum metal particles be released during metal processing, they would be rapidly oxidized.

5.3.2.2 Water

The trivalent aluminum ion is surrounded by six water molecules in solution (Cotton and Wilkinson 1988). The hydrated aluminum ion undergoes "hydrolysis," in which a stepwise replacement of

coordinated "water of hydration" molecules by hydroxyl ions occurs with the release of a proton from each water molecule into solution (Snoeyink and Jenkins 1980). This results in the formation of hydroxyaluminum species such as $AI^{2}(OH_{2}^{4},Al(OH)_{3}$ (insoluble), and $AI(OH)_{4}^{-}$ (Snoeyink and Jenkins 1980). Additional hydrated species such as $Al_{2}(OH)_{2}^{4+}$ $Al(OH)_{5}^{-2}$ and hydroxy polymers such as $Al_{13}(OH)_{32}^{7+}$ have been reported (Bodek et al. 1988; Martell and Motekaitis 1989). The hydrated trivalent aluminum ion is the predominant form at pH levels below 4. Between pH 5 and 6, the predominant hydrolysis products are $AI(OH)^{2+}$ and $AI(OH)_{2}$+ while the solid $Al(OH)_{3}$ is most prevalent between pH 5.2 and 8.8 (Mar-tell and Motekaitis 1989). 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 and Wilkinson 1988). 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 (Hemenway and Fitzgerald 1984). Aluminum has a stronger attraction for fluoride in an acidic environment compared to other inorganic ligands (Brusewitz 1984), and fluoride complexes of aluminum have been shown to be more toxic to fish than aluminum-organic complexes are (Plankey and Patterson 1987). 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.

5.3.2.3 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 kaolin&e 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 electron rich species such as fluoride, sulfate, and phosphate.

5.4 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. 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 various environmental media are detailed in Chapter 6.

5.4.1 Air

Aluminum is found in the atmosphere mainly as aluminosilicates associated with crustal particulate matter. 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 levels of aluminum in the atmosphere generally range from 0.005 to 0.18 ng/m^3 (Hoffman et al. 1969; Poetzl 1970; Sorenson et al. 1974). In rural areas of Hawaii, aluminum concentrations have been measured at a range of 0.005-0.032 ng/m^3 (Hoffman et al. 1969), whereas a concentration range of 0.27-0.39 ng/m^3 has been reported in Manitoba National Park in Canada (Rahn 197 1). Atmospheric aluminum concentrations in U.S. cities and industrial areas are considerably higher, ranging from about 0.4 to 10 ng/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 and East St. Louis were 22-539 ng/m^3

(125 ng/m^3 mean) and 24-1370 ng/m^3 (153 ng/m^3 mean), respectively for tine particles and 8.2-1760 ng/m^3 (390 ng/m^3 mean) and 17-2120 ng/m^3 (442 ng/m^3 mean), respectively for coarse particles. At a rural site (Bondville, IL), the aluminum concentrations in fine and coarse particles were 32-293 ng/m^3 (95 ng/m^3 mean) and 32-3120 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).

Aluminum levels can also vary with seasonal meteorological conditions. For example, in Mackinac Island, Michigan, summer levels averaged about 0.25 ng/m^3, while winter levels were only about 0.18 ng/m^3 (Rahn 1971).

Aluminum has been identified in air samples collected at 9 of the 427 NPL hazardous waste sites where it has been detected in som environmental media (HazDat 1996).

5.4.2 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 pH 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 (ppm) (Brusewitz 1984; Miller et al. 1984; Sorenson et al. 1974; Taylor and Symons 1984). However, even at neutral pH levels, higher aluminum levels have been found in lakes with a high humic acid content (Brusewitz 1984). 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 (ppm) 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 greater than 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 levels of 6.0 to 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 (ppm) with a mean concentration of 0.074 mg/L (ppm) in 456 of 1,577 raw surface water samples collected during a 5-year survey at various locations across the United States (Kopp and Kroner 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 (ppm) with a mean of 0.179 mg/L (ppm) (Kopp and Kroner 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 (ppm), while the maximum and minimum levels were 2.67 mg/L (ppm) and 0.051 mg/L (ppm) respectively (Miller et al. 1984). These authors further reported that the median aluminum concentration in finished water that received no coagulation treatment was 0.043 mg/L (ppm) (range, 0.016-1.167 mg/L) compared to the median of 0.112 mg/L (ppm) (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 aluminumlevels 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 greater than 0.05 mg/L. In another study, the aluminum content in treated water at facilities using alum coagulation treatment of raw waters ranges from about 0.01 to 1.3 mg/L (ppm) with a mean of about 0.157 mg/L (ppm) (Letterman and Driscoll 1988).

Most recently, Schenck 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 (Table 5-3). Although aluminumlevels in household tap water may range from 0 to 1.029 mg/L (ppm), aluminum levels in most drinking water in the United States were <0.1 ppm (Schenck et al. 1989). While several water sources in the west coast states (California, Oregon, and Washington) were found to contain undetectable levels of aluminum (<0.001 ppm), several cities in other geographic areas of the U.S. had high aluminum concentrations (>0.4 ppm). These included Peoria, Illinois (0.467 ppm); Coos Bay, Oregon (0.483 ppm); Watertown, South Dakota (0.502 ppm); Waco, Texas (0.520 ppm); Yellowstone National Park, Wyoming (0.608 ppm); Philadelphia, Pennsylvania (0.688 ppm); and Charleston, South Carolina (1.029 ppm).

Aluminum has been measured in atmospheric precipitation (i.e., rain and snow) in the United States at concentrations up to 1.2 mg/L (ppm) (Dantzman and Breland 1970; Feth et al. 1964; Fisher et al. 1968; Norton 1971). Most recently, aluminum has been measured in rainwater samples collected on-board

Table 5-3. Aluminum Concentrations Detected in Drinking Water in Various Regions of the United States

U.S. States	Aluminum Concentration (ppb)[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

Source: Schenk et al. 1989

[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)

ship 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 3 rainfall events in the North Atlantic were 33.7, 12.2, and 1.99 μg/L (ppb). Overall, the acid-leached concentrations of aluminum in rainwater for seven rainfall events ranged from 1.14 to 35.2 μg/L (ppb). These values were compared with acid-leachable aluminum concentrations in precipitation from remote areas which ranged from 2.1 to 15.44 μg/L (ppb) (Lim and Jickells 1990). Total (dissolved plus particulate) aluminum concentrations in North Atlantic precipitation samples collected in 1988 ranged from 6.1 to 824 μg/L (ppb). A comparison with atmospheric aluminum concentrations presented previously indicates that one liter of precipitation cleanses the aluminum from an equivalent of 0.5 to 7 million cubic meters of air.

Aluminum levels in marine waters tend to be much lower (i.e., <0.001 mg/L [<1 ppb]) than those found in fresh water lakes and streams (Brusewitz 1984), probably because of increased alkalinity in marine waters compared to fresh waters.

Aluminum levels in groundwater wells at neutral pH generally fall below 0.1 mg/L (100 ppb) (Brusewitz 1984). In areas receiving acid precipitation, aluminum levels in groundwater may be more than 10 times the levels 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. (1984) reported that the median concentration of aluminum in finished water obtained from groundwater was 0.031 mg/L (ppm) (range, 0.014-0.290 mg/L) as compared to the median concentration in surface water of 0.043 mg/L (ppm) (range, 0.016-l. 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 (ppm).

Aluminum has been identified in surface water, leachate, and groundwater samples collected at 227,54, and 336 of the 427 NPL hazardous waste sites, respectively, where it has been detected in some environmental media (HazDat 1996).

5.4.3 Sediment and Soil

Aluminum is the third most abundant element and the most common metal in the earth's crust, comprising about 8% of the lithosphere (Lide 1997). Its concentration in soils varies widely, ranging from about 0.07 percent by weight or 700 mg/kg (ppm) to over 10 percent by weight or 100,000 mg/kg (ppm) (Shacklette and Boerngen 1984; Sorenson et al. 1974). Data gleaned from texts and literature reviewed by soil scientists suggest a typical aluminum concentration in soil as 71,000 mg/kg (Frink 1996). 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). For example, in different soils of Missouri, aluminum concentrations ranged from 4,800 to 58,000 mg/kg (ppm) (USGS 1972). In Hawaii, aluminum contents were much higher with concentrations ranging from 79,000 to 317,000 mg/kg (ppm) (Moomaw et al. 1959). Soils in Florida and parts of Georgia, Texas, Oklahoma, and Michigan contain less than 20,000 mg/kg of soil, whereas soils from portions of the Pacific Northwest, New England, Colorado, and Nevada have concentrations greater than 80,000 mg/kg (Sparling and Lowe 1996). The aluminum content in cultivated and uncultivated soil samples collected during a number of field studies ranged from 7,000 mg/kg to over 100,000 mg/kg (ppm) (mean concentration of 33,000 mg/kg) for subsurface soils in the eastern United States, from 5,000 mg/kg to over 100,000 mg/kg (ppm) (mean concentration of 54,000 mg/kg) for subsurface soils in the western United States, and from 13,000 to 76,000 mg/kg (ppm) for surface horizon soils collected in Colorado (mean concentration of 57,000 mg/kg) (Connor and Shacklette 1975). The aluminum content of soils is strongly correlated with its clay content (Ma et al. 1997).

Aluminum levels in soil also vary with different vegetation types. For example, aluminum levels 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. An analysis of aluminum in soils by depth could improve the understanding of this process.

Aluminum has been identified in soil and sediment samples collected at 203 and 15 1 of the 427 NPL hazardous waste sites, respectively, where it has been detected in some environmental media (HazDat 1996).

5.4.4 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). Because of the variability of reported levels 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 5-4. Most unprocessed foods, (with the exception of some herbs and tea leaves) typically contain less than 5 mg/kg (ppm) aluminum (Greger 1992). Furthermore, only small quantities of herbs are consumed by most individuals, and most of the aluminum in tea leaves is in an insoluble form. The measured levels of aluminum in unprocessed foods range from about 0.1 mg/kg (ppm) in eggs, apples, raw cabbage, corn, and cucumbers to 7.16 mg/kg (ppm) in lettuce (Schenck et al. 1989). Unregulated and unanalyzed natural dietary supplements represent an uncertain introduction of aluminum into the diet.

It should be noted, however, that the aluminum content of some plants known to be aluminum accumulators can vary greatly, depending on the plant variety and soil conditions, including pH in which it is grown (Greger 1992). Preliminary data indicate that plants grown on soil amended with a low weight percentage of ash from power plants take up aluminum to a higher extent than from unamended soil (Bathe et al. 1991). This suggests that aluminumin ash is more available to plants than that in ordinary soil and that the aluminum content in plants will be affected by the nature of aluminum-containing amendments, both intentional and unintentional, to soil. The broad variation in the occurrence of aluminum in food plants is exemplified in the tea plant. The aluminum content in tea (1% extract) usually ranges from 0.378 to 2.445 mg/L (ppm). Because the tea plant is able to grow in very acidic soils, where aluminum is readily available for uptake by the roots, the tea leaves serve as a sink, accumulating up to 10,000 mg/kg (ppm) (Lewis 1989). However, herbal tea contains lower levels of aluminum than ordinary tea (0.140-1 .065 mg/L [ppm]) (Schenck et al. 1989). The aluminum content in ash samples from other cultivated plants (e.g., lima beans, cabbage, soybeans, and tomatoes) collected during a number of field studies in Georgia, Missouri, and Wisconsin ranged from 50 to 30,000 mg/kg (ppm) (mean concentration range: 200-1 ,700 mg/kg [ppm]) with the highest levels

Table 5-4. Estimated Aluminum Concentrations of Selected Foods

Foods	Aluminum concentration (μg/g)	Reference
Beverages (mg/L)		
Fruit juices (e.g., orange, reconstituted lemon, peach)	0.043–4.130	Derived from Schenk et al. 1989
Soft drinks (e.g., ginger ale, diet cola)	0.103–2.084	Derived from Schenk et al. 1989
Cola, carbonated	0.1	Pennington 1987
Alcoholic beverages (e.g., beer, wine, wine coolers, champagne)	0.067–3.20	Derived from Schenk et al. 1989
Beer, canned	0.07	Pennington 1987
Spirits (e.g., brandy, vodka, whiskey)	0.148–0.635	Derived from Schenk et al. 1989
Tea, steeped from tea bags	0.424–2.931	Derived from Schenk et al. 1989
Herbal teas (1% extract)	0.14–1.065	Derived from Schenk et al. 1989
Tea, steeped	4.3	Greger et al. 1985b
Instant coffee (1% solution)	0.02–0.581	Derived from Schenk et al. 1989
Whole coffee (3% extract)	0.235–1.163	Derived from Schenk et al. 1989
Animals Products		
Beef, cooked[a]	0.2[b]	Greger et al. 1985b
Cheese (e.g., Swiss, cheddar, bleu)	3.83–14.10	Derived from Schenk et al. 1989
Cheese, cheddar	0.2	Pennington 1987
Cheese, cottage, creamed	0.1	Pennington 1987
Cheese, processed	297[b]	Greger et al. 1985b
Chicken, with skin, cooked[a]	0.7	Greger et al. 1985b
Egg	0.107	Derived from Schenk et al. 1989
Eggs, scrambled	2.865	Derived from Schenk et al. 1989
Eggs, cooked[a]	0.1	Greger et al. 1985b
Fish (cod), cooked[a]	0.4	Greger et al. 1985b
Fish, salmon	5.44	Derived from Schenk et al. 1989
Fish, herring	0.127	Derived from Schenk et al. 1989
Ham, cooked[a]	1.2	Greger et al. 1985b

Table 5-4. Estimated Aluminum Concentrations of Selected Foods *(continued)*

Foods	Aluminum concentration (μg/g)	Reference
Milk, whole	0.06	Pennington 1987
Milk (skim, whole, and powdered)	0.102–1.409	Derived from Schenk et al. 1989
Salami	1.1	Pennington 1987
Yoghurt, plain low-fat	1.1	Pennington 1987
Fruits		
Apple	0.1	Pennington 1987
Banana, fresh	0.05	Pennington 1987
Grapes	0.5[b]	Sorenson et al. 1974
Orange juice, frozen reconstituted	0.06	Pennington 1987
Peaches	0.4[b]	Sorenson et al. 1974
Raisins, dried	3.1	Pennington 1987
Strawberries, fresh	2.2	Pennington 1987
Grains		
Biscuits, baking powder, refrigerated	16.3	Pennington 1987
Bread, white	3	Sorenson et al. 1974
Bread, white	0.351	Derived from Schenk et al. 1989
Bread, pumpernickel	13.2	Derived from Schenk et al. 1989
Bread, whole wheat	5.4	Sorenson et al. 1974
Cereal (e.g., Post Raisin Bran®, Malt-o-Meal Wheat Cereal®)	0.040–29.33	Derived from Schenk et al. 1989
Corn chips	1.2	Pennington 1987
Cornbread, homemade	400	Pennington 1987
Muffin, blueberry	128	Pennington 1987
Oatmeal, cooked	0.7	Pennington 1987
Oats	2.21–4.18	Derived from Schenk et al. 1989

Table 5-4. Estimated Aluminum Concentrations of Selected Foods *(continued)*

Foods	Aluminum concentration (μg/g)	Reference
Rice, cooked[a]	1.7	Greger et al. 1985b
Rice, yellow, Rice-a-Roni®	1.97	Derived from Schenk et al. 1989
Spaghetti, cooked[a]	0.4	Greger et al. 1985b
Vegetables and Legumes		
Asparagus	4.4[b]	Schlettwein-Gsell and Mommsen-Straub 1973
Beans, green, cooked[a]	3.4	Greger et al. 1985b
Beans, navy, boiled	2.1	Pennington 1987
Cabbage, raw	0.1	Greger et al. 1985b
Cauliflower, cooked	0.2	Greger et al. 1985b
Corn	0.1	Pennington 1987
Cucumber, fresh, pared	0.1	Pennington 1987
Lettuce	0.6	Schlettwein-Gsell and Mommsen-Straub 1973
Lettuce	7.16	Derived from Schenk et al. 1989
Peanut butter	5.8	Pennington 1987
Peanut butter, natural	6.29	Derived from Schenk et al. 1989
Peas, frozen, Pict Sweet®	1.64	Derived from Schenk et al. 1989
Peas, green, cooked	1.9	Greger et al. 1985b
Potatoes, unpeeled, boiled[a]	0.1	Greger et al. 1985b
Potatoes, unpeeled, baked	2.4	Greger et al. 1985b
Potato, red	3.63	Derived from Schenk et al. 1989
Potato, sweet	1.01	Derived from Schenk et al. 1989
Spinach, cooked[a]	25.2[b]	Schlettwein-Gsell and Mommsen-Straub 1973
Tomatoes, cooked[a]	0.1	Greger et al. 1985b
Herbs and Spices		
Basil	3,082[b]	Sorenson et al. 1974

Table 5-4. Estimated Aluminum Concentrations of Selected Foods *(continued)*

Foods	Aluminum concentration (μg/g)	Reference
Celery seed	465[b]	Sorenson et al. 1974
Cinnamon	82[b]	Sorenson et al. 1974
Oregano	600[b]	Sorenson et al. 1974
Pepper, black	143[b]	Sorenson et al. 1974
Thyme	750[b]	Sorenson et al. 1974
Other Food Products		
Baking powder	2,300[b]	Sorenson et al. 1974
Candy, milk chocolate	6.8	Pennington 1987
Chocolate cookie, Oreo	12.7	Derived from Schenk et al. 1989
Cocoa	45	Schlettwein-Gsell and Mommsen-Straub 1973
Cream substitute, powdered	139	Pennington 1987
Nondairy creamer	25.7–94.3	Derived from Schenk et al. 1989
Pickles with aluminum additives	39.2[b]	Greger et al. 1985b
Pickles	0.126–9.97	Derived from Schenk et al. 1989
Salad dressing, Kraft Miracle Whip®	3.7	Derived from Schenk et al. 1989
Salt with aluminum additives	164[b]	Greger et al. 1985b
Salt	31.3–36.6	Derived from Schenk et al. 1989
Soup	0.032–3.6	Derived from Schenk et al. 1989

[a]Food reported to *not* be stored or cooked in aluminum pans, trays, or foil.
[b]Value is an average of several values reported in the reference.

occurring in cabbage and lima beans from Georgia and the lowest levels occurring in Missouri soybeans and Georgia tomatoes (Connor and Shacklette 1975). The aluminum content in ash samples from corn in Georgia, Missouri, and Wisconsin ranged from 50 to 3,000 mg/kg (ppm) with mean concentrations ranging from 200 to 1,000 n&kg (ppm) (Connor and Shacklette 1975).

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); 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).

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, non-dairy creamers, and many other powdered materials (Table 5-4) (Schenck 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 sulphates (acidifying agents); bentonite (materials-handling aid); aluminum color additives (lakes) from various food dyes, and aluminum silicates (anti-caking agents) (Greger 1992).

Aluminum has also been found in infant milk formulas although it is not clear whether it is contained in one of the ingredients or has been introduced during processing (Koo et al. 1988; Simmer et al. 1990; Weintraub et al. 1986). Aluminumlevels were measured in 175 samples of whole milk, milk formulas, and other nutrient products commonly used for infants as part of a study of the possible relationship between ingested aluminum and bone disorders. Aluminum content was lowest in human milk, various cow milk preparations, bottled sterile water and glucose water, and most oral multivitamin preparations. Aluminum levels were highest in modified infant formulas, including soy formula, premature infant formula, and products for specific metabolic disorders (Koo and Kaplan 1988; Simmer et al. 1990; Weintraub et al. 1986). The mean concentration of aluminum in U.S. infant milk formulas has been reported to range from 0.14 to 3.74 mg/L (ppm) for liquid formulas and from 6.25 to 11.8 mg/kg (ppm) for powdered formulas (Weintraub et al. 1986). This corresponds to an aluminum content of

0.125-1.89 ppm of feed for liquid formulas and 0.935-1.78 ppm of feed for powdered formulas. Compared with a liter of breast milk (0.012-0. 147 ppm) (Simmer et al. 1990), the aluminum content per liter of reconstituted formula (i.e., diluted according to the manufacturer's recommendations) was up to 63 times greater (Weintraub et al. 1986). These authors also reported that infant formulae from other countries contained up to 165 times the aluminum content of breast milk or cows milk. A more recent study in the United Kingdom found aluminum levels in cows' milk, soy milk, and human breast milk in the range of 4-33 μg/L (14 μg/L mean), 5 to 285 μg/L (160 μg/L mean), and 3 to 79 μg/L (27 μg/L mean), respectively (Baxter et al. 1991). Mean aluminum concentrations in the soy and cows' milk-based samples were, on average, 37% and 45% lower, respectively, than the same brands purchased between 1985 and 1987. The authors also surveyed 1990 retail samples of infant formula. The estimated concentration of aluminum in'the prepared feed ranged from 530 to 640 μg/L in soy-based formula and 27 to 120 μg/L in cows' milk-based formula. Aluminum levels in breast milk, humanized infant formulae, and in special purpose infant formulae are summarized in Table 5-5.

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. 1985b; King et al. 1981; Muller et al. 1993b; Nagy and Nikdel 1986). Table 5-6 compares the concentrations of aluminum in a variety of foods prepared in aluminum cookware as compared to stainless steel cookware. 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 (ppm), while concentrations in the foods after cooking in conditioned aluminum pans and stainless steel pans ranged from 0.24 to 125 mg/kg (ppm) and from < 0.1 to 3.4 mg/kg, respectively (Greger et al. 1985b). In the Greger et al. (1985b) study, some foods seemed to readily accumulate aluminum when cooked in aluminum rather than stainless steel. Ranked in order of increasing migration, foods that accumulated aluminum when cooked in aluminum rather than stainless steel pans were: grits, cauliflower, beef, eggs, cabbage, applesauce, and tomato sauce. Acidic foods, such as tomatoes, tomato sauce, and applesauce, especially when cooked for more than 15 minutes, tended to accumulate more aluminum than other foods (Greger et al. 1985b). Greger et al. (1985b) 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 levels in the foods prepared in any aluminum cookware (old, new, or treated to simulate use) had higher aluminum levels than the same foods cooked in stainless steel cookware. Previous analyses suggested that the use of an aluminum pot to prepare tomato sauce could add up to

Table 5-5. Comparison of Aluminum Levels (μg/L) in Breast Milk, Humanized Infant Formulae, and in Special Purpose Infant Formulae

	Mean ($\bar{x}$)	Range[a]
Breast milk	49	12–147
Humanized infant formulae		
Nan powder	1,463	1,201–1,960
Nan ready to feed	1,218	
Lactogen powder	335	77–827
Lactogen liquid	470	366–627
Lactogen ready to feed	248	
S26 powder	192	120–370
S26 powder/sachet	140	92–165
S26 ready to feed	311	
SMA powder	113	103–130
S26 Progress powder/sachet	165	
Enfalac powder	201	188–210
Enfalac ready to feed	350	
Enfalac (reduced iron) powder	246	238, 254[b]
Enfamil powder	112	95, 132[b]
Similac powder	72	70, 74[b]
Karitane powder	448	447, 448[b]
Karitane follow-on powder	363	
Special purpose infant formulae		
Preterm formulae		
Alprem powder	184	
S26 low birth weight ready to feed	275	
Premature Enfalac powder	337	240, 434[b]
Premature Enfamil ready to feed	1,106	919–1,312
Enfamil breast milk fortifier		
0.96 g/25 mL water	134	
0.96 g/25 mL breast milk	171	122–207
Soy formulae		
Isomil liquid	1,238	
Isomil powder	1,192	
Infa Soy powder	1,670	
Prosobee powder	1,711	1,613–1,861
Special formulae		
Pregestimil powder	939	846, 1,031[b]
Nutamigen powder	835	
Alfare powder	456	451, 460[b]
Portagen powder	493	
Delact powder	62	
Digestelac powder	82	
Karitane goat's milk	360	

Source: Simmer et al. 1990

[a]Range provided where three or more batches of milk or infant formulae were analyzed
[b]Only two batches of formulae were tested

Table 5-6. Concentrations of Aluminum (ppm wet weight) in Foods Before and After Cooking in Aluminum[a] and Stainless Steel Cookware

Food	Uncooked	Cooked in aluminum cookware	Cooked in stainless steel cookware
Apple sauce	0.13	7.1[b]	0.12
Beans, green	3.8	3.8	3.4
Beef, rump roast	0.19	0.85[b]	0.21
Cabbage	0.13	3.6[b]	0.20
Cauliflower	0.19	0.72	0.19
Chicken	0.47	1.00	0.66
Cod	0.35	0.47	0.40
Eggs	0.10	1.6[b]	0.13
Grits	0.62	0.60	0.17
Ham	0.85	1.2	1.2
Peas	1.9	1.9	1.9
Pudding	21.3[c]	4.2	4.0
Rice	1.5	1.7	1.7
Spaghetti	1.7	0.78	0.45
Tomato sauce	0.10	57.1	0.16

Source: Greger et al. 1985b.

[a]Aluminum pans conditioned through standardized cooking procedures
[b]Products cooked in aluminum pans contained significantly ($p<0.05$) more aluminum than unprocessed product or product cooked in stainless steel pans.
[c]Dry product had significantly ($p<0.05$) higher aluminum concentration than either cooked product.

4 mg aluminum to each serving of the sauce (Lione 1983). In a small sampling of canned drinks stored at 15-20 °C, the aluminum content ranged from less than 0.1 to 74 ppm depending on the product and storage time (Abercrombie and Fowler 1997). The 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.

It has been estimated that brewing coffee in a new aluminum pot can add from 0.88 mg (immediately after brewing) to 1.18 mg aluminum (after a further 12-hour storage in the pot and subsequent reheating) to each cup (Lione et al. 1984). Percolators that have been used repeatedly are less susceptible to mobilization of aluminum by coffee, and brewing in these increases the aluminum content of each cup of coffee by only 0.4 mg immediately after brewing and by 0.58 mg after storage for 12 hours in the pot and reheating. The aluminum content of ground coffee beans has been measured at 51.8 mg/kg (ppm) (Lione et al. 1984).

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 (ppb) in Coca-Cola® (storage for 40-101 days) and from 14 to 250 μg/L (ppb) in diet Coca-Cola® (storage for 44-173 days), respectively. These authors also assessed the migration of aluminum from aluminum cans into 0.08% nitric acid solutions. As was shown for Coca-Cola® 's unlacquered cans, the total amount of aluminum that migrated into the nitric acid solutions increased with increasing storage period.

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; NRC 1982). In addition, antacids and buffered aspirin contain 4-562 mg/kg (ppm) of aluminum (Schenck et al. 1989; Shore and Wyatt 1983). Lione (1985a) reported aluminum content/dose (single tablet or 5 mL liquid) for antacids, internal analgesics (buffered aspirins), antidiarrheals, and anti-ulcerative drugs (Table 5-7). 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.

Table 5-7. Aluminum-containing Non-prescription Drugs and Sucralfate*

Drug class	Aluminum salts used	Aluminum content/ dose** (mg)	Possible daily dose Al (mg)
1. Antacids	a. aluminum hydroxide	35–208	840–5,000
	b. dihydroxyaluminum acetate	45–72	
	c. aluminum carbonate	n.a.	
	d. aluminum oxide	41	
	e. bismuth aluminate	55	
	f. magaldrate	51–61	
	g. dihydroxyaluminum aminoacetate	100	
	h. dihydroxyaluminum sodium carbonate	63	
2. Internal analgesics (buffered aspirins)	a. aluminum hydroxide	9–52	126–728
	b. aluminum glycinate	35,717	
3. Antidiarrheals	a. kaolin	120–1,450	
	b. aluminum magnesium silicate	36	
	c. attapulgite	500–600	
4. Anti-ulcerative	a. aluminum sucrose sulfate	207	828

* Data modified from Lione 1985a
** Single tablet or 5 mL liquid
Brand name (manufacturer) for the aluminum salts used to each drug class:

1a. Albicon (Pfeiffer), AlternaGel (Stuart), Aludrox (Wyeth), Aluminum Hydroxide Gel (Philips Roxane), Alurex (Rexall), Amphojel (Wyeth), A.M.T. (Wyeth) Antacid Powder (DeWitt), Banacid (Buffington), Basaljel Extra Strength (Wyeth), Camalox (Rorer). Creamalin (Winthrop), Delcid (Merrell-Dow), Dialume (Armour), Di-Gel (Plough). Estomul-M (Riker), Flacid (Amfre-Grant), Gaviscon (Marion), Gaviscon-2 (Marion), Gelumina (Amer. Pharm.), Gelusil (Warner-Chilcott), Gelusil II (Warner-Chilcott), Gelusil M (Warner-Chilcott), Glycogel (Central Pharm.). Kessadrox (McKesson), Kolantyl (Merrill-Dow), Kudrox (Kremers-Urban), Liquid Antacid (McKesson), Maalox (Rorer). Maalox No. 1 (Rorer), Maalox No. 2 (Rorer), Maalox Plus (Rorer), Maalox TC (Rorer), Magna Gel (No. American), Magnatril (Lannett), Mylanta (Stuart), Mylanta II (Stuart). Nephrox (Fleming), Noralac (No. American), Nutrajel (Cenci). Silain-Gel (Robins), Simeco (Wyeth), Syntrogel (Reed and Carnrick), Tempo (Richardson-Vicks), Tralmag (O'Neal, Jones, and Feldman), Trimagel (Columbia Medical), Trisogel (Lilly), WinGel (Winthrop)

1b. Aluscop (O'Neal)
1c. Basaljel (Wyeth)
1d. Magnesia and Alumina Oral Suspension (Philips Roxane), Nutramag (Cenci).
1e. Noralac (No. American)
1f. Riopan (Ayerst), Riopan Plus (Ayerst)
1g. Robalate (Robins), Tralmag (O'Neal, Jones, and Feldman)
1h. Rolaids (Warner-Lambert)
2a. Arthritis Pain Formula (Whitehall), Ascriptin (Rorer), Ascriptin A/D (Rorer). B-A (O'Neal, Jones, and Feldman). Cama (Dorsey), Cope (Glenbrook), Pabrin (Dorsey), Vanquish Caplet (Glenbrook)
2b. Arthritis Strength Bufferin (Bristol-Myers), Bufferin (Bristol-Myers)
3a. Amogel (No. American), Bislad (Central). Diabismul (O'Neal, Jones, and Feldman), Dia-eze (Central), Donnagel-PG (Robins). Donnagel (Robins), Kaodene Non-Narcotic (Pfeiffer), Kaodene with Paregoric (Pfeiffer), Kaolin Pectin Suspension (Philips Roxane), Kaopectate (Upjohn), Kaopectate Concentrate (Upjohn) Parepectolin (Rorer). Pargel (Parke-Davis), Pektamalt (Warren-Teed)
3b. Pabisol with Paregoric (Rexall)
3c. Quintese (Lilly). Rheaban (Pfizer)
4a. Carafate (Marion Labs)
n.a. = not available

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, anticoagulants, as well as the container itself. Aluminum levels in a 5% pooled human albumin solution was 0.507 μg/mL, (Progar et al. 1996).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Exposure to aluminum is inevitable due to its natural abundance in the earth's crust and its many uses. The intake of aluminum is chiefly oral, and the major sources for human exposure to aluminum are drinking water, residues in foods, cooking utensils, food and beverage packaging, antacid formulations, and antiperspirant formulations (Marquis 1989). Aluminum is present in the human diet, in amounts varying from relatively low concentrations in animal products to relatively high concentrations in some processed foods. However, the gastrointestinal absorption of aluminum is low (<0.1%) and renal elimination is very effective in removing aluminum in healthy individuals (Muller et al. 1993b).

Aluminum is inhaled from air primarily as aluminosilicates associated with airborne dust particles (Koo and Kaplan 1988). Since a large aqueous concentration of aluminum (i.e., >100 mg/L) can only occur when the pH is < 5 (Sorenson et al. 1974), the levels of aluminum in most natural waters (pH>6) are not expected to be of significant concern to human health. Miller et al. (1984) reported that the median aluminum levels in finished drinking water throughout the United States varied from 0.026 mg/L to 0.161 mg/L (ppm). More recently, Schenck et al. (1989) reported concentrations of aluminum in finished drinking water in various regions of the United States were highly variable, ranging from undetectable to 1.029 mg/L (ppm). The median and mean aluminum concentrations in finished drinking water from 384 Norwegian waterworks sampled on four occasions (autumn 1982, winter, spring, and summer 1983) were 0.06 and 0.11 mg/L (ppm), respectively with a range of < 0.04-4.1 mg/L (Flaten 1991). The median aluminum concentrations in drinking water from 346 surface water and 35 groundwater sources were 0.06 and 0.02 mg/L, respectively. A correlation between aluminum and SO_4^{2-}, Mn, and pH were ascribed to the effects of acid precipitation.

Aluminum is present naturally in tea and some vegetables. Aluminum is introduced into grain products and processed cheese from aluminum-containing food additives. These products are used as acidifiers, buffers, leavening agents, emulsifiers, stabilizers, thickeners, and anticaking agents. For example,

sodium aluminum sulfate is found in baking powder and sodium silicates are used as anticaking agents in salt and other dry and powdered ingredients. 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 range from 2 to 14 rug/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 mgfday and that for adult females was about 7 mg/day. Dietary intakes for 2-year-old, 6-year-old, 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 to 0.15 mg/kg, except for 14-16-year-old males which was 0.18 mg/kg. More recently, Greger (1992) estimated that most adults consume from 1 to 10 mg aluminum per day from natural sources.

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 less than 1 mg/kg for 47% of the food examined and less than 10 mg/kg for 85% of the food examined (Pennington and Schoen 1995). However, intake of aluminum from foods containing food additives varies greatly (0-95 mg aluminum/day) among residents of North America, depending on the amount of processed foods consumed. The median intake of aluminum for adults was estimated to be 24 mg/day (Greger 1992). In an Italian study in which samples of daily diets were collected and analyzed, the intake of aluminum ranged from 2.5 to 6.3 mg/day (Gramiccioni et al. 1996). The migration of aluminum from cookware into food was reported to be relatively low. The results of dietary studies indicate that exposure to aluminum through food is low and the total dietary intake of aluminum is correlated with the total food intake. The migration of aluminum from cookware into food will increase with the acidity of the food and the duration of exposure. In a worst-case example, red current juice was prepared by boiling berries for 3 hours in an aluminum or in a stainless steel pot (Valkonen and Aitio 1997). The aluminum concentration of the juice prepared in the aluminum and stainless steel pots were 89.1 mg/L and 1.83 mg/L,, respectively. 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). Antacids and buffered aspirin, which are often taken in multiple daily doses for prolonged periods, contain 4-562 mg/kg (ppm) of aluminum (Lione 1983; Schenck et al. 1989; Shore and Wyatt 1983). For example, according to Pennington and Schoen (1995), antacids may contain 50 mg of aluminum per tablet and buffered aspirin may contain 10-20 mg of aluminum per tablet. Another source lists the $Al(OH)_3$ content of several popular antacid preparations (tablet or 5 mL liquid), which range from 400 to 600 mg (140-210 mg of aluminum) (Harman and Limbird 1996).

Reports available on normal dietary levels of aluminum suggest that approximately 20 mg/day may be an acceptable representation (Lione 1983; Underwood 1977). More recently, Greger (1992) reported a median concentration of 24 mg/day, which is comparable. Lione (1985a) estimated that from 126 to 728 mg and 840 to 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 less than 1% of the intake amount in healthy individuals (Gorsky et al. 1979, Kaehny et al. 1977; Reiber et al. 1995).

In recent years, a numbers of investigators have become concerned about the aluminum content of infant formulae (Koo et al. 1988; Simmer et al. 1990; Weintraub et al. 1986). The aluminum content of human breast milk or cows' milk is very low (< 0.05 μg/mL [ppm]) (Koo et al. 1988; Simmer et al. 1990; Weintraub et al. 1986). Dabeka and McKenzie (1990) reported that ready-to-use milk-based and soybased formulae contained 0.01-0.36 and 0.40-6.4 μg/g, respectively. Thus, 1-3-month-old infants consuming certain soy-based formulae could ingest as much as 2.1 mg aluminum a day. This is compared to infants fed human breast milk or cows' milk who would consume only 3 μg aluminum a day. Infants fed the soy-based infant formulae would thereby ingest 700 times more aluminum than infants fed human breast milk or cows' milk (Dabeka and McKenzie 1990; Greger 1992).

As discussed in Section 5.4.2, the median concentration of aluminum in drinking water not receiving coagulation treatment and that receiving coagulation treatment is 0.043 mg/L and 0.112 mg/L, respectively. If the total dose of aluminum obtained from water is calculated based on an estimated consumption of 2 L/day, the amount of aluminum ingested would respectively be 0.08 and 0.224 milligrams per day or roughly 1% of the 7-9 milligrams per day for adults from dietary sources.

Although the intake of aluminum is chiefly through ingestion of food and drinking water, aluminum is also drawn into the lungs from breathing atmospheric dust (Browning 1969). As discussed in Section 5.4.1, background levels of aluminum in the atmosphere generally range from 0.005 to a maximum of 0.18 ng/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 ng/m^3 would be 3.6 nanograms per 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 milligrams per day. However, the aluminum content of air in urban and industrial areas has been reported to be considerable higher, ranging from 0.4 to 10 ng/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 m3/day, then the total amount of aluminum inhaled would range from 8 to 200 nanograms per 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.

Because of inherent problems with sensitivity and contamination, levels of aluminum in body tissues are difficult to measure and levels found can be method-dependent (Schenck et al. 1989). Aluminum levels reported in studies prior to 1980 are often much higher than those reported in more recent studies. Normal values of aluminum in whole blood have been reported to range from 0.14 to 6.24 mg/L (ppm), and in plasma from 0.13 to 0.16 mg/L (ppm) (Sorenson et al. 1974). Normal values in serumhave been reported at 1.46 and 0.24 mg/L (ppm), using neutron activation and atomic absorption analysis, respectively (Berlyne et al. 1970). A normal value of 0.037 mg/L (ppm) for serum using flameless atomic absorption analysis has also been reported (Fuchs et al. 1974). Drablos et al. (1992) analyzed aluminum serum levels in 230 nonexposed workers (controls) and reported a mean aluminum serum level of 0.005$\pm$0.002 mg/L (ppm). Research has shown that the levels of aluminum in the serum in the general population do not exceed 0.01 mg/L (ppm) (Cornelis 1982). Nieboer et al. (1995) reviewed 34 studies on aluminum levels in serum or plasma, and also reported that aluminum serum levels in the general population were typically < 0.01 mg/L (ppm).

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. The normal levels reported in some older studies of aluminum range from 0.05 to 1 mg/L (ppm) in the urine (Kehoe et al. 1940; Tipton et al. 1966). Drablos et al. (1992) analyzed aluminumurine levels in 230 nonexposed workers (controls) and reported a mean aluminum urine level of 0.005±0.003 mg/L (ppm) (range, 0.001-0.037 mg/L). Nieboer et al. (1995) reviewed 8 studies on aluminumlevels in urine and reported that aluminum urine levels in healthy individuals typically ranged from 0.0027 to 0.0081 mg/L (ppm). In a recent 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 2 1 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. The mean serumlevel on the nonexposed people was much lower than the mean serum level reported by Drablos et al. (1992). Gitelman et al. (1995) investigated the relationship between the concentration of aluminum in serum and urine and occupational exposure to airborne aluminum in a large number of workers in the aluminum industry (15 plants). Occupational exposure was estimated from aluminum measurements of total and respirable (< 10 μ m) particulate matter in air. The study showed that workers with occupational exposure to airborne aluminum had statistically significant increases in urinary aluminum/creatinine ratios over controls; however, changes in serum aluminum were borderline. Similarly, in an investigation of workers at an open bauxite mine in Surinam, serum aluminum levels 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).

Recent measurements of aluminum concentrations in human tissues for estimation of exposures are primarily limited to bone and brain tissues (Nieboer et al. 1995). Background levels of aluminumin bone are in the order of l-3 μg/g (ppm, dry weight). These authors also reported that background aluminum levels in brain tissues (primarily grey matter) of healthy individuals typically ranges from 1 to 3 μg/g (ppm, dry weight) or co.5 μg/g (wet weight).

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 aluminummetal fumes in the foundry (Drablos et al. 1992; IARC 1984; Nieboer et al. 1995). Drablos et al. (1992) studied aluminum concentrations in workers at an aluminum fluoride plant. Mean aluminum levels in urine were 0.011±0.007 mg/L (range, 0.002-0.046 mg/L) for 15 plant workers, 0.032±0.023 mg/L (range, 0.006-0. 136 mg/L) for 7 foundry workers, and 0.054±0.063 mg/L (range, 0.005-0.492 mg/L) for 12 potroom workers as compared to 0.005±0.003 mg/L (range, 0.001-0.037 mg/L) for 230 unexposed controls.

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; however, rather 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

The most recent National Occupational Exposure Study (NOES) conducted by NIOSH from 1981 to 1983, estimated the number of workers potentially exposed to aluminum and aluminum compounds (NIOSH 1991). Results of this survey are summarized in Table 5-8. The NOES was based on observational field surveys of 4,490 facilities and was designed as a nationwide survey based on a statistical sample of virtually all workplace environments, except mining and agriculture, in the United States where eight or more persons are employed and only provides estimates of the numbers of workers

Table 5-8. Estimated Number of Workers Potentially Exposed to Aluminum and Its Compounds in the Workplace

Aluminum compound	Number of potentially exposed workers
Aluminum - pure	31,369
Aluminum dust	1,833
Aluminum - unknown	1,033,235
Aluminum oxide	1,345,659
Aluminum oxide, powder	172,756
Aluminum hydroxide	325,788
Aluminum hydroxide, gel	37,772
Dried aluminum hydroxide gel	7,006
Aluminum chloride	49,913
Aluminum chloride hydroxide	1,579
Aluminum sulfate	212,239
Aluminum sulfate, liquid	23,354
Aluminum sulfate, powder	1,496
Aluminum nitrate	34,929
Aluminum phosphide	622
Aluminum phosphate	19,526
Aluminum phosphate, gel	4,228
Aluminum fluoride	175
Aluminum, calcined	27,670

Source: National Occupational Exposure Study (NOES) NIOSH 1991, 1992

potentially exposed to chemicals in the workplace (NIOSH 1988). It does not contain information on the frequency, concentration, or duration of occupational exposure to any of the chemicals listed. 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.

5.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans and briefly considers potential pre-conception exposure to germ cells. Differences from adults in susceptibility to hazardous substances are discussed in Section 2.6.

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, and 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; they put things in their mouths; they may ingest inappropriate things such as dirt or paint chips; they spend more time outdoors. Children also are closer to the ground, and they do not have the judgement of adults in avoiding hazards (NRC 1993).

As with adults, exposures of children to aluminum from breathing air, drinking water, and eating food is low. However, children are much more likely to ingest dirt, which contains high amounts of aluminum than adults. They are likely to ingest dirt from their unwashed hands or when playing with contaminated soils. In addition, children living in proximity to hazardous waste sites may be exposed to aluminum 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. Aluminum found at hazardous waste sites may be in a more labile form than that found in ordinary soil.

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 5-9. 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 is shown in Table 5-10. 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. A comparison of aluminum concentrations in breast milk, humanized infant formulas, and special purposed infant formulas appears in Table 5-5.

Aluminum levels have also been reported for human breast milk. The median aluminum level in breast milk collected from 12 Canadian women was reported to be 14 μg/L (ppb, 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 (ppb) in nursing mothers. More recently, Simmer et al. (1990) reported a mean aluminum concentration of 49 μg/L (ppb) in breast milk collected from Australian women. Hawkins et al. (1994) reported breast milk aluminum concentrations of 9.2 μg/L (ppb) (95% confidence interval from 5.6 to 12.7 μg/L) collected from 15 nursing mothers in the United Kingdom. The aluminum content of human milk from 42 nursing Croatian women in the winter of 1992-1993 ranged from 4 to 2,670 μg/L (ppb) with a mean of 380 μg/L (ppb) (Mandic et al. 1995). While some differences in aluminum content of milk was found depending the participant's age, number of deliveries, postpartum days, weight gain during pregnancy, refugee status, and smoking status, correlations with these factors were not statistically significant. The investigators were unable to explain the high values obtained for aluminum in the milk of the Croatian women, especially since there was no data on aluminum in Croatian foodstuffs. Since their measurements using standard reference serum were acceptable, contamination in the analytical procedure was ruled out. While steps were taken to avoid contamination in the collection process, no controls to gauge the effectiveness of these steps were reported.

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 also be exposed to aluminum from vaccinations, parenteral feeding of premature infants, dialysis fluids, and treatment for hyperphosphatemia.

Table 5-9. Dietary Intakes of Aluminum in Children

Age-sex group	Aluminum Intake (mg/day)	Aluminum Intake (mg/kg)
6–11-month-old infants	0.7	0.10
2-year-old children	4.6	0.35
6-year-old children	6.5	0.30
10-year-old children	6.8	0.11
14–16-year-old females	7.7	0.15
14–16-year-old males	11.5	0.18

Source: Pennington and Schoen 1995.

Table 5-10. Major Sources of Aluminum in Food by Age-Sex Group

Foods by age-sex group (Al/day)	Aluminum/day mg	Aluminum/day % 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
Muffins	0.207	3.0
Chocolate cake with icing	0.141	2.1

Table 5-10. Major Sources of Aluminum in Food by Age-Sex Group *(continued)*

Foods by age-sex group (Al/day)	Aluminum/day mg	Aluminum/day % of total intake
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

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to individuals who are occupationally exposed to aluminum (see Section 5.5), 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. However, exposure to higher levels of aluminum may not be hazardous if the exposed individual has normal renal function (see Section 2.5).

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. Aluminum has been detected in air samples collected at 9 of the 427 NPL hazardous waste sites where it has been detected in some environmental media (HazDat 1996). 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. Aluminum has been detected in soil and sediment samples at 203 and 151 of 427 NPL hazardous waste sites, respectively, where it has been detected in some environmental media (HazDat 1996). 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. Aluminum has been detected in groundwater at 336 of 427 NPL hazardous waste sites where it has been detected in some environmental media (HazDat 1996).

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; Lione 1985a; Muller et al. 1993b). 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, Ward (199 1) reported increased serum aluminum concentrations in hemodialysis patients who were prescribed effervescent analgesic tablets which increased gastrointestinal absorption mediated by the acidity of citric acid that increased aluminum solubility and therefore availability of aluminum for uptake.

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-olds (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 vs. 0.18 and 0.15 mg aluminum/kg body weight) (Greger 1992). Infants fed milk-based or soy-based infant formulae can be exposed to considerably higher concentrations of aluminum than infants fed breast milk or cow's milk (see Section 5.4.4). 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 5.4.4, 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 from 126 to 728 mg and 840 to 5,000 mg were possible daily doses of aluminum consumed in buffered aspirins for rheumatoid arthritis and antacid products, respectively. These doses are from 6 to 40 times and 42 to 250 times greater, respectively, than aluminum doses obtained from consumption of foods (20-24 mg/day).

5.8 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 the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 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.

5.8.1 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 (Budavari et al. 1989; HSDB 1995; Lewis 1993; Sax and Lewis 1989; Weast et al. 1989; Weiss 1986).

Production, Import/Export, Use, Release, and Disposal. 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; Budavari et al. 1989; Hawley 1977; Sax and Lewis 1987; Stokinger 1981; Venugopal and Lucky 1978), the potential for human exposure to these compounds through ingestion of food and water and inhalation of airborne particulates is substantial. Recent information on production volumes is available and it appears that, while primary production of aluminum has decreased from 1991 to 1996, secondary recovery of aluminum (recycling) increased during this same period (USGS 1996, 1997a). The United States relies on imports for some of its consumption needs; however, imports declined slightly in 1995, reversing a increasing trend that began in 1992 (USGS 1996, 1997a). Exports have remained relatively constant from 1991 through 1996 (USGS 1996, 1997a). Consumption data for aluminumused in areas impacting on exposure such as food additives are not available. Information on disposal of aluminum compounds is limited. Additional information on disposal would be useful in assessing the potential for the release of and exposure to aluminum compounds.

According to the Emergency Planning and Community Right-to-Know Act of 1986,42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), presently contains this information for 1996. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. Aluminum partitions to air, water, soil, and plant material. 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, anionic compounds, 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 (Cranmer et al. 1986). 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.

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 (Baes et al. 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 (Baes et al. 1984). The fact that in studies dealing with aluminumin 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) (Pennington and Schoen 1995), 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 somewhat 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. There are reliable data to characterize the potential for human exposure from drinking water (Kopp and Kroner 1970; Letterman and Driscoll 1988; Miller et al. 1984; Schenck et al. 1989) and food sources (Brusewitz 1984; Connor and Shacklette 1975; Koo and Kaplan 1988; Lewis 1989; Pennington 1987; Schenck et al. 1989; Sorenson et al. 1974; Weintraub et al. 1986). However, recent (i.e., within 3 years) monitoring data for all media are currently not available. Estimates of human exposure to aluminum from food (Greger 1992; Lione 1983; Pennington 1987; Underwood 1977), drinking water (Kopp and Kroner 1970; Miller et al. 1984; Schenck 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 1985a; Schenck et al. 1989; Shore and Wyatt 1983). 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.

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 burdens of aluminum to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Measurements of the aluminum content in human tissues, especially in blood (Berlyne et al. 1970; Cornelis 1982; Drablos et al. 1992; Fuchs et al. 1974; Nieboer et al. 1995; Sorenson et al. 1974), urine (Alessio et al. 1989; Drablos et al. 1992; Kehoe et al. 1940; Nieboer et al. 1995; Tipton et al. 1966), and breast milk (Hawkins et al. 1994; Koo and Kaplan 1988; Simmer et al. 1990; Weintraub et al. 1986), are available. Measurements of aluminum in bone and brain tissue are also available (Nieboer et al. 1995). However, recent (i.e., within 3 years) 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 not available. This information would be useful in assessing both the normal aluminum content of children and the effect of exposure on aluminum levels 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. We also do not know 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. Such information 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). We also know that the aluminum content of human breast milk or cow's milk is very low (< 0.05 μg/mL [ppm]) (Koo et al. 1988; Simmer et al. 1990; Weintraub et al. 1986).

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

5.8.2 Ongoing Studies

A search of Federal Research in Progress (FEDRIP 1996) identified numerous research studies that are currently being conducted that may fill some of the data needs for aluminum discussed in Section 5.8.1. These studies are summarized in Table 5- 11.

Table 5-11. Ongoing Studies on Aluminum

Investigator	Affiliation	Research description	Sponsor
Adams J	Auburn University, Auburn, AL	Research on the effects of ecosystems on soil acidity and aluminum toxicity to determine the effects of organic matter derived from forest and agricultural ecosystems on soil pH and aluminum content, determine the quantity and rate of production of low-molecular-weight di- and tri-carboxylic organic acid production in forest and agricultural ecosystems to evaluate aluminum-organic acid complex equilibrium in soils.	U.S. Department of Agriculture
Bondy SC	University of California, Irvine, CA	There is suspicion that aluminum is involved in several neurological diseases associated with aging and there is evidence the potential of iron for enhancing free radical generation in nervous tissue is enhanced by aluminum. It is hoped the results of this project will so reveal.	U.S. Department of Health And Human Services; Public Health Service; National Institute of Health, National Institute of Environmental Health Sciences
Burau R	University of California, Land, Air, and Water Resources Department	Conducting work under the National Atmospheric Deposition Program. As part of this project, acid metal-containing surface waters will be neutralized to determine the degree to which dissolved iron and aluminum can be precipitated and the degree to which these materials can remove other toxic trace elements. The studies will include a characterization of precipitates as well as a determination of the factors which affect the rates of formation of the oxides and oxyhydroxides.	U.S. Department of Agriculture

Table 5-11. Ongoing Studies on Aluminum *(continued)*

Investigator	Affiliation	Research description	Sponsor
Cavallaro N and Snyder V	University of Puerto Rico, Agronomy and Soils Department, Mayaguez, Puerto Rico	Conducting research on the mobility of aluminum and major nutrient cations in acid ultisols and oxisols. The objective of this study is to evaluate movement and changes in the exchangeable fraction and soluble forms of major cations and anions in a soil profile with different sources and methods of application of materials to reduce soil acidity.	U.S. Department of Agriculture
Etherton B and Cumming J	University of Vermont, Botany Department, Burlington, VT	Conducting a study of membrane transport processes during aluminum exposure in the bean *(Phaseolus vulgaris)*. The objective of this study is to measure net ion fluxes at the root apex during exposure to aluminum and the acquisition of aluminum tolerance, and to determine the role of organic acids in conferring aluminum tolerance in *P. vulgaris*.	U.S. Department of Agriculture
Golub MS	University of California, Davis, CA	Using mice, the objective of this project is to determine biological actions relevant to toxicological effects, and clarify potential human health risks associated with ingestion of aluminum in food, water, and pharmaceuticals.	U.S. Department of Health and Human Services; Public Health Service; National Institute of Health, National Institute of Environmental Health Sciences
Grunes D and Norvell W	Agricultural Research Service, Ithaca, NY	Work on factors limiting the availability and movement of nutrients in soil. This research will examine factors limiting the availability of nutritionally important elements in soil, movement of these elements to the root-soil interface, and their uptake by plants. Measurements will be made of the form and levels of elements in soil, movement of elements to plant roots, uptake of elements by plant roots, and translocation to above-ground, and edible portions of plants. The elements to be studied include magnesium, calcium, potassium, zinc, phosphorous, nitrogen, iron, manganese, copper, and aluminum.	U.S. Department of Agriculture

Table 5-11. Ongoing Studies on Aluminum *(continued)*

Investigator	Affiliation	Research description	Sponsor
Lewis Lovelace JL	Biomed Environ Res In, Albuquerque, NM	Determination of the specific disposition of inhaled toxicants in the olfactory system; assessment of the importance as a human health risk factor of the phenomenon of olfactory transport.	U.S. Department of Health and Human Services; Public Health Service; National Institute of Health, National Institute on Deafness and Other Communication Disorders
Longnecker MP	NIEHS, NIH	Toenail levels may provide a means of measuring exposure for a group of 12 elements that is linked with chronic disease, because toenails reflect exposure over a longer period of time than blood or urine, and are less influenced by contamination.	U.S. Department of Health and Human Services; Public Health Service; National Institute of Health, National Institute of Environmental Health Sciences
Murdoch P	U.S. Geological Survey in Southeastern New York	A study of biogeochemical processes controlling nitrogen cycling and associated hydrogen and aluminum leaching in an undeveloped headwater basin of the Delaware River. Nitric acid is the primary mineral acid causing pH depressions and increases in inorganic aluminum concentrations in streams during storms and snowmelt in the Catskill Mountains of New York. Processes controlling nitrogen movement in forested catchments is poorly understood. An understanding of nitrogen processes and movement in forest soils would allow greater insight into the flowpath of water and the transport of toxic aluminum in watersheds.	Department of the Interior

Table 5-11. Ongoing Studies on Aluminum *(continued)*

Investigator	Affiliation	Research description	Sponsor
Norwell W, Grunes D, and Duxbury J	Cornell University, Ithaca, NY	A project on plant availability and geographic distribution of essential and toxic elements. Develop useful maps of nutrient availability and toxic element distribution by using geostatistics and graphical information system techniques to interpret plant and soil composition along with soil genetic information and geological data. Determine effects of aluminum and root exudates on the uptake and translocations of magnesium, calcium, and potassium by aluminum-sensitive and aluminum-tolerant wheat seedlings.	U.S. Department of Agriculture
Robarge W	North Carolina State University, Soil Sciences Department, Raleigh, NC	Research to enhance understanding of how soils can either be a source or can ameliorate various airborne pollutants. As part of this project they will develop a stochastic model of the effect of acidic deposition on the activity of aluminum in soil ecosystems.	U.S. Department of Agriculture
Rufty T	North Carolina State University, Crop Sciences Department Raleigh, NC	Research on the mechanism of aluminum toxicity in plants. This study will determine the extent of aluminum accumulation inside cells at the root apex using microanalytical techniques and will define associated effects on cell division, cell expansion, and cellular accumulation of calcium and magnesium.	U.S. Department of Agriculture
Sakhaee K	University of Texas Southwest Medical Center, Dallas, TX	A project on aluminum absorption and the effect of calcium citrate on aluminum-containing antacids. The objective of this study is to determine whether calcium citrate given together with aluminum-containing antacids would enhance intestinal absorption of aluminum in humans.	National Center for Research Resources

Table 5-11. Ongoing Studies on Aluminum *(continued)*

Investigator	Affiliation	Research description	Sponsor
Stilwell D	Connecticut Agricultural Experiment Station, New Haven, CT	Research on the heavy metal content of municipal solid waste. This project will develop methods of analysis and determining the variability of heavy metals and other selected elements in composted municipal solid waste (MSW). Analytical methods will be developed for the determination of several heavy metals, and other selected elements including aluminum, arsenic, boron, calcium, potassium, molybdenum, nitrogen, and phosphorous.	U.S. Department of Agriculture
Zasoski R	University of California, Land, Air, and Water Resources Department, Davis, CA	A study as part of the National Atmospheric Deposition Program which provides the scientific community, resource managers, and policy makers with information on the exposure of both natural and managed ecosystems to biologically important chemical deposition and other stresses resulting from changes in the chemical climate. Acid soils of natural and anthropogenic origins will be characterized for various elements including aluminum and utilized to grow cultivated and native tree species with the objective of determining the composition and character of the rhizosphere associated with these species.	U.S. Department of Agriculture

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, and/or 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 rhods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL SAMPLES

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), neutron activation analysis (NAA), inductively coupled plasma-atomic emission spectrometry (ICP-AES), inductively coupled plasma-mass spectrometry (ICP-MS), and laser ablation microprobe mass analysis (LAMMA) (Maitani et al. 1994; Owen et al. 1994; Van Landeghem et al. 1994) (see Table 6-1). 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 concentration of radioactive ^{26}Al and 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

Table 6-1. 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

Table 6-1. Analytical Methods for Determining Aluminum in Biological Materials *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Whole blood	Dilution with Triton X-100	GFAAS	1.9 μg/L in serum; 1.8 μg/L in plasma; 2.3 μg/L in 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	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
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; digestion with nitric acid; dilution with water	GFAAS	0.5 μg/g	80–117%	Bouman et al. 1986
Kidney, liver, urine	Acid digestion; dilution with water	ICP-AES	No data	98.8% ± 8.6% in liver	Maitani et al. 1994

Table 6-1. Analytical Methods for Determining Aluminum in Biological Materials *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Kidney, liver, femur	Microwave digestion with nitric acid; addition of internal standard and 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 $K_2Cr_2O_7$ 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	Wash with isopropanol; digestion with nitric acid; dilution with water	GFAAS	0.65 μg/g	84–105%	Chappuis et al. 1988
Human blood, urine, serum, feces	Acid digestion using Parr bomb technique, microwave, or hot plate method	ICP-AES	1 μg/L	> 75%	Que Hee and Boyle 1988
All	None	AMS	1 ppq	NA	Flarend and Elmore 1997

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

the body, but is dependent upon the availability of the radioactive ^{26}Al tracer, which is 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. This method is used to assess the ^{26}Al content and the $^{26}Al/^{27}Al$ ratio (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; Schaller and Valentin 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 columu (Van Landeghem et al. 1994).

NAA has been used to determine low levels of aluminum in biological tissues and urine (Blotch 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 μg 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 and, 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 more than 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).

LAMMA has been utilized for the analysis of aluminum in brain tissue affected with Alzheimer's disease (Lovell et al. 1993). This new 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. LAMMA was 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.

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.

6.2 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, phosphorirxtry, chromatography and gas chromatography equipped with an electron capture detector (GUECD) (Andersen 1987, 1988; Benson et al. 1990; Carrillo et al. 1992; Dean 1989; De La Campa et al. 1988; Ermolenko and Dedkov 1988; Fleming and Lindstrom 1987; Gardiner et al. 1987; Gosink 1975; Jones et al. 1988; Kopp and McKee 1978; NIOSH 1984b; Pastor et al. 1987; Tapparo and Bombi 1990; Woolfson and Gracey 1988). They are summarized in Table 6-2.

NIOSH has recommended Methods 7013 (FAAS) and 7300 (ICP-AES) for detecting aluminum and other elements in filter samples of workplace air particulates. The applicable working ranges are 0.5-10 mg/m^3 for a 100-L air sample by Method 7013 and 0.005-2.0 mg/m^3 for a 500-L air sample by Method 7300 (NIOSH 1984b).

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 (Kopp and McKee 1978). Detection limits of 100 μg of aluminum/L of sample and 3 μg of aluminum/L of sample were obtained using the FAAS and GFAAS techniques, respectively (Kopp and McKee 1978). Spectrophotometry and GUECD have also been employed to measure low-ppb (11μg/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

Table 6-2. Analytical Methods for Determining Aluminum in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collect sample on cellulose filter and digest with nitric acid	Method 7013 (FAAS)	2 μg/sample	NA	NIOSH 1984b
Air	Collect sample on cellulose filter and digest with nitric acid	Method 7300 (ICP-AES)	1 μg/sample	NA	NIOSH 1984b
Water	Add *o,o'*- and *o,p*-dihydroxyazo compounds to sample and analyze at 545 nm	Spectro-photometer	4 μg/L	NA	Ermolenko and Dedkov 1988
Water	Add acetate and trifluoroacetylacetone in benzene to sample and shake; add sodium hydroxide, shake, and analyze extract	GC/EDC	Low μg/L levels	No data	Gosink 1975
Water and waste water	Digest sample with nitric acid and analyze	FAAS or GFAAS	100 μg/L (FAAS); 3 μg/L (GFAAS)	NA	Kopp and McKee 1978 (Methods 202.1 and 202.1)
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	NA	Fleming and Lindstrom 1987
Plants	Digest sample with nitric acid and analyze	Spectro-photometer	7 μg/L	NA	Dean 1989
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

Table 6-2. Analytical Methods for Determining Aluminum in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Dialysis fluids (continued)	Add Ferron and cetyltrimethyl-ammonium bromide solution to sample and measure phosphor-escence at 586 nm	Phosphor-imetry	5.4 μg/L	No data	De La Campa et al. 1988
Rock, soil	Digest with acid	AMS	10^{-15} g/g sample	NA	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; NA = not applicable; NAA = neutron activation analysis

laboratory setting, with detection limits as low as 0.3 μg/L. Ion chromatography using spectrophotometric 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.

6.3 ADEQUACY OF THE DATABASE

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

6.3.1 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; Schaller and Valentin 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). These techniques are sensitive for measuring background levels of aluminum in the population and levels of aluminum at which health effects might begin to occur.

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.

At present, no biomarkers of exposure and effect other than the parent compounds are available for aluminum There are no data to indicate whether other biomarkers, if available, would be preferred over chemical analysis for monitoring exposure to aluminum.

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 1984b). For measuring aluminum in water and waste water, spectrophotometry (Benson et al. 1990; Carrillo et al. 1992; Ermolenko and Dedkov 1988), GUECD (Gosink 1975), and FAAS and GFAAS (Kopp and McKee 1978) 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 (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 (Kopp and McKee 1978) 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 aluminumlevels in water and waste water (Kopp and McKee 1978). 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.

6.3.2 Ongoing Studies

No ongoing studies have been identified.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding aluminum in air, water, and other media are summarized in Table 7- 1.

No MRLs for any duration of exposure for inhalation were determined for aluminum. An intermediate-duration oral exposure MRL of 2.0 mg/kg/day has been derived. This MRL is based on a NOAEL for neurotoxicity in mice (Golub et al. 1989). No acute- or chronic-duration oral MRLs were determined. EPA has not derived an RfD or RfC for aluminum (IRIS 1999).

The EPA has not classified aluminum for human carcinogenicity (IRIS 1999). The American Conference of Governmental Industrial Hygienists (ACGIH) has determined that aluminum is not classifiable as to its human carcinogenicity, and has assigned it to their group A4 (ACGIH 1996). The International Agency for Research on Cancer has assigned aluminum production to the Group 1 cancer classification (IARC 1987). The total body of evidence as reviewed by the IARC Work Group indicates that there is a causal relationship between human exposures to PAHs and other carcinogens in the aluminum production industry and human cancer, and that the evidence is sufficient enough to classify aluminum production as carcinogenic to humans (IARC 1984, 1987).

OSHA requires employers of workers who are occupationally exposed to aluminum to institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limits (PELs). The employer must use engineering and work practice controls, if feasible, to reduce exposures to or below an 8-hour time-weighted average (TWA) of 15 mg/m^3 for total aluminum dust or 5 mg/m^3 for respirable fractions (OSHA 1974). Both ACGIH and NIOSH have established guideline values that range from 2 mg/m^3 for soluble salts to 10 mg/m^3 for aluminum or total dust (ACGIH 1996; NIOSH 1992). Various states have established regulations and guidelines based mainly on 8- or 24-hour average values.

The EPA regulates aluminum and certain aluminum compounds under the Clean Air Act (CAA). They are not, however, designated as hazardous air pollutants (HAPS). The two stationary source categories for which EPA has promulgated performance standards in an effort to control emissions to the atmosphere are primary and secondary aluminum plants (EPA 1977a, 1982a).

Table 7-1. Regulations and Guidelines Applicable to Aluminum

Agency	Description	Information	References
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenic classification (aluminum production)	Group 1[a]	IARC 1984 IARC 1987
WHO	Drinking water guidelines aesthetic quality	0.2 mg/L	WHO 1984
NATIONAL			
Regulations:			
a. Air:			
OSHA	Occupational Safety and Health Standards—Limits for Air Contaminants (aluminum)	8-hour, TWA	29 CFR 1910.1000 OSHA 1974
	Total dust	15 mg/m^3	
	Respirable fraction	5 mg/m^3	
EPA OAR	Standards of Performance for New Stationary Sources		
	Addresses; primary aluminum reduction plants	Yes	40 CFR 60.4 EPA 1990a
	Priority List—Major source categories (secondary aluminum)	Yes	40 CFR 60.16 EPA 1982a
	Primary Aluminum Reduction Plants	Yes	40 CFR 60, Subpart S EPA 1977a
b. Water:			
EPA ODW	National Secondary Drinking Water Regulations—Secondary maximum contaminant levels	0.05 to 0.2 mg/L	40 CFR 143.3 EPA 1979a
	Monitoring	Yes	40 CFR 143.4 EPA 1979b
EPA OW	Designation of Hazardous Substances—List of hazardous substances (aluminum sulfate)	Yes	40 CFR 116.4 EPA 1978a
	Determination of Reportable Quantities for Hazardous Substances—RQ designated pursuant to Section 311 of the CWA aluminum sulfate	5,000 pounds (2,270 kg)	40 CFR 117.3 EPA 1985a
	EPA Administered Permit Programs: The National Pollution Discharge Elimination System—Primary industry category	Yes	40 CFR 122, App. A EPA 1983a
	Permit application testing requirements	Yes	40 CFR 122, App. D EPA 1983a
	Counties with unincorporated urbanized areas greater than 100,000, but less than 250,00–sludge treatment and disposal processes	Group A: total aluminum Hazardous substances: aluminum sulfate	40 CFR 122, App. I EPA 1990b

Table 7-1. Regulations and Guidelines Applicable to Aluminum *(continued)*

Agency	Description	Information		References
NATIONAL (cont.)				
	Electroplating Point Source Category—Applicability	Yes		40 CFR 413.10 EPA 1981d
	Inorganic Chemical Manufacturing Point Source Category— Aluminum chloride production subcategory-Applicability	Yes		40 CFR 415, Subpart A EPA 1982b
	Aluminum sulfate production subcategory-BPT, BAT, NSPS, PSES, PSNS	Yes		40 CFR 415, Subpart B EPA 1982c
	Aluminum fluoride production subcategory-BPT, BAT, NSPS, PSES, PSNS	Yes		40 CFR 415, Subpart W EPA 1982d
	Iron and Steel Manufacturing Point Source Category—Hot forming subcategory	Yes		40 CFR 420, Subpart G EPA 1982e
	Nonferrous Metals Manufacturing Point Source Category—Applicability	Yes		40 CFR 421.1 EPA 1984b
	Primary aluminum smelting subcategory–BAT for:	1-day Max.	Monthly Avg.	40 CFR 421, Subpart B EPA 1984c
		mg/kg (lbs./10^6 lbs.)		
	anode and cathode paste plant wet air pollution control	8.31E-01	3.69E-01	
	anode contact cooling and briquette quenching	1.277	5.66E-01	
	anode bake plant wet air pollution control (closed top ring furnace)	26.420	11.720	
	anode bake plant wet air pollution control (open top ring furnace with spray tower only)	3.06E-01	1.36E-01	
	anode bake plant wet air pollution control (open top ring furnace with wet electrostatic precipitator and spray tower)	4.461	1.979	
	anode bake plant wet air pollution control (tunnel kiln)	6.953	3.084	
	cathode reprocessing (operated with dry potline scrubbing and not commingled with other precess or nonprocess waters)	273.200	122.600	
	cathode reprocessing (operated with dry potline scrubbing and commingled with other precess or nonprocess waters)	214.000	94.930	
	cathode reprocessing (operated with wet potline scrubbing)	0.000	0.000	

Table 7-1. Regulations and Guidelines Applicable to Aluminum *(continued)*

Agency	Description	Information		References
NATIONAL (cont.)				
	potline wet air pollution control (operated with cathode reprocessing and not commingled with other process or nonprocess water)	6.537	2.933	
	potline wet air pollution control (operated with cathode reprocessing and commingled with other process or nonprocess water)	5.120	2.271	
	potroom wet air pollution control	10.140	4.499	
	potline SO_2 emissions wet air pollution control	8.194	3.634	
	degassing wet air pollution control	15.940	7.071	
	repair and pot soaking	0.000	0.000	
	direct chill casting contact cooling	8.120	3.602	
	continuous rod casting contact cooling	6.36E-01	2.82E-01	
	stationary casting or shot casting contact cooling	0.00	0.00	
	Primary aluminum smelting subcategory–NSPS for:	1-day Max.	Monthly Avg.	
		mg/kg (lbs./10^6 lbs)		
	anode and cathode paste plant wet air pollution control	0.000	0.000	
	anode contact cooling and briquette quenching	1.277	5.66E-01	
	anode bake plant wet air pollution control	0.000	0.000	
	cathode reprocessing (operated with dry potline scrubbing and not commingled with other precess or nonprocess waters)	273.200	122.600	
	cathode reprocessing (operated with dry potline scrubbing and commingled with other precess or nonprocess waters)	214.000	94.930	
	potline wet air pollution control	0.000	0.000	
	potroom wet air pollution control	0.000	0.000	
	potline SO_2 emissions wet air pollution control	8.194	3.634	
	degassing wet air pollution control	0.000	0.000	

Table 7-1. Regulations and Guidelines Applicable to Aluminum *(continued)*

Agency	Description	Information		References
NATIONAL (cont.)				
	pot repair and pot soaking	0.000	0.000	
	direct chill casting contact cooling	8.120	3.602	
	continuous rod casting contact cooling	6.36E-01	2.82E-01	
	stationary casting or shot casting contact cooling	0.00	0.000	
	Secondary aluminum smelting subcategory–Applicability	Yes		40 CFR 421, Subpart C EPA 1984d
	Secondary aluminum smelting subcategory–BAT and NSPS for:	1-day Max. mg/kg (lbs./10^5 lbs)	Monthly Avg.	
	scrap drying wet air pollution	0.000	0.000	
	scrap screening and milling	0.000	0.000	
	BAT-dross washing NSPS-dross washing	66.410 0.000	29.450 0.000	
	demagging wet air pollution control	4.711	2.090	
	delaquering wet air pollution control	2.035	9.03E-01	
	direct chill casting contact cooling	8.120	3.602	
	ingot conveyor casting contact cooling (when chlorine demagging wet air pollution control is not practiced on-site)	4.09E-01	1.82E-01	
	ingot conveyor casting contact cooling (when chloride demagging wet air pollution control is practiced on-site)	0.000	0.000	
	stationary casting contact cooling	0.000	0.000	
	shot casting contact cooling	0.000	0.000	
	Metal Finishing Point Source Category— Metal finishing subcategory	Yes		40 CFR 433, Subpart A EPA 1983b
	Ore Mining and Dressing Point Source Category— Aluminum ore subcategory– BPT, BA, and NSPS	Yes		40 CFR 440, Subpart B EPA 1982f
	Metal Molding and Casting Point Source Category—General definitions	Yes		40 CFR 464.02 EPA 1985b
	Aluminum casting subcategory Applicability	Yes		40 CFR 464, Subpart A EPA 1985c

Table 7-1. Regulations and Guidelines Applicable to Aluminum *(continued)*

Agency	Description	Information		References
NATIONAL (cont.)				
	Coil Coating Point Source Category— Aluminum basis material subcategory–	1-day Max.	Monthly Avg.	40 CFR 465, Subpart C EPA 1982g
		mg/m² (lbs./10⁶ ft²)		
	BPT	15.3 (3.14)	6.26 (1.28)	
	BAT	4.49 (0.92)	1.84 (0.38)	
	NSPS	1.44 (0.30)	1.59 (0.121)	
	Can making subcategory	1-day Max.	Monthly Avg.	40 CFR 465, Subpart D EPA 1982g
		(g [lbs]/10⁶ cans manufactured)		
	BPT	1382.45 (3.048)	688.00 (1.517)	
	BAT	539.48 (1.189)	268.48 (0.592)	
	NSPS	408.95 (0.902)	203.52 (0.449)	
	Porcelain Enameling Point Source Category— Steel basis material subcategory–	1-day Max.	Monthly Avg.	40 CFR 466, Subpart A EPA 1982h
		mg/m² (lbs./10⁶ ft²)		
	BPT metal preparation	182.20 (37.22)	74.47 (15.26)	
	BPT coating operations	38.87 (7.55)	15.07 (3.09)	
	BAT metal preparation	182.00 (37.32)	78.48 (15.26)	
	BAT coating operations	5.74 (1.18)	2.35 (0.84)	
	NSPS metal preparation	30.3 (6.21)	12.4 (2.54)	
	NSPS coating operations	3.82 (0.78)	1.56 (0.84)	
	Cast iron basis material subcategory–	1-day Max.	Monthly Avg.	40 CFR 466, Subpart B EPA 1982h
		mg/m² (lbs./10⁶ ft²)		
	BPT	13.86 (2.84)	8.32 (1.71)	
	BAT	5.74 (1.18)	2.35 (0.48)	
	NSPS	3.82 (0.78)	1.56 (0.32)	

Table 7-1. Regulations and Guidelines Applicable to Aluminum *(continued)*

Agency	Description	Information		References
NATIONAL (cont.)				
	Aluminum basis material subcategory–	1-day Max.	Monthly Avg.	40 CFR 466, Subpart C EPA 1982i
		mg/m² (lbs./10⁶ ft²)		
	BPT and BAT metal preparation	176.98 (36.25)	72.35 (14.82)	
	BPT coating operations	68.44 (14.02)	27.98 (5.73)	
	BAT coating operations	5.74 2.35 (1.18)	(0.48)	
	NSPS metal preparation	29.45 (6.03)	12.06 (2.47)	
	NSPS coating operations	3.82 1.56 (0.78)	(0.32)	
	Copper basis material subcategory	1-day Max.	Monthly Avg.	40 CFR 466, Subpart D EPA 1982j
		mg/m² (lbs./10⁶ ft²)		
	NSPS metal preparation	50.97 (10.44)	20.66 (4.27)	
	NSPS coating operations	3.82 1.56 (0.78)	(0.32)	
	Aluminum Forming Point Source Category— Applicability; monitoring and reporting requirements; and removal allowance for pretreatment standards	Yes		40 CFR 467.01-.05 EPA 1983c
	Rolling with neat oils subcategory–BPT for:	1-day Max.	Monthly Avg.	40 CFR 467, Subpart A EPA 1983d
		mg/off-kg (lbs./10⁶ off-lbs.)		
	core with an annealing furnace scrubber	5.25E-01	2.57E-01	
	core without an annealing furnace scrubber	3.56E-01	1.74E-01	
	continuous sheet casting spent lubricant	1.27E-02	6.30E-03	
	solution heat treatment contact cooling water	49.55	24.66	
	cleaning or etching bath	1.15	5.73E-01	
	cleaning or etching rinse	89.46	44.52	
	cleaning or etching scrubber liquor	102.24	50.88	
	BAT for: core with an annealing furnace scrubber	5.25E-01	2.57E-01	
	core without an annealing furnace scrubber	3.56E-01	1.74E-01	
	continuous sheet casting spent lubricant	1.27E-02	6.30E-03	

Table 7-1. Regulations and Guidelines Applicable to Aluminum *(continued)*

Agency	Description	Information		References
NATIONAL (cont.)				
	solution heat treatment contact cooling water	13.10	6.518	
	cleaning or etching bath	1.151	5.73E-01	
	cleaning or etching rinse	8.944	4.45	
	cleaning or etching scrubber liquor	12.43	6.186	
	NSPS for: core with an annealing furnace scrubber	4.99E-01	2.21E-01	
	core without an annealing furnace scrubber	3.38E-01	1.50E-01	
	continuous sheet casting spent lubricant	1.20E-02	5.30E-03	
	solution heat treatment contact cooling water	12.45	5.52	
	cleaning or etching bath	1.094	4.85E-01	
	cleaning or etching rinse	8.50	3.70	
	cleaning or etching scrubber liquor	11.81	5.24	
	Rolling with emulsions subcategory–BPT for:	1-day Max. / mg/off-kg (lbs./10^6 off-lbs.)	Monthly Avg.	40 CFR 467, Subpart B EPA 1983e
	core	8.4E-01	4.16E-01	
	direct chill casting contact cooling water	8.55	4.26	
	solution heat treatment contact cooling water	49.55	24.66	
	cleaning or etching bath	1.15	5.73E-01	
	cleaning or etching rinse	89.46	44.52	
	cleaning or etching scrubber liquor	102.24	50.88	
	BAT for:	1-day Max. / mg/off-kg (lbs./10^6 off-lbs.)	Monthly Avg.	
	core	8.4E-01	4.2E-01	
	direct chill casting contact cooling water	8.55	4.26	
	solution heat treatment contact cooling water	13.10	6.52	
	cleaning or etching bath	1.15	5.73E-01	
	cleaning or etching rinse	8.95	4.45	

Table 7-1. Regulations and Guidelines Applicable to Aluminum *(continued)*

Agency	Description	Information		References
NATIONAL (cont.)				
	cleaning or etching scrubber liquor	12.43	6.19	
	NSPS for:	1-day Max.	Monthly Avg.	
		mg/off-kg (lbs./10^6 off-lbs.)		
	core	8.0E-01	3.5E-01	
	direct chill casting contact cooling water	8.12	3.60	
	solution heat treatment contact cooling water	12.45	5.52	
	cleaning or etching bath	1.094	4.85E-01	
	cleaning or etching rinse	8.50	3.77	
	cleaning or etching scrubber liquor	11.81	5.24	
	Extrusion subcategory– BPT for:	1-day Max.	Monthly Avg.	40 CFR 467, Subpart C EPA 1983f
		mg/off-kg (lbs./10^6 off-lbs.)		
	core	2.34	1.16	
	extrusion press leakage	9.51	4.73	
	direct chill casting contact cooling water	8.55	4.26	
	press heat treatment contact cooling water	49.55	24.66	
	solution heat treatment contact cooling water	49.55	24.66	
	cleaning or etching bath	1.15	5.73E-01	
	cleaning or etching rinse	102.24	50.88	
	degassing scrubber liquor	16.78	8.35	
	BAT for:	1-day Max.	Monthly Avg.	
		mg/off-kg (lbs./10^6 off-lbs.)		
	core	2.19	1.09	
	extrusion press leakage	9.51	4.73	
	direct chill casting contact cooling water	8.55	4.26	
	press heat treatment contact cooling water	13.10	6.52	
	solution heat treatment contact cooling water	13.10	6.52	
	cleaning or etching bath	1.15	5.8E-01	
	cleaning or etching rinse	25.00	13.00	

Table 7-1. Regulations and Guidelines Applicable to Aluminum *(continued)*

Agency	Description	Information		References
NATIONAL (cont.)				
	cleaning or etching scrubber liquor	12.43	6.19	
	NSPS for:	1-day Max.	Monthly Avg.	
		mg/off-kg (lbs./10^6 off-lbs.)		
	core	2.07	9.2E-01	
	extrusion press leakage	1.82	8.1E-01	
	direct chill casting contact cooling water	8.12	3.60	
	press heat treatment contact cooling water	12.45	5.52	
	solution heat treatment contact cooling water	12.45	5.52	
	cleaning or etching bath	1.094	1.79	
	cleaning or etching rinse	8.5	3.77	
	cleaning or etching scrubber liquor	11.81	5.24	
	Forging subcategory– NSPS for:	1-day Max.	Monthly Avg.	40 CFR 467, Subpart D EPA 1983g
		mg/off-kg (lbs./10^6 off-lbs.)		
	core	3.05E-01	1.35E-01	
	forging scrubber liquor	5.76E-01	2.56E-01	
	solution heat treatment contact cooling water	12.45	5.52	
	cleaning or etching bath	1.094	4.85E-01	
	cleaning or etching rinse	8.85	3.77	
	cleaning or etching scrubber liquor	11.81	5.24	
	Drawing with neat oils subcategory–BPT for:	1-day Max.	Monthly Avg.	40 CFR 467, Subpart E EPA 1983h
		mg/off-kg (lbs./10^6 off-lbs.)		
	core	3.20E-01	1.60E-01	
	continuous rod casting spent lubricant	1.27E-02	6.30E-03	
	continuous rod casting contact cooling water	10.00	4.98	
	solution heat treatment contact cooling water	49.55	24.66	
	cleaning or etching bath	1.15	5.70E-01	
	cleaning or etching rinse	89.46	14.52	
	cleaning or etching scrubber liquor	102.24	50.88	

Table 7-1. Regulations and Guidelines Applicable to Aluminum *(continued)*

Agency	Description	Information		References
NATIONAL (cont.)				
	BAT for:	1-day Max.	Monthly Avg.	
		mg/off-kg (lbs./10^6 off-lbs.)		
	core	3.21E-01	1.60E-01	
	continuous rod casting spent lubricant	1.27E-02	6.30E-03	
	continuous rod casting contact cooling water	1.25	6.21E-01	
	solution heat treatment contact cooling water	13.10	6.52	
	cleaning or etching bath	1.15	5.63E-01	
	cleaning or etching rinse	8.94	4.51	
	cleaning or etching scrubber liquor	12.43	6.19	
	NSPS for:	1-day Max.	Monthly Avg.	
		mg/off-kg (lbs./10^6 off-lbs.)		
	core	3.04E-01	1.35E-01	
	continuous rod casting spent lubricant	2.00E-03	6.00E-03	
	continuous rod casting contact cooling water	1.19	5.26E-01	
	solution heat treatment contact cooling water	12.45	5.52	
	cleaning or etching bath	1.09	4.85E-01	
	cleaning or etching rinse	8.50	3.77	
	cleaning or etching scrubber liquor	11.81	5.24	
	Drawing with emulsions or soaps subcategory	1-day Max.	Monthly Avg.	40 CFR 467, Subpart F EPA 1983i
		mg/off-kg (lbs./10^6 off-lbs.)		
	BPT for:			
	core	3.00	1.50	
	continuous rod casting spent lubricant	1.30E-02	7.00E-03	
	continuous rod casting contact cooling water	10.00	4.98	
	solution heat treatment contact cooling water	49.55	24.66	
	cleaning or etching bath	1.15	5.73E-01	
	cleaning or etching rinse	89.46	44.52	
	cleaning or etching scrubber liquor	102.24	50.88	

Table 7-1. Regulations and Guidelines Applicable to Aluminum *(continued)*

Agency	Description	Information		References
NATIONAL (cont.)				
	BAT for:	1-day Max.	Monthly Avg.	
		mg/off-kg (lbs./10^5 off-lbs.)		
	core	3.00	1.49	
	continuous rod casting spent lubricant	1.30E-02	6.30E-03	
	continuous rod casting contact cooling water	1.25	6.20E-01	
	solution heat treatment contact cooling water	13.10	6.52	
	cleaning or etching bath	1.15	5.70E-01	
	cleaning or etching rinse	8.95	4.45	
	NSPS for:	1-day Max.	Monthly Avg.	
		mg/off-kg (lbs./10^5 off-lbs.)		
	core	2.850	1.27	
	continuous rod casting spent lubricant	1.2E-02	5.3E-03	
	continuous rod casting contact cooling water	1.18	5.26E-01	
	solution heat treatment contact cooling water	12.45	5.52	
	cleaning or etching bath	1.09	4.9E-01	
	cleaning or etching rinse	8.50	3.77	
	cleaning or etching scrubber liquor	1.18	5.24	
c. Food: EPA	Tolerances and Exemptions from Tolerances for Pesticide Chemicals In or On Raw Agricultural Commodities—Specific tolerances aluminum phosphide; tolerances for residues	0.1 ppm		40 CFR 180.225 EPA 1977b
	Exemptions from tolerances aluminum hydroxide (diluent carrier) aluminum oxide (diluent)	Yes		40 CFR 180.1001 EPA 1971
	Tolerances for Pesticides in Animal Feeds—Feed additives permitted in animal feed aluminum phosphide	Yes		40 CFR 186.200 EPA 1977c
	Tolerances for Pesticides in Foods—Food additives permitted in food for human consumption aluminum phosphide	Yes		40 CFR 185.200 EPA 1988a

Table 7-1. Regulations and Guidelines Applicable to Aluminum *(continued)*

Agency	Description	Information	References
NATIONAL (cont.)			
d. Other:			
EPA OAR	Health and Environmental Protection Standards for Uranium and Thorium Mill Tailings—Standards for the control of residual radioactive materials from inactive uranium processing sites aluminum phosphide	Yes	40 CFR 192, App. I EPA 1995c
EPA OSW	Identification and Listing of Hazardous Waste Hazardous waste from non-specific sources–hazardous waste codes for aluminum	F006 and F019	40 CFR 261.31 EPA 1981a
	Hazardous waste from specific sources–hazardous waste codes for primary aluminum	K008	40 CFR 261.32 EPA 1981b
	Discarded commercial chemical products, off-species, container residues, and spill residues–hazardous waste codes:		40 CFR 261.33 EPA 1980
	primary aluminum	K008	
	aluminum phosphide	P006	
	Identification and Listing of Hazardous Waste—Hazardous constituents; hazardous waste code P006 aluminum phosphide		40 CFR 261, App. VIII EPA 1988b
	Waste excluded under 40 CFR 260.20 and 260.22 (aluminum)	Yes	40 CFR 261, App. IX EPA 1984a
	Standard for Owners and Operators of Hazardous Waste Treatment, Storage, and Disposal Facilities—Examples of potentially incompatible waste (aluminum)	Yes	40 CFR 264, App. V EPA 1981c
	Standards for the Management of Specific Hazardous Wastes and Specific Types of Hazardous Waste Management Facilities—Reference air concentration		40 CFR 266, App. IV EPA 1991
	aluminum phosphide	0.3 $\mu g/m^3$	
	Health-based limits for exclusion of waste-derived residues–Residue concentration limits	1.0E-02 mg/kg	40 CFR 266, App. VII EPA 1991
	Land Disposal Restrictions—Waste specific prohibitions–spent aluminum potliners; reactive; and carbamate wastes (aluminum)	Yes	40 CFR 268.39 EPA 1996a
	Applicability of treatment standards		
	aluminum	F006, F019, K088	40 CFR 268.40 EPA 1994
	aluminum phosphide	P006	

Table 7-1. Regulations and Guidelines Applicable to Aluminum *(continued)*

Agency	Description	Information	References
NATIONAL (cont.)			
	Treatment standards for hazardous debris	Yes	40 CFR 268.45 EPA 1992a
	Metal bearing waste prohibited from dilution in a combustion unit according to 40 CFR 268.3(c) aluminum	F006 and F019	40 CFR 268, App. XI EPA 1996b
	Requirements for Authorization of State Hazardous Waste Programs-Land disposal restrictions phase III	Spent aluminum potliners	40 CFR 271.1 EPA 1992b
EPA OERR	Designation, Reportable Quantities, and Notification—List of hazardous substances and reportable quantities	Statutory RQ / Final RQ lbs. (kg)	40 CFR 302.4 EPA 1993
	aluminum phosphide	1 (0.454) / 100 (45.4)	
	aluminum sulfate	5,000 (2,270) / 5,000 (2,270)	
	Emergency Planning and Notification—List of extremely hazardous substances and their threshold planning quantities (aluminum phosphide)	Reportable Quantity: 100 lbs. Threshold Planning Quantity: 500 lbs.	40 CFR 355, App. A EPA 1987a
	Toxic chemical release reporting; Community right-to-know aluminum (fume or dust) aluminum oxide (fibrous forms)	Yes	40 CFR 372.65 EPA 1987c
	Toxic chemical release reporting; Community right-to-know aluminum phosphide	Yes	40 CFR 372.65 EPA 1995d
EPA OPPTS	Pesticide Registration and Classification Procedures—Pesticides classified for restricted use (aluminum phosphide)	Yes	40 CFR 152.175 EPA 1978b
Guidelines: a. Air: ACGIH	TLV TWA Aluminum		ACGIH 1996
	metal dust	10 mg/m^3	
	pyro powders, as Al	5 mg/m^3	
	welding fumes, as Al	5 mg/m^3	
	soluble salts, as Al	2 mg/m^3	
	alkyls (not otherwise classified)	2 mg/m^3	
	Aluminum oxide	10 mg/m^3	
NIOSH	REL— Aluminum		NIOSH 1992
	Total dust	10 mg/m^3 TWA	
	Respirable fraction	5 mg/m^3 TWA	
	Pyro powders	5 mg/m^3 TWA	
	Welding fumes	5 mg/m^3 TWA	
	Soluble salts	2 mg/m^3 TWA	
	Alkyls	2 mg/m^3 TWA	

Table 7-1. Regulations and Guidelines Applicable to Aluminum *(continued)*

Agency	Description	Information	References
NATIONAL (cont.)			
b. Water:			
EPA OW	Water Quality Guidance for the Great Lakes Systems—Acute Water Quality Criteria for Protection of Aquatic Life in Ambient Water Pollutants that are not bioaccumulative chemicals of concern: Aluminum	Yes	40 CFR 132, Table 1 EPA 1995b
c. Other:			
ACGIH	Cancer Classification	A4[b]	ACGIH 1996
DOT	Hazardous Materials	Yes	49 CFR 172.101 DOT 1990
STATE			
Regulations and Guidelines:	Acceptable Ambient Air Concentrations		NATICH 1992
a. Air:			
	Aluminum		
CT	8-hour	4.00E+01 $\mu g/m^3$ (0.013 ppm)	
FL-PINELLA	8-hour 24-hour	1.00E+02 $\mu g/m^3$ (0.031 ppm) 2.40E+01 $\mu g/m^3$ (0.008 ppm)	
ND	8-hour	1.00E-01 mg/m^3 (0.031 ppm)	
NV	8-hour	2.38E-01 mg/m^3 (0.075 ppm)	
OK	24-hour 24-hour	1.00E+02 $\mu g/m^3$ (0.031 ppm) 5.00E+02 $\mu g/m^3$ (0.157 ppm)	
TX	30-minute Annual	5.00E+01 $\mu g/m^3$ (0.016 ppm) 5.00 $\mu g/m^3$ (0.002 ppm)	
VA	24-hour	3.30E+01 $\mu g/m^3$ (0.010 ppm)	
WA-SWEST	24-hour	6.70 $\mu g/m^3$ (0.002 ppm)	
	Aluminum Chloride		
OK	24-hour	2.00E+02 $\mu g/m^3$ (0.037 ppm)	
	Aluminum Compounds		
ND	8-hour	2.00E-02 mg/m^3	
OK	24-hour	2.00E+02 $\mu g/m^3$	
	Aluminum Oxide		
AZ	1-hour	4.50E+02 $\mu g/m^3$ (0.108 ppm)	
	24-hour	1.5E+02 $\mu g/m^3$ (0.036 ppm)	
FL-PINELLA	8-hour	1.00E+02 $\mu g/m^3$ (0.024 ppm)	
	24-hour	2.40E+1 $\mu g/m^3$ (0.006 ppm)	
ND	8-hour	1.00E-01 mg/m^3 (0.024 ppm)	
TX	30-minute	5.00E+02 $\mu g/m^3$ (0.120 ppm)	

Table 7-1. Regulations and Guidelines Applicable to Aluminum *(continued)*

Agency	Description	Information	References
STATE (cont.)			
	Annual	5.00E+01 $\mu g/m^3$ (0.012 ppm)	
VA	24-hour	1.67E+02 $\mu g/m^3$ (0.040 ppm)	
b. Water:	Drinking water quality guidelines and standards		FSTRAC 1995
AZ	Guideline	73 $\mu g/L$	
CA	Standard	1,000 $\mu g/L$	
ME	Guideline	1,430 $\mu g/L$	

[a]Group 1: There is sufficient evidence of carcinogenicity in humans for certain exposures in the aluminum products industry.
[b]A4: Not classifiable as a human carcinogen

ACGIH = American Conference of Governmental Industrial Hygienists; BAT = Best Available Technology Economically Achievable; BPT = Best Practicable Control Technology Currently Available; EPA = Environmental Protection Agency; IARC = International Agency for Research on Cancer; NIOSH = National Institute for Occupational Safety and Health; NSPS = New Source Performance Standards; ODW = Office of Drinking Water; OAR = Office of Air and Radiation; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Wastes; REL = Recommended Exposure Limit; PSES = Performance Standards Existing Sources; PSNS = Performance Standards New Sources; TLV = Threshold Limit Value; TWA = Time-Weighted Average; WHO = World Health Organization

The EPA also regulates aluminum under the Safe Drinking Water Act (SDWA). Although the EPA has not promulgated maximum contaminant levels (MCLs) for aluminum in drinking water, the Agency has established a secondary MCL (SMCL) at a concentration range of 0.05-0.2 mg/L (EPA 1979a; IRIS 1997). The SMCLs are nonenforceable but establish limits for contaminants which could affect the aesthetic qualities of drinking water (IRIS 1997). Aluminum is also regulated by the EPA under the authority of the Clean Water Act (CWA). The regulated point-source categories include electroplating (EPA 1981d), inorganic chemical manufacturing (EPA 1982b), iron and steel manufacturing (EPA 1982e), ore mining and dressing (EPA 19820, coil coating (EPA 1982g), porcelain enameling (EPA 1982h), metal finishing (EPA 1983b), aluminum forming (EPA 1983c), nonferrous metals manufacturing (EPA 1984b), and metal molding and casting (EPA 1985b). Aluminum (fume or dust), aluminum oxide (EPA 1987c), and aluminum phosphide (EPA 1995d) are on the list of chemicals appearing in "Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986". Aluminum sulfate has been assigned a reportable quantity (RQ) limit of 5,000 pounds (2,270 kg) (EPA 1985a); aluminum phosphide has an RQ of 100 pounds (45.4 kg) (EPA 1993). The RQ represents the amount of a designated hazardous substance which, when released to the environment, must be reported to the appropriate authority.

EPA recommends a criterion continuous concentration (CCC) of 87 μg/L and a criteria maximum concentration (CMC) of 750 μg/L (EPA 1999). The CCC is an estimate of the highest concentration of aluminum in fresh water to which aquatic organisms can be exposed indefinitely without resulting in an unacceptable effect; the CMC is the highest concentration in fresh water to which aquatic organisms can be exposed for a brief period without resulting in an unacceptable effect.

The EPA has established a tolerance limit of 0.1 ppm for residues of aluminum phosphide in or on raw agricultural commodities such as almonds, barley, corn, dates, rice, sesame seeds, and wheat when it is used as a post-harvest treatment (EPA 1977b).

The Association for the Advancement of Medical Instrumentation has issued a standard recommending that water used in the preparation of dialysate solution contain less than 10 μg aluminum per liter. The purpose is to limit the unintentional administration of aluminum to dialysis patients whose renal dysfunction and the inefficiency of dialysis equipment to remove aluminum could cause an aluminum buildup to biologically hazardous levels (AAM 1998).

8. REFERENCES

*AAMI (Association for the Advancement of Medical Instrumentation). 1998. Water Quality for Dialysis, yd edition and Current Concepts in Hemodialyzer Reprocessing, 2nd edition. AAMI Dialysis Monograph Series.

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

Abernathy AR, Larson GL, Mathews RC Jr. 1984. Heavy metals in the surficial sediments of Fontana Lake, North Carolina (USA). Water Res 18:351-354.

Abraham-Peskir JV, Butler RD, Sigee DC. 1997. Seasonal changes in whole-cell metal levels in protozoa of activated sludge. Ecotoxicol Environ Saf 38:272-280.

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

Abreo K, Glass J. 1993. Cellular, biochemical, and molecular mechanisms of aluminum toxicity. Nephrol Dial Transplant Suppl 1:5-l 1.

Abreo K, Jangula J, Jain SK, et al. 1991. Aluminum uptake and toxicity in cultured mouse hepatocytes. J Am Sot Nephrol 1:1299-1304.

ACGIH. 1982. Threshold limit values for chemical substances and physical agents and biological exposure indices. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

ACGIH. 1992. Threshold limit values for chemical substances and physical agents and biological exposure indices. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

*ACGIH. 1996. 1995-1996 Threshold limit values for chemical substances and physical agents and biological exposure indices. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

Ackley DC, Yokel RA. 1997. Aluminum citrate is transported from brain into blood via the monocarboxylic acid transporter located at the blood-brain barrier. Toxicology 120:89-97.

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

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

*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 44:337-350.

---

*Cited in text

Aikoh H, Nishio MR. 1996. Aluminum content of various canned and bottled beverages. Bull Environ Contam Toxicol 56: 1-7.

Aitken RL, Moody PW, Compton BL. 1990. A simple bioassay for the diagnosis of aluminum toxicity in soils. Commun Soil Sci Plant Anal 215 11-529.

*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.

Albrecht J, Norenberg MD. 1991. Aluminum chloride stimulates NACl-dependent release of taurine and aminobutyric acid in rat cortical astrocytes. Neurochem Int 18: 125- 129.

*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.

Alessio L, Mussi I, Di Sipio I, et al. 1989. Behavior of some neuroendocrinal tests in aluminum Workers. WHO Environmental Health, 20. Trace Elements in Human Health And Disease, Second Nordic Symposium Odense, Denmark, August 1721, 1987.

Alessandri MV, Baretta L, Magarotto G. 1992. Bronchite cronica e funzionalita' respiratoria negli addetti alla produzione di alluminio primario. Med Lav 83:445-450. (Italian)

Alexander J, Nordal KP, Dahl E, et al. 1987. Serum levels of aluminum in healthy Norwegians. WHO Environmental Health 20.

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. Aluminumintoxication. N Engl J Med 310:1113-l 115.

Alfrey AC. 1985. Gastrointestinal absorption of aluminum Clin Nephrol 24:S84-S87.

Alfrey AC. 1986. Aluminum metabolism Kidney Int 29:S-8 to S-11.

*Alfrey AC. 1987. Aluminum metabolism and toxicity in uremia. Journal of the University of Occupational and Environmental Health 9: 1323- 132.

Alfrey AC. 1993a. Aluminum and renal disease. Contrib Nephrol 102:110-124.

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

*Alfrey AC, LeGendre GR, Kaehny WD. 1976. The dialysis encephalopathy syndrome: Possible aluminum intoxication. N Engl J Med 294: 184-l 88.

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

Ali N, Craxton A, Sumner M, et al. 1995. Effects of aluminum on the hepatic inositol polyphosphate phosphatase. Biochem J 305:557-561.

*Allain P, Mauras Y. 1979. Determination of aluminum in blood, urine, and water by inductively coupled plasma emission spectrometry. Anal Chem 5 1:2089-2091.

Allain P, Mauras Y, Krari N, et al. 1990. Plasma and urine aluminum concentrations in healthy subjects after administration of sucralfate. Br J Clin Pharmacol 29:391-395.

Allain P, Gauchard F, Krari N. 1996. Enhancement of aluminum digestive absorption by fluoride in rats. Res Commun Mol Pathol Pharmacol 91:225-23 1.

Alle DD, Orvig C, Yokel RA. 1995. Evidence for energy-dependent transport of aluminum out of brain extracellular fluid. Toxicology 983 1-39.

Allen DD, Yokel RA. 1992. Dissimilar aluminum and gallium permeation of the blood-brain barrier demonstrated by in vivo microdialysis. J Neurochem 58903-908.

Allen DD, Orvig C, Yokel RA. 1994. Pharmacokinetics and distribution of tris(maltolato)aluminum(III) into the central nervous system Neurotoxicology 15:37 1-378.

*Allen SK, Allen JM, Lucas S. 1996. Dissolved metal concentrations in surface waters from westcentral Indiana contaminated with acidic mine drainage. Bull Environ Contam Toxicol 56:240-243.

Alleva E, Rankin J, Santucci D. 1998. Neurobehavioral alteration in rodents following developmental exposure to aluminum Toxico1 Ind Health 14:209-221.

Al-Masalkhi A, Walton SP. 1994. Pulmonary fibrosis and occupational exposure to aluminum J Ky Med Assoc 92:59-61.

Al-Saleh I, Shinwari N. 1996. Aluminum in Saudi children. BioMetals 9:385-392.

*Altman PK, Dittmer DS. 1974. In: Biological handbooks: Biology data book. Vol. III, 2nd ed. Bethesda, MD: Federation of American Societies for Experimental Biology, 1987-2008, 2041.

Altmann P. 1993. Aluminum toxicity in dialysis patients: No evidence for a threshold serum aluminum concentration. Nephrol Dial Transplant Suppl 1:25-34.

*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.

Alveteg M, Sverdrup H, Warfvinge P. 1995. Developing a kinetic alternative in modeling soil aluminum Water Air Soil Pollut 79:377-389.

Ambre JJ. 1994. Aluminum toxicity. JAMA 272:242.

*Anane R, Bonini M, Creppy EE. 1997. Transplacental passage of aluminum from pregnant mice to fetus organs after maternal transcutaneous exposure. Hum Exp Toxicol 16501-504.

*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 69:568-57 1.

*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 6:29-33.

*Andersen ME, Krishnan K. 1994a. Relating in vitro to in vivo exposures with physiologically-based tissue dosimetry and tissue response models. Animal test alternatives. Salem ed. U.S. Army Chemical Research Development and Engineering Center, Aberdeen Proving Ground, Maryland.

Andersen ME, Krishnan K. 1994b. Physiologically based pharmacokinetics and cancer risk assessment. Environ Health Perspect Suppl 102:103-108.

*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: 185-205.

Andia J, Cannata B. 1996. Aluminum toxicity: Its relationship with bone and iron metabolism Nephrol Dial Transplant 11(Suppl. 3):69-73.

*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.

Anghileri LJ, Maincent P, Thouvenot P. 1994. Long-term oral administration of aluminum in mice. Aluminum distribution in tissues and effects on calcium metabolism Ann Clin Lab Sci 24:22-26.

Anonymous. 1992a. Three deaths associated with excess aluminum in dialysate. Nephrol News Issues 6:10.

Anonymous. 1992b. Is aluminum a dementing ion? Lancet 339:713-714.

*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 B21:191-205.

*Anusavice KJ. 1985. Report on base alloys for crown and bridge applications: Benefits and risks. J Am Dent Assoc 111:479-483.

Apostoli P, Lucchini R, Maccarrone R, et al. 1992. Monitoraggio biologico dell'esposizione professionale ad alluminio. Med Lav 83:475-483.

Arbuckle TE, Sherman GJ, Corey PN, et al. 1988. Water nitrates and CNS birth defects: A population-based case-control study. Arch Environ Health 43: 162-167.

*Arieff AI, Cooper JD, Armstrong D, et al. 1979. Dementia, renal failure, and brain aluminum Ann Intern Med 90:741-747.

Armstrong B, Theriault G. 1996. Compensating lung cancer patients occupationally exposed to coal tar pitch volatiles. Occup Environ Med 53: 160-l 67.

Armstrong B, Tremblay C, Baris D, et al. 1994. Lung cancer mortality and polynuclear aromatic hydrocarbons: a cas-cohort study of aluminum production workers in Arvida, Quebec, Canada. Am J Epidemiol 139:250-262.

*Armstrong RA, Winsper SJ, Blair JA. 1996. Aluminium and Alzheimer's disease: Review of possible pathogenic mechanisms. Dementia 7:1-9.

Armstrong VBG, Tremclay CG, Cyr D, et al. 1986. Estimating the relationship between exposure to tar volatiles and the incidence of bladder cancer in aluminum smelter workers. Stand J Work Environ Health 12:486-493.

*ATSDR. 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.

Atterwill CK, Johnson H, Thomas S . 1991. Models for the in vitro assessment of neurotoxicity. Neurotoxicology 12:788-789.

Atterwill CK, Johnston H, Thomas SM. 1992. Models for the in vitro assessment of neurotoxicity in the nervous system in relation to xenobiotic and neurotrophic factor-mediated events. Neurotoxicology 13:39-54.

Attrill MJ, Thomes RM. 1995. Heavy metal concentrations in sediment from the Thames estuary, UK. Mar Pollut Bull 30:742-744.

*Bathe CA, Rutzke M, Lisk DJ. 1991. Absorption of vanadium nickel, aluminum and molybdenum by Swiss chard grown on soil amended with oil fly ash or bottom ash. J Food Saf 12:79-84.

*Baes CF, Sharp RD, Sjoreen Al, et al. 1984. A review and analysis of parameters for assessing transport of environmentally released radionuclides through agriculture. US Department of Energy. ORNL-5786.

Bailey SW, Driscoll CT, Hombeck JW. 1995. Acid-base chemistry and aluminum transport in an acidic watershed and pond in New Hampshire. Biogeochem 28:69-91.

Banks WA, Kastin AJ. 1983. Aluminum increased permeability of the blood-brain barrier to labelled DSIP and beta-endorphin: Possible implications for senile and dialysis dementia. Lancet 2-1227-1229.

*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 betaprotein-40 by murine and human intracellular enzymes. Neurotoxicol Teratol 81:67 l-677.

Baris YI. 1991. Fibrous zeolite (Erionite)-related diseases in Turkey. Am J Ind Med 19:374-378.

*Barnes DC, Dourson M. 1988. Reference dose (RfD) description and use in health risk assessments. Regul Toxicol Pharmacol 8:47 l-486.

*Bast-Pettersen R, Drablos PA, Goffeng LO, et al. 1994. Neuropsychological deficit among elderly workers in aluminum production. Am J Ind Med 25:649-662.

Basu S, Chaudhuri D, Chaudhuri AN. 1997. Influence of calcium on the toxic effects of dietary aluminium J Food Sci Technol34:264-266.

Bauer S, Wolfe I, Werner N, et al. 1992. Toxicological investigations in the semiconductor industry: 1. Studies on the acute oral toxicity of a complex mixture of waste products from the aluminum plasma etching process. Toxicol Ind Health 8:141-156.

Baur S, Feger KH. 1992. Importance of natural soil processes relative to atmospheric deposition in the mobility of aluminum in forested watersheds of the Black Forest. Environ Pollut 77:99- 105.

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.

*Baxter MJ, Burrell JA, Crews H, et al. 1991. Aluminum levels in milk and infant formulae. Food Addit Contam 8:653-660.

Baydar T, Aydin A, Duru S, et al. 1997. Aluminum in enteral nutrition formulas and parenteral solutions. Clin Toxicol 35:277-281.

Becker PR, Mackey EA, Demiralp R, et al. 1997. Concentrations of chlorinated hydrocarbons and trace elements in marine mammal tissues archived in the U.S. National Biomonitoring Specimen Bank. Chemosphere 34:2067-2098.

Becker 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.

Begin R, Masse S, Sebastien P, et al. 1987. Sustained efficacy of aluminum to reduce quartz toxicity in the lung. Exp Lung Res 13:205-222.

Begin R, Masse S, Dufresne A. 1995. Further information on aluminum inhalation in silicosis. Occup Environ Med 52:778-780.

*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.

Bencze K, Pelikan CH, Bahemann-Hoffmeister A, et al. 1991. Lithium/aluminum alloys. A problem material for biological monitoring. Sci Total Environ 101:83-90.

*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, S weeting FW. 1990. On-line determination of residual aluminum in potable and treated waters by flow-injection analysis. Anal Chim Acta 238:177-182.

*Berlyne GM, Ben-Ari J, Pest D, et al. 1970. Hyperaluminaemia from aluminum resins in renal failure. Lancet 2:494-496.

Berninger K, Pennanen J. 1995. Heavy metals in perch (perca fluviatilis 1.) from two acidified lakes in the Salpausselka Esker area in Finland. Water Air Soil Pollut 81:283-294.

*Bernuzzi V, Desor D, Lehr P. 1986a. Development and learning abilities of rats prenatally intoxicated with aluminum [Abstract]. Neurosci Lett Suppl23:S32.

*Bernuzzi V, Desor D, Lehr PR. 1986b. Effects of prenatal aluminum exposure on neuron-rotor maturation in the rat. Neurobehav Toxicol Teratol 8115-l 19.

Bernuzzi V, Desor D, Lehr P. 1986c. Development and learning abilities of rats prenatally intoxicated with aluminum Neurosci Lett Suppl:S32.

*Bernuzzi V, Desor D, Lehr PR. 1989a. Effects of postnatal aluminum lactate exposure on neuromotor maturation in the rat. Bull Environ Contam Toxicol 42:45 l-455.

*Bernuzzi V, Desor D, Lehr PR. 1989b. Developmental alterations in offspring of female rats intoxicated by aluminum chloride or lactate during gestation. Teratology 40:2 1-27.

*Bertholf RL. 1987. Aluminum and Alzheimer's disease: Perspectives for a cytoskeletal mechanism CRC Crit Rev Clin Lab Sci 25: 195-2 10.

Bertholf RL, Wills MR, Savory J. 1988. Aluminum In: Seiler HG, Sigel H, eds. Handbook on toxicity of inorganic compounds. New York, NY: Marcel Dekker Inc., 34-43.

Berthon G, Dayde S. 1992. Why aluminum phosphate is less toxic than aluminum hydroxide. J Am Coll Nutr 11:340-348.

Bertolone G, Andriani M, Bonucci E, et al. 1993. Dynamics of bone aluminum over one year of functioning renal graft. Nephron 64:540-546.

*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.

Bielarczyk H, Tomaszewicz M, Szutowicz A. 1998. Effect of aluminum on acetyl-coa and acetylcholine metabolism in nerve terminals. J Neurochem 70: 1175- 1181.

Bilinski H, Horvath L, Trbojevic-Cepe M. 1992. Precipitation and characterization of an aluminosilicate from AlCl,-Na,SiO,-HCl in serum of interest for Alzheimer disease. Clin Chem 38:2019-2024.

*Bilkei-Gorzo A. 1993. Neurotoxic effect of enteral aluminum Food Chem Toxicol 31:357-361.
Birchall JD, Chappell JS. 1989. Aluminum water chemistry, and Alzheimer's disease [Letter]. Lancet i:953.

*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(supp 4):s37-s39.

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.

Bjornstad HE, Oughton DH, Salbu B. 1992. Determination of aluminum-26 using a low-level liquid scintillation spectrometer. Analyst 117:435-438.

*Blair HC, Finch JL, Avioli R, et al. 1989. Micromolar aluminumlevels reduce 3H-thymidine incorporation by cell line UMR 106-01. Kidney Int 35:1119-l 125.

*Blotcky AJ, Hobson D, Leffler JA, et al. 1976. Determination of trace aluminum in urine by neutron activation analysis. Anal Chem 48:1084-1088.

Boczko ML. 199 1. Dementia: A review of current environmental issues. Integ Psych 7: 194-202.

*Bodek I, Lyman WJ, Reehl WF, et al. eds. 1988. Environmental inorganic chemistry: properties, processes, and estimation methods. New York, NY: Pergamon Press, 6.7-l to 6.7-9.

*Boehler-Sommeregg er K, Lindemayr H. 1986. Contact sensitivity to aluminum Contact Dermatitis 15:278-281.

Bohmer J, Rahmann H. 1 9 9 1 . Ultrastructural aluminium detection in amphibian tissues by electron spectroscopic imaging and electron energy-loss spectroscopy. J Microsc 162:115-122.

Bolla KI, Briefel G, Spector D, et al. 1992. Neurocognitive effects of aluminum Arch Neurol49:1021-1026.

Borak J, Wise JPS. 1998. Does aluminum exposure of pregnant animals lead to accumulation in mothers or their offspring? Teratology 57:127-139.

Bosque-Sendra JM, Valencia C, Boudra S. 1994. Determination of trace amounts of aluminum in water by solid-phase spectrophotometry. Anal Lett 27:1579-1594.

Boudot J-P, Merlet D, Rouiller J, et al. 1994. Validation of an operational procedure for aluminum speciation in soil solutions and surface waters. Sci Total Environ 158:237-252.

*Bougle D, Bureau F, Voirin J, et al. 199 1. AIuminum levels in term and premature infants on enteral nutrition. Trace ElemMed 8:172-174.

Bougle D, Bureau F, Morello R, et al. 1997. Aluminum in the premature infant. Trace Elem Electrolytes 14:24-26.

*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 23:91-101.

*Bowdler NC, Beasley DS, Fritze C, et al. 1979. Behavioral effects of aluminum ingestion on animal and human subjects. Pharmacol Biochem Behav 10509-512.

Breitner JCS , Welsh KA. 1995. Genes and recent developments in the epidemiology of Alzheimer's disease and related dementia. Epidemiol Rev 17:39-47.

Brenner SR, Yoon K-W. 1994. Aluminum toxicity in rat hippocampal neurons. Neurosci Lett 178:260-262.

Bronner F, Coburn JW. 1981. Trace minerals. New York, NY: Academic Press, Inc.

*Brooks AW, White KN, Bailey SE. 1992. Accumulation and excretion of aluminium and iron by the terrestrial snail Helix Aspersa. Comp Biochem Physiol 103:577-583.

Browne BA, Driscoll CT. 1993. pH-dependent binding of aluminum by a fulvic acid. Environ Sci Technol 27:915-922.

*Browning E. 1969. Aluminum In: Browning E, ed. Toxicity of industrial metals. New York: Appleton-Century-Crofts, 3-22.

Bruce BW, McMahon PB. 1996. Shallow ground-water quality beneath a major urban center: Denver, Colorado, USA. J Hydrol 186:129-151.

*Brumbaugh WG, Kane DA. 1985. Variability of aluminum in organs and whole bodies of smalhnouth bass (micropterus dolomieui). Environ Sci Technol 19:828-83 1.

Brus R, Szkilnik R, Konecki J, et al. 1997a. Short-term changes in glucose uptake in rat brain and some peripheral tissues after consumption of aluminum, as a function of ontogenic development. Pharmacol Rev Commun 9:93-98.

Brus R, Szkilnik R, Popieluch I, et al. 1997b. Effect of aluminum exposure on central serotonin and muscarine receptor reactivity in rats. Med Sci Monit 3:63 1-636.

*Brusewitz S. 1984. Aluminum Vol203. Stockholm Sweden: University of Stockholm Institute of Theoretical Physics. 138.

*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 Toxico1 31:203-216.

*Budavari S, O'Neil MJ, Smith A, et al. 1989. The Merck index. 11th ed. Rahway, N.J.: Merck & Co., Inc.

*Budavari S, O'Neil MJ, Smith A, et al. 1996. The Merck index. 12'h ed. Whitehouse Station, N.J.: Merck & Co.. Inc.

*Buergel PM, Soltero RA. 1983. The distribution and accumulation of aluminum in rainbow trout following a whole-lake alum treatment. J Freshwater Ecol2:37-44.

Bunce HWF. 1996. Methods of monitoring smelter emission effects on a temperate rain forest. Fluoride 29:241-251.

Burgess E. 1991. Aluminum toxicity from oral sucralfate therapy. Nephron 59523-524.

*Burnatowska-Hledin MA, Doyle TM, Eadie MJ, et al. 1986. 1, 25Dihydroxy-vitamin D, increase serum and tissue accumulation of aluminum in rats. J Lab Clin Med 108:96-102.

Burnett JW. 1991. Cutaneous abnormalities induced by aluminum iron, and silica. Cutis 47:391-392.

Calamandrei G, Ricceri L, Santucci D, et al. 1996. Neurobehavioural abnormalities during neonatal development in a rodent model: The role of neurotrophic factors. Teratology 53:22A.

*Cam JM, Luck VA, Eastwood JB, et al. 1976. The effect of aluminum hydroxide orally on calcium phosphorus and aluminumin normal subjects. Clin Sci Mol Med 51:407-414.

Campbell IR, Cass JS, Cholak J, et al. 1957. Aluminum in the environment of man. AMA Arch Ind Health 15:359-448.

*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.

Candy JM, McArthur FK, Oakley AE, et al. 1992. Aluminum accumulation in relation to senile plaque and neurofibrillary tangle formation in the brains of patients with renal failure. J Neurol Sci 107:2 10-218.

Canizares P, Castro L de, Valcarcel M. 1994. Flow-through fluorimetric sensor for the determination of aluminum at the nanogram per milliliter level. Anal Lett 27:247-262.

*Cann CE, Prussin SG, Gordan GS. 1979. Aluminumuptake by the parathyroid glands. J Clin Endocrinol Metab 49:543-545.

*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.

Capdevielle MC, Scanes CG. 1995. Effect of dietary acid or aluminum on growth and growth-related hormones in mallard ducklings (anas platyrhynchos). Arch Environ Contam Toxicol 29:462-468.

Caramel0 CA, Cannata JB, Rodeles MR, et al. 1995. Mechanisms of aluminum-induced microcytosis: Lessons from accidental aluminum intoxication. Kidney Int 47: 164- 168.

*Carmichael KA, Fallon MD, Dalinka M, et al. 1984. Osteomalacia and osteitis fibrosa in a man ingesting aluminum hydroxide antacid. Am J Med 76: 1137-l 143.

Carpenter DO. 1994. The public health significance of metal neurotoxicity. Cell Mol Neurobiol 14:591-597.

*Carrillo F, Perez C, Camara C. 1992. Sensitive flow-injection-spectrofluorimetric method to determine aluminium III in water. Anal Chim Acta 262:91-96.

Carta P, Boscaro G, Mantovano S, et al. 1992a. Sintomi respiratori e funzione polmonare nell'industria italiana di alluminio primario. Med Lav 83:438-444. (Italian)

Carta P, Cocco PL, Flore C, et al. 1992b. Mortal&a nei lavoratori della fonderia di alluminio primario diportovesme in Sardegna. Med Lav 83530-535. (Italian)

Carter LF, Porter SD. 1997. Trace-element accumulation by hygrohypnum ochraceum in the Upper Rio Grande basin, Colorado and New Mexico, USA. Environ Toxicol Chem 16:252 l-2528.

Cefali EA, Nolan JC, McConnell WR, et al. 1995. Pharmacokinetic study of zeolite A, sodium aluminosilicate, magnesium silicate, and aluminum hydroxide in dogs. Pharm Res 12:270-274.

*Ghan JCM, Jacob M, Brown S, et al. 1998. Aluminum metabolism in rats: Effects of vitamin-D, dihydrotachysterol, 1,25-dihydroxyvitamin-D and phosphate binders. Nephron 48:61-64.

*Ghan-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, Duhaux L, Paolaggl F, et al. 1988. Analytical problems encountered in determining aluminum status from hair in controls and hemodialyzed patients. Clin Chem 34:2253-2255.

Chappuis P, Poupon J, Arnaud J, et al. 1991. About FDA recommendations for aluminum in parenteral solutions. Am J Clin Nutr 54:951-956.

Chaussidon M, Netter P, Kessler M, et al. 1993. Dialysis-associated arthropathy: Secondary ion mass spectrometry evidence of aluminum silicate in beta2-microglobulin amyloid synovial tissue and articular cartilage. Nephron 65:559-563.

Chazan JA, Lew NL, Lowrie EG. 199 1. Increased serum aluminum An independent risk factor for mortality in patients undergoing long-term hemodialysis. Arch Intern Med 15 1:3 19-322.

Chedid F, Fudge A, Teubner J, et al. 1991. Aluminium absorption in infancy. J Paediatr Child Health 27:164-166.

Cheetham ME. 1995. Cell stress genes and chronic neurodegenerative disorders. Neuropathol Appl Neurobiol21:486-488.

*Chemfinder. 1997. Aluminum http://chemfinder.camsoft.com/cg-win/cfserver.exe.

*Chen W-J, Monnat RJJ, Chen M, et al. 1978. Aluminum induced pulmonary granulomatosis. Hum Pathol 9:705-711.

Cherroet G, Burnel D, Lehr PR. 1996. [Effect of intraperitoneal aluminum chloride poisoning in the young and adult rat: Aluminemia, urinary elimination and cerebral choline acetyltransferase activity]. Bull Acad Sot lorraines sci 35:123-136. (French).

*Cherroret G, Bernuzzi V, Desor D, et al. 1992. Effects of postnatal aluminum exposure on choline acetyltransferase activity and learning abilities in the rat. Neurotoxicol Teratol 14:259-264.

Cherroret G, Capolaghi B, Hutin MF, et al. 1995. Effects of postnatal aluminum exposure on biological parameters in the rat plasma. Toxicol Lett 78:119-125.

Cherroret G, Desor D, Hutin MF, et al. 1996. Effects of aluminum chloride on normal and uremic adult male rats. Biol Trace Elem Res 54:43-53.

Chiba M, Masironi R. 1992. Toxic and trace elements in tobacco and tobacco smoke. Bull W H 0 70:269-275.

*Chines A, Pacifici R. 1990. Antacid and sucralfate-induced hypophosphatemic osteomalacia: A case report and review of the literature. Calcif Tissue Int 47:29 l-295.

Chmielnicka J, Nasiadek M. 1991. Tissue distribution and urinary excretion of essential elements in rats orally exposed to aluminum chloride. Biol Trace Elem Res 31: 131 - 13 8.

Chmielnicka J, Nasiadek M, Lewandowska-zyndul E, et al. 1996. Effect of aluminum on hematopoiesis after intraperitoneal exposure in rats. Ecotoxicol Environ Saf 33:201-206.

*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-l 116.

Christel PS. 1992. Biocompatibility of surgical-grade dense polycrystalline alumina. Clin Orthop Relat Res 282:10-18.

*Christie H, MacKay RJ, Fisher AM. 1963. Pulmonary effects of inhalation of aluminumby rats and hamsters. Am Ind Hyg Assoc J 24147-56.

Chugh SN, Pal R, Singh V, et al. 1995. Serial blood phosphine levels in acute aluminum phosphide poisoning. J Assoc Physicians India 44:184-l 85,841.

Clarke N, Danielsson L-G, Sparen A. 1994. Aluminum speciation: Variations caused by the choice of analytical method and by sample storage. Water Air Soil Pollut 72:213-233.

Clauberg M, Joshi JG. 1992. Effects of prolonged chronic dietary treatment with aluminum chloride on selected metabolisms and memory in rats. Ann N Y Acad Sci 648:289-290.

Clauberg M, Joshi JG. 1993. Regulation of serine protease activity by aluminum Implications for Alzheimer disease. Proc Natl Acad Sci U S A 90:1009-1012.

Claveri B, Guerold F, Pihan JC. 1995. Use of transplanted mosses and autochthonous liverworts to monitor trace metals in acidic and non-acidic headwater streams (Vosges mountains, France). Sci Total Environ 175:235-244.

Clayton RM, Sedowofia SKA, Rankin JM, et al. 1992. Long-term effects of aluminum on the fetal mouse brain. Life Sci 51:1921-1928.

Cleveland L, Little EE, Hamilton SJ, et al. 1986. Interactive toxicity of aluminum and acidity to early life stages of brook trout. Trans Am Fish Sot 115:610-620.

*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.

*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.

*Clewell HJ III, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health l:lll-113.

Coburn JW, Mischel MG, Goodman WG, et al. 1991. Calcium citrate markedly enhances aluminum absorption from aluminum hydroxide. Am J Kidney Dis 17:708-7 11.

Cohn J, Cox C, Cory-Slechta DA. 1993. The effects of lead exposure on learning in a multiple repeated acquisition and performance schedule. Neurotoxicology 14:329-346.

*Colomina MT, Esparza JL, Corbella J et al. 1998. The effect of maternal restraint on developmental toxicity of aluminum in mice. Neurotoxicol Teratol 20:65 l-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 77:95-106.

Colomina MT, Gomez M, Domingo JL, et al. 1993. Study of the embryotoxic and fetotoxic potential of aluminum in mice: Influence of ascorbic acid. Toxicologist 13:299.

*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 741236-239.

*Commissaris RL, Cordon JJ, Sprague S, et al. 1982. Behavioral changes in rats after chronic aluminum and parathyroid hormone administration. Neurobehav Toxicol Teratol4:403-410.

*Connor DJ, Jope RS, Harrell LE. 1988. Chronic, oral aluminum administration to rats: Cognition and cholinergic parameters. Pharmacol Biochem Behav 3 1:467-474.

*Connor DJ, Harrell LE, Jope RS. 1989. Reversal of an aluminum-induced behavioral deficit by administration of deferoxamine. Behav Neurosci 103:779-783.

*Connor JJ, Schacklette HT. 1975. Background geochemistry of some rocks, soils, plants, and vegetables in the conterminous United States. United States Geological Survey. Professional Paper 574-F.

Conway EL, O'Callaghan C, Drummer OH, et al. 1994. A single-dose comparison of the bioavailability of aluminum from two formulations of sucralphate in normal volunteers. Biopharm Drug Dispos 15:253-261.

*Cooke K, Gould MH. 1991. The health effects of aluminium-a review. J R Sot 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.

Copestake P. 1993. Aluminum and Alzheimer's disease-an update. Food Chem Toxicol 3 1:679-685.

*Cornelis R. 1982. Variability in reported plasma AI-concentrations. CEC-Commission of European Communities (1982) international workshop on the role of biological monitoring in prevention of aluminum toxicity in man. Aluminum assay in biological fluids. Luxembourg:. July 5-7, 1982.

Corrin B. 1963. Aluminum pneumoconiosis II. Effects on the rat lung of intratracheal injections of stamped aluminum powders containing different lubricating agents and of a granular aluminum powder. Br J Ind Med 20:268-276.

*Cotton FA, Wilkinson G. 1988. Advanced organic chemistry. 5th ed. New York, NY: John Wiley and Sons.

*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. 1 9 8 1 . Aluminum localization in bone from hemodialyzed patients: Relationship to matrix mineralization. Kidney Int 20:375-385.

Courtijn E, Vandecasteele C, Dams R. 1990. Speciation of aluminum in surface water. Sci Total Environ 90: 19 l-202.

Crable JV, Keenan RG, Wolowicz FR, et al. 1967. The mineral content of bituminous coal miners' lungs. Am Ind Hyg Assoc J 28:8-12.

*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 7:601-608.

*Crapper DR, DeBoni U. 1978. Brain aging and Alzheimer's disease. Can Psychiatr Assoc J 23:229-233.

Crapper DR, De Boni U. 1980. Aluminum In: Spencer PS, Schaumburg HH, eds. Experimental and clinical neurotoxicology. Baltimore, MD: Williams and Wilkins, 326-335.

Crapper-McLachlan DR. 1986. Aluminum and Alzheimer's disease. Neurobiol Aging 7:525-533.

*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.

Crapper McLachlan DR, Farnell BJ. 1985a. Aluminum and neuronal degeneration. In: Gabay S, Harris J, Ho BT, eds. Metal ions in neurology and psychiatry. New York, NY: Alan R. Liss, Inc., 69-87.

*Crapper-McLachlan DRC, Farnell BJ. 1985b. Aluminum and neuronal degeneration. Neurol Neurobiol 15:69-87.

*Crapper-McLachlan DR, Farnell BJ. 1986. Cellular mechanisms of aluminum toxicity. Ann 1st Super Sanita 221697-702.

Crapper-McLachlan DR, Dalton AJ, Kruck TPA, et al. 1991 a. Intramuscular desferrioxamine in patients with Alzheimer's disease. Lancet 337: 1304- 1308.

Crapper-McLachlan DR, Kruck TP, Lukiw WJ, et al. 1991b. Would decreased aluminum ingestion reduce the incidence of Alzheimer's disease? Can Med Assoc J 145:793-804.

CRC. 1996-97. Handbook of chemistry and physics. 77'h edition. Boca Raton, FL: CRC Press, 4-37 to 4-38.

Crockett AB. 1997. Water and wastewater quality monitoring, McMurdo Station, Antarctica. Environ Monit Assess 47:39-57.

Crockett AB. 1998. Background levels of metals in soils, McMurdo Station, Antarctica. Environ Monit Assess 50:289-296.

*Crombie DW, Blaisdell JL, MacPherson G. 1944. The treatment of silicosis by aluminum powder. Can Med Assoc J 50:3 18-328.

Cronan CS, Schofield CL. 1990. Relationships between aqueous aluminum and acidic deposition in forested watersheds of North America and Northern Europe. Environ Sci Technol 24:1100-1105.

Cronan CS, Walker WJ, Bloom PR. 1986. Predicting aqueous aluminum concentrations in natural waters. Nature 324:140-143.

Cronan CS, Driscoll CT, Newton RM, et al. 1990. A comparative analysis of aluminum biogeochemistry in a northeastern and a southeastern forested watershed. Water Resour Res 26: 1413-1430.

Cruts M, Backhovens J, Wang S-Y, et al. 1995. Molecular genetic analysis of familial early-onset Alzheimer's disease linked to chromosome 14q24.3. Hum Mol Gen 4:2363-237 1.

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-l 614.

Cullen MR, Checkoway H, Alexander BH. 1996. Investigation of a cluster of pituitary adenomas in workers in the aluminum industry. Occup Environ Med 53:782-786.

Culora GA, Ramsay AD, Theaker JM. 1996. Aluminum and injection site reactions. J Clin Pathol 49:844-847.

*Dabeka RW, McKenzie AD. 1990. Aluminum levels in Canadian infant formulae and estimation of aluminum intakes from formulae by infants 03 months old. Food Addit Contam 7(2):275282.

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 75:949-953.

*Dahlgren RA, Ugolini FC. 1989. Aluminum fractionation of soil solutions from unperturbed and tephra-treated spodosols, Cascade range, Washington, USA. Soil Sci Sot Am J 53:559-566.

D'Ambrosio GP, Iaderosa G, Zuliani M. 1992. Situazione laringea nei lavoratori di due impianti di produzione di alluminio primario. Med Lav 83:456-460.

Damiano J. 1995. Quantitative exposure assessment strategies and data in the Aluminum Company of America. Appl Occup Environ Hyg 10:289-298.

*Dantzman CL, Breland HL. 1970. Chemical status of some water sources in south central Florida. Soil Sci Sot Am Proc 29:18-28.

Daskalakis KD, O'Connor TP. 1995a. Distribution of chemical concentrations in US coastal and estuarine sediment. Mar Environ Res 40:381-398.

Daskalakis KD, O'Connor TP. 1995b. Normalization and elemental sediment contamination in the coastal United States. Environ Sci Technol 29:470-477.

Dauvalter V. 1995. Influence of pollution and acidification on metal concentrations in Finnish Lapland sediments. Water Air Soil Pollut 85:853-858.

David-Net0 E, Jorgetti V, Soeiro NMR, et al. 1993. Reversal of aluminum-related bone disease after renal transplantation. Am J Nephrol 13:12-17.

Davis WM. 1993. Is aluminum an etiologic contributor to alcoholic amnesia and dementia? Med Hypotheses 41:341-343.

*Day JP, Barker J, Evans WA, et al. 1991. Aluminum absorption studied by 26Al tracer. Lancet 337:1345.

Dayde S, Filella M, Berthon G. 1990. Aluminum speciation studies in biological fluids. Part 3. Quantitative investigation of aluminum-phosphate complexes and assessment of their potential significance in vivo. J Inorg Biochem 38:241-259.

*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 287:509-514.

Dehm B, Letzel S, Raithel HJ, et al. 1996. [Pulmonary fibrosis following occupational exposure to aluminum dust]. Arbeitsmed Soziahned Umweltmed 31:161- 164. (German).

*de Kom JFM, Dissels H MH, van der Voet GB, et al. 1997. Serum aluminum levels of workers in the bauxite mines. Clin Toxico1 35:645-651.

*De La Campa MRF, 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.

Del Caskillo P, Llorente AR, Gomez A, et al. 1990. New fluorescence reactions in DNA cytochemistry 2. Microscopic and spectroscopic studies on fluorescent aluminum complexes. Anal Quant Cytol Histol 12:11-20.

Deloncle R, Guillard 0. 1990. Mechanism of Alzheimer's disease: Arguments for a neurotransmitteraluminum
complex implication. Neurochem Res 15 : 1239- 1245.

Demircan M, Ergun 0, Coker C, et al. 1998. Aluminum in total parenteral nutrition solutions produces portal inflammation in rats. J Pediatr Gastroenterol Nutr 26274-278.

Desjardins A, Bergeron J-P, Ghezzo H, et al. 1994. Aluminum potroom asthma contirmed by monitoring of forced expiratory volume in one second. Am J Respir Crit Care Med 150: 17 14-17 17.

*DeVoto E Yokel RA. 1994. The biological speciation and toxicokinetics of aluminum Environ Health Perspect 102:940-951.

*De Vuyst P, Dumortier P, Rickaert F, et al. 1986. Occupational lung fibrosis in an aluminum polisher. Eur J Respir Dis 68:131-140.

*De Vuyst P, Dumortier P, Schandene L, et al. 1987. Sarcoidlike lung granulomatosis induced by aluminum dusts. Am Rev Respir Dis 135:493-497.

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-l 884.

D'Haese PC, Couttenye MM, DeBroe ME. 1996. Diagnosis and treatment of aluminum bone disease. Nephrol Dial Transplant 11(Suppl. 3):74-79.

*Dick RB, Krieg EFJ, Sim MA, et al. 1997. Evaluation of tremor in aluminum production workers. Neurotoxicol Teratol 19:447-453.

*Dinman BD. 1983. Aluminum alloys, and compounds. Encyclopedia of occupational health and safety. Vol. 1, 131-135.

*Dinman BD. 1987. Aluminum in the lung: The pyropowder conundrum J Occup Med 29:869-876.

Dion M, Loranger S, Kennedy G, et al. 1993. Evaluation of black spruce (picea mariana) as a bioindicator of aluminum contamination. Water Air Soil Pollut 71:29-41.

*DiPaolo JA, Casto BC. 1979. Quantitative studies of *in vitro* morphological transformation of Syrian hamster cells by inorganic metal salts. Cancer Res 39:1008-1013.

*Dixon RL, Sherins RJ, Lee IP. 1979. Assessment of environmental factors affecting male fertility. Environ Health Perspect 30:53-68.

*Dombrowski T. 1993. Clays. In: Kroschwitz I, Howe-Grant M, eds. Kirk-Othmer encyclopedia of chemical technology. New York: John Wiley & Sons, Inc, 381-405.

Domingo JL. 1994. Metal-induced developmental toxicity in mammals: A review. J Toxicol Environ Health 42:123-141.

*Domingo JL. 1995. Reproductive and developmental toxicity of aluminum: A review. Neurotoxicol Teratol 17:515-521.

*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 Pharmacol57: 129-132.

*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 Patho1 Pharmacol56:409-419.

Domingo JL, Paternain JL, Llobet JM, et al. 1987c. The effects of aluminum ingestion of reproduction and postnatal survival in rats. Life Sci 41:1127-l 131.

*Domingo JL, Gomez M, Bosque MA, et al. 1989. Lack of teratogenicity of aluminum hydroxide in mice. Life Sci 451243-247.

*Domingo JL, Gomez M, Llobet JM, et al. 1991. Influence of some dietary constituents on aluminum absorption and retention in rats. Kidney Int 39:598-601.

*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 Pharmacol79:377-380.

*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 58:1387-1395.

*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 11:345-35 1.

Dong D, Thornton I, Ramsey MH. 1993. Influence of soil-extractable aluminum and pH on the uptake of aluminum from soil into the soybean plant (glycine max). Environ Geochem Health 15: 105- 111.

Dorhout Mees EJ, Basci A. 1991. Citric acid in calcium effervescent tablets may favour aluminum intoxication. Nephron 59:322.

Dorsch MM, Scragg RKR, McMichael AJ, et al. 1984. Congenital malformations and maternal drinking water supply in rural South Australia: a case-control study. Am J Epidemiol 119:473-482.

DOT. 1980. Department of Transportation. Code of Federal Regulations. 49 CFR 172.102.

DOT. 1985. CHRIS (Chemical Hazard Response Information System) hazardous chemical data.

Department of Transportation, US Coast Guard. Washington, DC: US Government Printing Office.

*DOT. 1990. U.S. Department of Transportation. Code of Federal Regulations. 49 CFR 172.101.

*Drablos PA, Hetland S, Schmidt F et al. 1992. Uptake and Excretion of Aluminum in Workers Exposed to Aluminum Fluoride and Aluminum Oxide. Aluminum Assoc/et al. Aluminum & Health 2nd Int Conf, Tampa, FL 157(4) Feb 26, 92.

*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 aluminumchloride-
hydroxide. Arch Environ Health 28:321-326.

*Driscoll CT, Letterman RD. 1988. Chemistry and fate of aluminum (III) in treated drinking water. J Environ Eng 114:21-37.

Driscoll CT, Schecher WD. 1990. The chemistry of aluminum in the environment. Environ Geochem Health 12:28-49.

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 92:63-67.

*Dryssen D, Haraldsson C, Nyberg E, et al. 1987. Complexation of aluminum with DNA. J Inorg Biochem 29:67-75.

Dufresne A, Loosereewanich P, Armstrong B, et al. 1996. Inorganic particles in the lungs of five aluminum smelter workers with pleuro-pulmonary cancer. Am Ind Hyg Assoc J 57:370-375.

*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.

*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 29:67-75.

*Dzubay TG. 1980. Chemical element balance method applied to dichotomous sampler data. Ann N Y Acad Sci 338:126-144.

Easthouse KB, Spyridakis DE, Welch EB. 1993. Aluminum chemistry in two pristine alpine lakes of the central Cascades, Washington. Water Air Soil Pollut 71:377-390.

Eastwood JB, Levin GE, Pazianas M, et al. 1990. Aluminum deposition in bone after contamination of drinking water supply. Lancet 336:462-464.

Ebrahim S. 1989. Aluminum and Alzheimer's disease. Lancet 1:267-269.

Ecelbarger CA, Greger JL. 1991. Dietary citrate and kidney function affect aluminum zinc and iron utilization in rats. J Nutr 121:1755-1762.

Ecelbarger CA, MacNeil GG, Greger JL. 1994a. Importance of kidney function and duration of exposure on aluminum accumulation in mature rats. Nutr Res 14:577-586.

Ecelbarger CA, MacNeil GG, Greger JL. 1994b. Aluminum retention by aged rats fed aluminum and treated with desferrioxamine. Toxicol Lett 73:249-257.

Eckel WP, Jacob TA. 1988. Ambient levels of 24 dissolved metals in U.S. surface and ground waters. Prepr Pap Natl Meet AmChem Sot Div Environ Chem 28:371-372.

*Edling NPG. 1961. Aluminum pneumoconiosis: A roentgendiagnostic study of five cases. Acta Radiol 56:170-178.

Edwardson JA, Candy JM, Ince PG, et al. 1992. Aluminum accumulation, beta-amyloid deposition and neurofibrillary changes in the central nervous system In: Aluminum in biology and medicine. Chichester: John Wiley and Sons, 165-185.

*Edwardson JA, Moore PB, Ferrier IN, et al. 1993. Effect of silicon on gastrointestinal absorption of aluminum Lancet 342:21 l-212.

Eeckhaoudt S, Vandeputte D, Van Praag H, et al. 1992. Laser microprobe mass analysis (LAMMA) of aluminum and lead in fine roots and their ectomycorrhizal mantles of Norway spruce *picea abies* (1.) karst.). Tree Physiol 10:209-215.

Eeckhaoudt S, Jacob W, Witters H, et al. 1993. X-ray micro-analysis of aluminumin pumpkinseed gills. Eur J Morphol 3 1:42-45.

Eichhorn GL. 1993. Is there any relationship between aluminum and Alzheimer's disease? Exp Gerontol28:493-498.

*Eisenreich SJ. 1980. Atmospheric input of trace metals to Lake Michigan (USA). Water Air Soil Pollut 13:287-302.

Elinder CG. 1987. Biological monitoring of metals. Copenhagen, Denmark: World Health Organization. BIOSIS/88/17979, 114-l 17.

Elinder CG, Ahrengart L, Lidums V, et al. 1991. Evidence of aluminum accumulation in aluminum welders. Br J Ind Med 48:735-738.

Elkin BT, Bethke RW. 1995. Environmental contaminants in caribou in the Northwest Territories, Canada. Sci Total Environ 160/161:307-321.

*Ellenhorn MJ, Barceloux DG. 1988. Metals and related compounds. In: Ellenhorn MJ, Barceloux DG, eds. Medical toxicology: diagnosis and treatment of human poisoning. New York, NY: Elsevier, 1009-1011.

Elliot MA, Edwards HM. 1991. Some effects of dietary aluminum and silicon on broiler chickens. Poultry Sci 70: 1390- 1402.

*Elmore D, Phillips FM. Accelerator mass spectrometry for measurement of long-lived radioisotopes. Science 236:543-550.

Elwood PC, Aberwethy M, Morton M. 1974. Mortality in adults and trace elements in water. Lancet 2:1470-1472.

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 Patho1 Bacterial 77:407-416.

*EPA. 197 1. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 180.1001,

*EPA. 1977a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 60.190-60.195 (Subpart S).

*EPA. 1977b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 180.225.

*EPA. 1977c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 186.200.

*EPA. 1978a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 116.4.

*EPA. 1978b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 152.175.

*EPA. 1979a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 143.3.

*EPA. 1979b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 143.4.

*EPA. 1980. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261.33.

*EPA. 1981 a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261.3 1.

*EPA. 1981b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261.32.

*EPA. 1981c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 264, App. V.

*EPA. 1981 d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 413.10.

*EPA. 1982a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 60.16.

*EPA. 1982b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 415, Subpart A.

*EPA. 1982c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 415, Subpart B.

*EPA. 1982d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 415, Subpart W.

*EPA. 1982e. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 420, Subpart G.

*EPA. 1982f. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 440, Subpart B (440.20 - 440.24).

*EPA. 1982g. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 465, Subpart C (465.30 - 465.33) and Subpart D (465.41-465.43).

*EPA. 1982h. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 466, Subpart A (466.11 - 466.23) and Subpart B (466.2 l-466.23).

*EPA. 1982i. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 466, Subpart C (466.30 - 466.33).

*EPA. 1982j. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 466, Subpart D (466.40 - 466.43).

*EPA. 1983a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 122. Appendices A and D.

*EPA. 1983b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 433, Subpart A (433.10).

*EPA. 1983c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 467.01 - 467.05 .

*EPA. 1983d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 467, Subpart A (467.10 - 467.16).

*EPA. 1983e. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 467, Subpart B (467.22 - 467.26).

*EPA. 1983f. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 467, Subpart C (467.31 - 467.36).

*EPA. 1983g. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 467, Subpart D (467.44 - 467.46).

*EPA. 1983h. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 467, Subpart E (467.52 - 467.56).

*EPA. 19831. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 467, Subpart F (467.62 - 467.66).

*EPA. 1984a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261, App. IX.

*EPA. 1984b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 42 1.1.

*EPA. 1984c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 42 1, Subpart B (421.23 - 421.26).

*EPA. 1984d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 421, Subpart C (421.30 - 421.36).

EPA. 1984e. Drinking Water Criteria Document for Aluminum Of&e of Health and Environmental Assessment. Office of Drinking Water, Washington, D.C. External Review Draft. (As cited in EPLA 1987b--Health Effects Assessment for Aluminum).

*EPA. 1985a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 117.3.

*EPA. 1985b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 464.02.

*EPA. 1985c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 464, Subpart A (464.10).

EPA. 1986. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 117.3.

*EPA. 1987a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 355, Appendix A.

EPA. 1987b. Health Effects Assessment for aluminum Cincinnati, OH: U.S. Environmental Protection Agency. Environmental Criteria and Assessment Office. EPA/600/8-881016.

*EPA. 1987c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.65.

*EPA. 1987d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.65.

*EPA. 1988a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 185.200.

*EPA. 1988b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261, App. VIII.

EPA. 1988c. Ambient water quality criteria for album-1988. Washington, DC: U.S. Environmental Protection Agency, Office of Water Regulations and Standards. EPA 440/5-86-008.

*EPA. 1988d. 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. EPA/600/6-871008.

EPA. 1989a. U.S. Environmental Protection Agency. Federal Register 54:16376.

EPA. 1989b. U.S. Environmental Protection Agency. Federal Register 54:22062.

*EPA. 1990a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 60.4,

*EPA. 1990b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 122, Appendix I.

*EPA. 1990c. Interim methods for development of inhalation reference doses. Washington, DC: US. Environmental Protection Agency, Office of Health and Environmental Assessment. EPA 600/8-88/066F.

*EPA. 1991. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 266, App. IV and VII.

*EPA. 1992a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.45.

*EPA. 1992b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 271.1.

*EPA. 1993. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4.

*EPA. 1994. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.40.

EPA. 1995a. U.S. Environmental Protection Agency. Drinking Water Regulations and Health Advisories.

*EPA. 1995b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 132., Table 1.

*EPA. 1995c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 192, App. I .

*EPA. 1995d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.65.

*EPA. 1995e. Toxic Chemical Release Inventory Reporting Form R and Instructions- Revised 1994 version. Office of Pollution Prevention, US Environmental Protection Agency, EPA 745-K-95-05 1 Washington, DC.

*EPA. 1996a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.39.

*EPA. 1996b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268, App. XI.

*EPA. 1999. National Recommended Water Quality Criteria. Office of Water, US Environmental Protection Agency, EPA 822-z-99-001. http://www.epa.gov/ost/pc/revcom/pdf, May 1999.

*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.

Esteves da Silva JCG, Machado AASC, Ramos MA. 1997. Variation of the stability of complexes of Al(3) with a fulvic acid extracted from a humic cambisol soil in the pH range three to five. Environ Toxicol Chem 16: 1845-l 850.

Evans LJ. 1989. Chemistry of metal retention by soils. Environ Sci Technol 23:1046-1056.

Exley C. 1996. Aluminum in the brain and heart of the rainbow trout. J Fish Biol48:706-713.

Exley C, Birchall JD. 1992. The cellular toxicity of aluminum J Theor Biol 159:83-98.

Exley C, Chappell JS, Birchall JD. 1991. A mechanism for acute aluminum toxicity in fish. J Theor Biol 151:417-428.

*Exley C, Burgess E, Day JP, et al. 1996. Aluminum toxicokinetics. J Toxicol Environ Health 48:569-584.

Fairweather-Tait S, Hickson K, McGaw B, et al. 1994. Orange juice enhances aluminum absorption from antacid preparation. Eur J Clin Nutr 48:7 1-73.

Farrar G, Blair JA. 1989. Aluminum and Alzheimer's disease. Lancet 1:267-269.

Fatemi SJA, Kadir FHA, Moore GR. 1991. Aluminum transport in blood serum - binding of aluminum by human transferrin in the presence of human albumin and citrate. Biochem J 280:527-532.

FDA. 1975. Food and Drug Administration. Code of Federal Regulations. 21 CFR 193.20.

FDA. 1988. Food and Drug Administration. Code of Federal Regulations. 21 CFR 73.

FEDRIP. 1996. Federal Research in Progress [database].

*FEDRIP. 1998. Federal Research in Progress [database].

*Feinroth M, Feinroth MV, Berlyne GM. 1982. Aluminum absorption in the rat everted gut sac. Miner Electrolyte Metab 8:29-35.

Felkner C, Quinn H, Connery J. 1988. Comparative health effects assessment of drinking water treatment technologies: Report to Congress. Temple Hills, MD: Borriston Labs, Inc. EPA/570/9-881009.

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-Sanjurjo MJ, Alvarez E, Garcia-Rodeja E. 1998. Speciation and solubility control of aluminum in soils developed from slates of the river Sor watershed (Galicia, NW Spain). Water Air Soil Pollut 103:35-53.

*Feth JH, Rogers SM, Robertson CE. 1964. Chemical composition of snow in the Northern Sierra Nevada and other areas. US Geol Surv Water Supply Paper. U.S. Department of Interior. Report No. 1535-J.

Fiejka M, Fiejka E, Dlugaszek M. 1996. Effect of aluminumhydroxide administration on normal mice: Tissue distribution and ultrastructural localization of aluminum in liver. Pharmacol Toxicol 78:123-128.

*Filipek LH, Nordstrom DK, Ficklin WH. 1987. Interaction of acid mine drainage with waters and sediIllents of West Squaw Creek in the West Shasta mining district, California. Environ Sci Technol 21:388-396.

Fimreite N, Hansen 00, Pettersen HC. 1997. Aluminum concentrations in selected foods prepared in aluminum cookware, and its implications for human health. Bull Environ Contam Toxicol 58: l-7.

*Finberg L, Dweck HS, Holmes F, et al. 1986. Aluminum toxicity in infants and children. Pediatrics 78:1150-l 154.

*Finehi 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, 46-50.

*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-l 126.

*Flarend RE, Elmore D. 1997. Aluminum Toxicity in Infants Health and Disease. Zatta PF, Alfrey AC, eds. Singapore: World Scientific, 16-39.

*Flarend RE, Hem SL, White JL, et al. 1997. In vivo absorption of aluminum-containing vaccine adjuvants using 26Al. Vaccine 15:1314-1317.

Flaten AK, Lund W. 1997. Speciation of aluminum in tea infusions studied by size exclusion chromatography with detection by post-column reaction. Sci Total Environ 207 :21-28.

*Flaten TP. 1991. A nation-wide survey of the chemical composition of drinking water in Norway. Sci Total Environ 102:35-73.

Flaten TP, Glattre E, Viste A, et al. 199 1. Mortality from dementia among gastroduodenal ulcer patients. J Epidemiol Commun Health 45:203-206.

Flaten TP, Alfrey AC, Birchall JD, et al. 1996. Status and future concerns of clinical and environmental aluminum toxicology. J Toxicol Environ Health 48:527-541.

*Fleming J, Joshi JG. 1987. Ferritin: Isolation of aluminum-ferritin complex from brain. Proc Natl Acad Sci U S A 84:7866-7870.

*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.

*Flora SJS, Dhawan M, Tandon SK. 1991. Effects of combined exposure to aluminum and ethanol on aluminum body burden and some neuronal, hepatic and hematopoietic biochemical variable in the rat. Hum Exp Toxicol 10:45-48.

*Florence AL, Gauthier A, Ponsar C, et al. 1994. An experimental animal model of aluminum overload. Neurodegeneration 3:315-323.

*Fornon 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-l 175.

Forbes WF, Agwani N. 1994. A suggested mechanism for aluminum biotoxicity. J Theor Biol 17 1:207-214.

*Forbes WF, McLachlan DRC. 1996. Further thoughts on the aluminum-Alzheimer's disease link. J Epidemiol Commun Health 50:401-403.

Forbes WF, Gentleman JF, Maxwell CJ. 1995. Concerning the role of aluminum in causing dementia. Exp Gerontol 30:23-32.

Forrester TM, Yokel RA. 1985. Comparative toxicity of intracerebroventricular and subcutaneous aluminum in the rabbit. Neurotoxicology 6:71-80.

*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 49:253-258.

*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 47:210-217.

Friberg L, Nordberg GR, Vouk VB. 1979. Handbook on the toxicology of metals. New York, NY: Elsevier, 275-281.

*Frick KG, Herrmann J. 1990. Aluminum accumulation in a lotic mayfly at low pH-a laboratory study. Ecotoxicol Environ Saf 19:81-88.

*Frink CR. 1996. A perspective on metals in soils. J Soil Contam 51329-359.

*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 114:237-242.

*Froment DPH, Molitoris BA, Buddington B, et al. 1989b. Site and mechanism of enhanced gastrointestinal absorption of aluminum by citrate. Kidney Int 36:978-984.

FSTRAC. 1988. Summary of state and federal drinking water standards and guidelines. U.S. Environmental Protection Agency. Chemical Communications Subcommittee, Federal State Toxicology and Regulatory Alliance Committee.

FSTRAC. 1990. Summary of state and federal drinking water standards and guidelines. U.S. Environmental Protection Agency. Chemical Communications Subcommittee, Federal State Toxicology and Regulatory Alliance Committee.

*FSTRAC. 1995. Summary of state and federal drinking water standards and guidelines. U.S. Environmental Protection Agency. Chemical Communications Subcommittee, Federal State Toxicology and Regulatory Alliance Committee.

*Fuchs C, Brasche M, Paschen K, et al. 1974. [Aluminum determination in serum by flameless atomic absorption]. Clin Chim Acta 52:71-80. (German)

Fuge R, Pearce NJG, Perkins WT. 1992. Unusual sources of aluminum and heavy metals in potable waters. Environ Geochem Health 14:15-18.

*Gabler RC Jr, Stoll RL. 1983. Removal of leachable metals and recovery of alumina from utility coal ash. Washington, DC: US Department of the Interior, Bureau of Mines. NTIS/PB83-191650.

*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 76222-227.

*Ganrot PO. 1986. Metabolism and possible health effects of aluminum Environ Health Perspect 6.51363441.

Garbossa G, Gutnisky A, Nesse A. 1996. Depressed erythroid progenitor cell activity in aluminumoverloaded mice. Miner Electrolyte Metab 22:2 14-218.

Garbossa G, Galvez G, Castro ME, et al. 1998a. Oral aluminum administration to rats with normal renal function. 1. Impairment of erythropoiesis. Hum Exp Toxicol 17:312-317.

Garbossa G, Galvez G, Perez G, et al. 1998b. Oral aluminum administration to rats with normal renal function. 2. Body distribution. Hum Exp Toxicol 17:318-322.

*Gardiner PE, S toeppler M. 1987. Optimisation of the analyticaI 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 12857-66.

*Gardiner PE, Schierl R, Kreutzer K. 1987. Aluminum speciation in soil solutions as studied by size exclusion chromatography. Plant Soil 103:151-154.

Gardner MJ, Gunn AM. 1995. Speciation and bioavailability of aluminum in drinking water. Chem Speciat Bioavail7:9-16.

Garfield RE. 1995. Mechanism underlying phasic contractions of pregnant rat myometrium simulated by aluminum fluoride. Am J Obstet Gynecol 173:348-349.

Garruto RM, Shankar SK, Yanagihara R, et al. 1989. Low-calcium high-aluminum diet-induced motor neuron pathology in cynomolgus monkeys. Acta Neuropatho178:2 10-219.

Garry VF, Good PF, Manivel JC, et al. 1993. Investigation of a fatality nonoccupational aluminum phosphide exposure: Measurement of aluminum in tissue and body fluids as a marker of exposure. J Lab Clin Med 122:739-747.

Gault MH, Purchase L. 1992. Would decreased aluminum ingestion reduce the incidence of Alzheimer's disease? Can Med Assoc J 147:845-847.

*Gautrin D, Gauthier S. 1989. Alzheimer's disease: Environmental factors and etiologic hypotheses. Can J Neurol Sci 16:375-387.

Gaytan-Garcia S, Kim H, Strong MJ. 1996. Spinal motor neuron neuroaxonal spheroids in chronic aluminum neurotoxicity contain phosphate-resistant high molecular weight neurofilament (NFH). Toxicology 108:17-24.

George DB, Berk SG, Adams VD, et al. 1995. Toxicity of alum sludge extracts to a freshwater alga, protozoan, fish, and marine bacterium Arch Environ Contam Toxicol 29:149-158.

Gerhardsson L, Chettle DR, Englyst V, et al. 1992. Kidney effects in long term exposed lead smelter workers. Br J Ind Med 49:186-192.

Gerhartz W, Yamamoto YS, Campbell FT, et al. 1985. Ullmann's encyclopedia of industrial chemistry. Vol. Al. Fifth ed. Weinheim, Germany: VCH, 460.

Ghazi-Khansari M, Oreizi S. 1995. A prospective study of fatal outcomes of poisoning in Tehran. Vet Hum Toxicol 37:449-452.

Gibbs GW. 1985. Mortality of aluminum reduction plant workers, 1950 through 1977. J Occup Med 27:761-770.

*Gibbs GW, Horowitz I. 1979. Lung cancer mortality in aluminum reduction plant workers. J Occup Med 21:347-353.

Gilbert ME, Shafer TJ. 1996. In vitro exposure to aluminum does not alter long-term potentiation or glutamate release in rat hippocampal slices. Neurotoxicol Teratol 18: 175-180.

Gitelman HJ. 1995. Aluminum exposure and excretion. Sci Total Environ 163: 129- 135.

*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: 181-191.

Gjessing ET, Riise G, Petersen RC, et al. 1989. Bioavailability of aluminum in the presence of humic substances at low and moderate ph. Sci Total Environ 81/82:683-690.

Glynn AW, Sparen A, Danielson LG, et al. 1995. Bioavailability of labile aluminum in acidic drinking water: A study in the rat. Food Chem Toxicol 33:403-408.

Godal A, Langseth W, Sivertsen T, et al. 1995. Determination of aluminum in liver from reindeer, moose and sheep by electrothermal atomic absorption spectrometry. Sci Total Environ 168:249-254.

*Goenaga X, Williams DJA. 1988. Aluminum speciation in surface waters from a Welsh upland area. Environ Pollut 52: 13 1 - 149.

Goenaga X, Williams DJA. 1990. Determination of aluminum speciation in acid waters. In: Edwards RW et al, eds. Acid waters in Wales. Dordrecht, Netherlands: Kluwer Academic Publishers, 189-201.

Goldberg AM. 1980. Mechanisms of neurotoxicity as studied in tissue culture systems. Toxicology 17:201-208.

*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 48:585-597.

*Golub MS, Germann SL. 1998. Aluminum effects on operant performance and food motivation of mice. Neurotoxicol Teratol 20:42 1-427.

Golub MS, Kaaekuahiwi MA. 1993. Effects of intrapartum meperidine on distress vocalizations of guinea pigs during maternal separation. Teratology 47:457.

*Golub MS, Gershwin ME, Donald JM, et al. 1987. Maternal and developmental toxicity of chronic aluminum exposure in mice. Fundam Appl Toxicol 8:346-357.

*Golub MS, Donald JM, Gershwin ME, et al. 1989. Effects of aluminum ingestion on spontaneous motor activity of mice. Neurotoxicol Teratol 11:23 1-235.

Golub MS, Han B, Keen CL. 1991. Al and Mn: Interactions in adult and developing mice. Teratology 43:490.

*Golub MS, Keen CL, Gershwin ME. 1992a. Neurodevelopmental effect of aluminum in mice: fostering studies. Neurotoxicol Teratol 14:177-182.

*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: 154- 160.

Golub MS, Han B, Keen CL, et al. 1993a. Developmental patterns of aluminum in mouse brain and effects of dietary aluminum excess on manganese deficiency. Toxicology 81:33-47.

*Golub MS, Takeuchi PT, Gershwin ME, et al. 1993b. Influence of dietary aluminum cytokine production by mitogen-stimulated spleen cells from Swiss Webster mice. Immunopharmacol Immunotoxicol 15:605-619.

*Golub MS, Han B, Keen CL, et al. 1994. Auditory startle in Swiss Webster mice fed excess aluminum in diet. Neurotoxicol Teratol 16:423-425.

*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 133:64-72.

*Golub MS, Han B, Keen CL. 1996a. Iron and manganese uptake by offspring of lactating mice fed a high aluminum diet. Toxicology 109:111-118

Golub MS, Han B, Keen CL. 1996b. Developmental patterns of aluminum and five essential mineral elements in the central nervous system of the fetal and infant guinea pig. Biol Trace Elem Res 55:241-251.

*Gomez M, Domingo JL, Llobet JM, et al. 1986. Short-term oral toxicity study of aluminum in rats. Arch Farmacol Toxicol 12: 145- 15 1.

*Gomez M, Domingo JL, Llobet JM. 199 1. Developmental toxicity evaluation of oral aluminum in rats: influence of citrate. Neurotoxicol Teratol 13:323-328.

*Gomez M, Sanchez DJ, Llobet JM, et al. 1997a. The effect of age on aluminum retention in rats. Toxicology 116:1-8.

*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.

Gomez M, Esparaza JL, Domingo JL, et al. 1998. Aluminum distribution and excretion: A comparative study of a number of chelating agents in rats. Pharmacol Toxicol 82:295-300.

Gonda 2, Lehotzky K. 1996. Effect of prenatal aluminum lactate exposure on conditioned taste aversion and passive avoidance task in the rat. J Appl Toxicol 16529-532.

Gonda Z, Lehotzw K. 1997. Behavioural teratogenic effect of aluminum exposure in rat offspring. Neurotoxicology 18: 1092.

Gonda Z, Lehotzky K, Miklosi A. 1996. Neurotoxicity induced by prenatal aluminum exposure in rats. Neurotoxicology 17:459-470.

Gonda Z, Miklosi A, Lehotzky K. 1997. The effect of social learning on a conditioned avoidance response of rats treated prenatally with aluminum lactate. Neurotoxicol Teratol 19:59-63.

Good PF, Olanow CW, Perl DP. 1992a. Neuromelanin-containing neurons of the substantia nigra accumulate iron and aluminum in Parkinson's disease: A LAMMA study. Brain Res 593:343-346.

Good PF, Perl DP, Bierer LM, et al. 1992b. Selective accumulation of aluminum and iron in the neurotibrillary tangles of Alzheimer's disease: A laser microprobe (LAMMA) study. Ann Neurol 3 1:286-292.

Goralewski G. 1939. Klinische und tierexperimentelle studien sur frage der aluminum-staublunge. Arch Gewerbepathol Gewerbehyg 9:676-688. (German)

Goralewski G. 1940. Zur symptomalogie der aluminum-staublunge. Arch Gewerbepathol Gewerbehyg 10:384-408. (German)

Goralewski G. 1941. Zur klinik der aluminiumlunge. Arch Gewerbepathol Gewerbehyg 11: 106- 116. (German)

Goralewski G. 1943. Weitere erfahrungen zum krankheitsbild der aluminiumlunge. Dtsch Tuberk Bl 17:2-10. (German)

Goralewski G. 1947. Die aluminiumlunge-eine neue gewerbeerkrankung. Z Gesamte Inn Med 2:665-673. (German)

Gordon T, Amdur MO. 1991. Responses of the respiratory system to toxic agents. In: Amdur MO, Doull J, Klaassen CD eds. Casarett and Doull's toxicology: The basic science of poisons, 4th edition. New York, NY: McGraw-Hill, Inc. 383-406.

*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 25:1739-1743.

*Gosink TA. 1975. Rapid simultaneous determination of picogram quantities of aluminum and chromium from water by gas phase chromatography. Anal Chem 47: 165- 168.

Gotloib LC, Shostak A, Gotloib L. 199 1. Behavioral changes in mice induced by aluminum in drinking water. Dementia 2:278-282.

Gotow T, Tanaka J, Takeda M. 1995. The organization of neurofilaments accumulated in perikaryon following aluminum administration: Relationship between structure and phosphorylation of neurofilaments. Neuroscience 64:553-569.

Goyer RA. 1997. Toxic and essential metal interactions. Annu Rev Nutr 17:37-50.

*Gramiccioni L, Ingrao G, Milana MR, et al. 1996. Aluminum levels in Italian diets and in selected foods from aluminum utensils. Food Addit Contam 13:767-774.

Grandjean P, Horder M, Thomassen Y. 1990. Fluoride, aluminum, and phosphate kinetics in cryolite workers. J Occup Med 32:58-63.

*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.

Grayson M, Eckroth D, eds. 1978. Aluminum and aluminum alloys. Kirk-Othmer encyclopedia of chemical technology. Vol. 2. 3rd ed. New York, NY: John Wiley and Sons, 129-251.

Graziano JH, Blum CB, Lolacono NJ, et al. 1996. A human in vivo model for the determination of lead bioavailability using stable isotope dilution. Environ Health Perspect 104:176-179.

*Greger JL. 1985. Aluminum content of the American diet. Food Technol 39:73-78.

*Greger JL. 1992. Dietary and other sources of aluminum intake. In: Aluminum in biology and medicine. New York John Wiley & Sons, 26-49.

Greger JL, Baier MJ. 1983a. Effect of dietary aluminum on mineral metabolism of adult males. Am J Clin Nutr 38:411-419.

*Greger JL, Baier MJ. 1983b. Excretion and retention of low or moderate levels of aluminum by human subjects. Food Chem Toxicol 21:473-477.

*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: 1331-1334.

Greger JL, Powers CF. 1992. Assessment of exposure to parenteral and oral aluminum with and without citrate using a desferrioxamine test in rats. Toxicology 76: 119- 132.

Greger JL, Sutherland JE. 1997. Aluminum exposure and metabolism Crit Rev Clin Lab Sci 34:439-474.

Greger JL, Bula EN, Gum ET. 1985a. Mineral metabolism of rats fed moderate levels of various aluminumcompounds for short periods of time. J Nutr 115:1708-1716.

*Greger JL Goetz W, Sullivan D. 1985b. Aluminum levels in foods cooked and stored in aluminum pans, trays and foil. J Food Prot 48:772-777.

Greger JL, Chang MM, Radanowski GN. 1995. Comparison of tissue retention of aluminum and Ga-67: Effects of iron status in rats. Toxicology 100: 1-9.

*Griswold WR, Reznik V, Mendoza SA et al. 1983. Accumulation of aluminum in a nondialyzed uremic child receiving aluminum hydroxide. Pediatr 71: 56-58.

Gross P, Harley RA Jr, deTreville RTP. 1973. Pulmonary reaction to metallic aluminum powders. Arch Environ Health 26:227-236.

Grutzmacher P, Vlachojannis J, Schoeppe W. 1991. Aluminum and renal anemia. Trace Elem Med 8:S21-S25.

Gryllaki-Berger M, Mugny C, Perrenoud D, et al. 1992. A comparative study of formaldehyde detection using chromotropic acid, acetylacetone and HPLC in cosmetics and household cleaning products. Contact Dermatitis 26:149-154.

Gubala CP, Landers DH, Monetti M, et al. 1995. The rates of accumulation and chronologies of atmospherically derived pollutants in arctic Alaska. Sci Total Environ 160/l 61:347-361.

*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.

Guida L, Saidi 2, Hughes MN, et al. 1991. Aluminum toxicity and binding to *escherichia coli.* Arch Microbial 156:507-512.

*Guillard 0, 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.

Gun RT, Korten AE, Jorm AF, et al. 1997. Occupational risk factors for Alzheimer disease: A casecontrol study. Alzheimer Dis Assoc Disord 11:21-27.

Gupta MS, Malik A, Sharma VK. 1995a. Cardiovascular manifestations in aluminum phosphide poisoning with special reference to echocardiographic changes. J Assoc Physicians India 43:773-780.

Gupta MS, Singh H, Gupta BK, et al. 1995b. Acute myocardial injury in aluminum phosphide poisoning. J Assoc Physicians India 43:58.

Gupta S, Ahlawat SK. 1995. Aluminum phosphide poisoning- A review. Clin Toxicol 33:19-24.

Gupta SK, Waters DH, Gwilt PR. 1986. Absorption and disposition of aluminum in the rat. J Pharm Sci 75:586-589.

*Guzelian PS, Henry CJ, Olin SS. 1992. Similarities and Differences between children and adults: Implications for risk assessment. Washington, DC: International Life Sciences Institute Press.

Guzzo J, Guzzo A, DuBow MS. 1992. Characterization of the effects of aluminum on luciferase biosensors for the detection of ecotoxicity. Toxicol Lett 641651687-693.

*Hackenberg U. 1972. Chronic ingestion by rats of standard diet treated with aluminum phosphide. Toxicol Appl Pharmacol23:147-158.

*Haddad LM, Winchester JF. 1990. Clinical management of poisoning and drug overdose. 2nd ed. Philadelphia, PA: W.B. Saunders Co., 1029.

Haines A, Iliffe S, Morgan P, et al. 1991. Serum aluminum and zinc and other variables in patients with and without cognitive impairment in the community. Clin Chim Acta 198:261-266.

Hall LWJ, Ziegenfuss MC, Anderson RD, et al. 1995. Use of estuarine water column tests for detecting toxic conditions in ambient areas of the Chesapeake Bay watershed. Environ Toxicol Chem 14:267-278.

*Hamdy RC. 1990. Aluminum toxicity and Alzheimer's disease. Postgrad Med 88:239-240.

*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. 1972-1973. The concentration and distribution of some stable elements in healthy human tissues from the United Kingdom - an environmental study. Sci Total Environ 1:341-374.

Han B, Golub MS, Keen CL. 1997. Effects of aluminum exposure over the life span on brain and behavior of mice. Toxicologist 36:64-65.

*Hanninen H, Matikainen E, Kovala T, et al. 1994. Internal load of aluminum and the central nervous system function of aluminum welders. Stand J Work Environ Health 20:279-28X

Hantson P, Mahieu P, Gersdorff M, et al. 1994. Encephalopathy with seizures after use of aluminumcontaining
bone cement. Lancet 344: 1647.

Hardman JG, Limbird LE, Molinoff PB, et al. 1996. The pharmacological basis of therapeutics. grh ed. New York, NY: McGraw-Hill.

Hardy J, Hutton M. 1995. Two new genes for Alzheimer's disease. Trends Neurosci 18:436.

Hart MM, Adamson RH. 197 1. Antitumor activity and toxicity of salts of inorganic group IIIa metals: Aluminum gallium iridium and thallium Proc Natl Acad Sci U S A 681623-1626.

Hartikainen H. 1996. Soil processes and chemical transport. Soil response to acid percolation: Acidbase buffering and cation leaching. J Environ Qual 25:638-645.

Hashimoto Y, Sekine Y. 1992. Atmospheric aluminum fromhuman activities. Atmos Environ 26B:295-300.

Haugen A, Ovrebo S, Drablos PA. 1992. Biomonitoring of genotoxic exposure of aluminum plant workers. Med Lav 83:506-510.

*Hawkins NM, Coffey S, Lawson MS, et al. 1994. Potential aluminum toxicity in infants fed special infant formnla. J Pediatr Gastroenterol Nutr 19:377-381.

*Hawley GG. 1977. The condensed chemical dictionary. 9th ed. New York: Van Nostrand Reinhold co.

*HazDat. 1996. Database. Agency for Toxic Substances and Disease Registry (ATSDR), Atlanta, GA.

*HazDat. 1998. Database. Agency for Toxic Substances and Disease Registry (ATSDR), Atlanta, GA. October 29, 1998.

Hee SSQ, 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.

Heil M, Steffan I, Haschke F, et al. 1988. Aluminum in infant formulas and in breast milk. In: Berger H, ed. Vitamins and minerals in pregnancy and lactation. New York, NY: Vevey/Raven Press, Ltd., 353-354.

Heiny JS, Tate CM. 1997. Concentration, distribution, and comparison of selected trace elements in bed sediment and fish tissue in the South Platte River basin, U.S.A., 1992- 1993. Arch Environ Contam Toxicol 32:246-259.

*Hellou J, Fancey LL, Payne JF. 1992a. Concentrations of twenty-four elements in bluefin tuna, thunnus thynnus from the Northwest Atlantic. Chemosphere 24:2 1 l-2 18.

*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 24:452-458.

Hehners E. 1996. Trace metals in suspended particulate matter of Atlantic Ocean surface water (40 degrees N to 20 degrees S). Mar Chem 53:51-67.

Helmers E, Schrems 0. 1995. Wet deposition of metals to the tropical north and the south Atlantic Ocean. Atmos Environ 29:2475-2484.

*Hemenway DR, Fitzgerald B. 1984. Characterization of aluminum chemistry for acid precipitation. Burlington, Vermont: University of Vermont, Vermont Water Resources Research Center. Project Number G873-05. NTIS No. PB85-214542.

Hemmer W, Wantke F, Focke M, et al. 1996. Evaluation of cutaneous hypersenstivity to aluminum by routine patch testing with $AlCl_3$. Contact Dermatitis 34:217-218.

Hendriks L, Van Broeckhoven C. 1996. The beta A4 amyloid precursor protein gene and Alzheimer's disease. Eur J Biochem 237:6-15.

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.

Herrmann J, Frick K. 1995. Do stream invertebrates accumulate aluminum at low pH conditions? Water Air Soil Pollut 85:407-412.

Hewitt CD, Innes DJ, Herman MM, et al. 1992. Hematological changes after long-term aluminum administration to normal adult rabbits. Ann Clin Lab Sci 22:85-94.

*His E, Beiras R, Seaman MN, et al. 1996. Sublethal and lethal toxicity of aluminum industry effluents to early developmental stages of the *crassostrae gigas* oyster. Arch Environ Contam Toxicol 30:335-339.

Hodsman AB, Steer BM. 1992. Serum aluminum levels as a reflection of renal osteodystrophy status and bone surface aluminum staining. J Am Sot Nephro12: 1318- 1327.

*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.

Hojo Y, Kobayashi T, Shigemitsu Y, et al. 1998. Aluminum(3)-induced brain toxicity and hydroxyl radical generation: Comparison with trimethyltin. Eisei Kagaku 44: 10.

Holbrook MT. 1992. Chlorocarbons, hydrocarbons (CHC13). In: Kroschwitz JI and Howe-Grant M, eds. Kirk-Othmer encyclopedia of chemical technology. 4th Edition. New York, NY: John Wiley & Sons, Inc. 5:1028-1040.

*Hosovski E, Mastelica Z, Sunderic D, et al. 1990. Mental abilities of workers exposed to aluminum Med Lav 81:119-123.

Hosovski E, Vidakovic A, Hosovski M. 1998. Dermal and bronchial responsiveness of aluminum smelter workers. J Occup Health 40:44-49.

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.

HSDB. 1989. Hazardous Substance Data Bank. National Library of Medicine, National Toxicology Information Program Bethesda MD.

HSDB. 1992. Hazardous Substance Data Bank. National Library of Medicine, National Toxicology Information Program Bethesda MD. January 1992.

*HSDB. 1995. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Program (via TOXNET), Bethesda, MD. January 1995.

Huang J-Y, Huang C-C, Lim PS, et al. 1992. Effect of body iron stores on serum aluminum level in hemodialysis patients. Nephron 61:158-162.

Huang Y, Savory J, Herman MM, et al. 1995. Quantitative evaluation of Al maltolate-induced neurodegeneration with subsequent Al removal by desferrioxamine treatment. Neurotoxicology 16:29 l-296.

Huang Y, Herman MM, Liu J, et al. 1997. Neurofibrillary lesions in experimental aluminum-induced encephalopathy and Alzheimer's disease share immunoreactivity for amyloid precursor protein, A beta, alpha1 -antichymotrypsin and ubiquitin-protein conjugates. Brain Res 77 1:2 13-220.

Hunter D, Milton R, Perry KMA, et al. 1944. Effects of aluminum and alumina on the lung in grinders of duralumin aeroplane propellers. Br J Ind Med 1: 159- 164.

Hye-Won A, Jeffrey EH. 1994. Effect of aluminum on fluoride uptake by *salmonella zyphimurium* TA98; implications for the Ames mutagenicity assay. J Toxicol Environ Health 41:357-368.

Hypponen S, Kohila T, Tahti H. 1992. In-vitro and in-vivo effects of aluminum on cell membrane ATPase. Hum Exp Toxicol 11:415-416.

*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. 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. International Commission on Radiological Protection. Human respiratory tract model for radiological protection. Ann ICRP 66: 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.

IRIS. 1989. Integrated Risk Information System U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

IRIS. 1997. Integrated Risk Information System (database). U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Cincinnati, OH.

*IRIS. 1999. Integrated Risk Information System (database). U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Cincinnati, OH.

*Ittel,.TH, Buddington B, Miller NL, et al. 1987. Enhanced gastrointestinal absorption of aluminum in uremic rats. Kidney Int 32:821-826.

Ittel TH, Kinzel S, Ortmanns A, et al. 1996. Effect of iron status on the intestinal absorption of aluminum: A reappraisal. Kidney Int 50:1879-1888.

Ittel TH, Steinhausen C, Kislinger G, et al. 1997. Ultrasensitive analysis of the intestinal absorption and compartmentalization of aluminum in uraemic rats: a 26al tracer study employing accelerator mass spectrometry. Nephrol Dial Transplant 12:1369-1375.

Itzhaki RF. 1984. Possible factors in the etiology of Alzheimer's disease. Mol Neurobio19: l-l 3.

*Iyengar GV, Tanner JT, Wolf WR, et al. 1987. Preparation of a mixed human diet material for the determination of nutrient elements, selected toxic elements and organic nutrients: a preliminary report. Sci Total Environ 61:235-252.

Jackson ML, Huang PM. 1983. Aluminum of acid soils in the food chain and senility. Sci Total Environ 28:269-276.

Jacqmin H, Commenges D, Letenneur L, et al. 1994. Components of drinking water and risk of cognitive impairment in the elderly. Am J Epidemiol 139:48-57.

Jaehde U, Sorgel F, Stephan U, et al. 1994. Effect of an antacid containing magnesium and aluminum on absorption, metabolism and mechanism of renal elimination of perfloxacin in humans. Antimicrob Agents Chemother 38:1129-l 133.

*James BR, Riha SJ. 1989. Aluminum leaching by mineral acids in forest soils: I. Nitric-sulfuric acid differences. Soil Sci Sot Am J 53:259-264.

James JR, Nordberg A. 1995. Genetic and environmental aspects of the role of nicotinic receptors in neurodegenerative disorders: emphasis on Alzheimer's disease and Parkinson's disease. Behav Gen 25:149-159.

Janssen RPT, Peijnenburg WJGM, Posthuma L, et al. 1997. Equilibrium partitioning of heavy metals in Dutch field soil. 1. Relationship between metal partition coefficients and soil characteristics. Environ Toxicol Chem 16:2470-2478.

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 Toxico1 Environ Health 48:649-665.

*Jephcott CM. 1948. Fume exposure in the manufacture of alumina abrasives. Occup Med 5:701-725.

*Jernelov A. 197 1. Phosphate reduction in lakes by precipitation with aluminum sulphate. In: Jenkins SH, ed. Advances in water pollution. I-15/1 to I-1516.

*Johanson CE. 1980. Permeability and vascularity of the developing brain: cerebellum vs cerebral cortex. Brain Res 190:3-16.

*Jones KC, Bennett BG. 1986. Exposure of man to environmental aluminum-An exposure commitment assessment. Sci Total Environ 52:65-82.

Jones P. 1991. The investigation of aluminum speciation in natural and potable waters using shortcolumn ion chromatography. Int J Environ Anal Chem 44: 1- 10.

*Jones P, Ebdon L, Williams T. 1988. Determination of trace amounts of aluminum by ion chromatography with fluorescence detection. Analyst 113 :64 l-644.

*Jope RS, Johnson GVW. 1992. Neurotoxic effects of dietary aluminum In: Aluminum in biology and medicine. Chichester: John Wiley & Sons, 254-267.

*Jordan JW. 196 1. Pulmonary fibrosis in a worker using an aluminum powder. Br J Ind Med 18:21-23.

Jouhanneau P, Lacour B, Raisbeck G, et al. 1993. Gastrointestinal absorption of aluminum in rats using 26Al and accelerator mass spectrometry. Clin Nephrol 40:244-248.

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: 1023- 1028.

Julka D, Gill KD. 1995. Development of a possible peripheral marker for aluminum neurotoxicity. Med Sci Res 23:311-314.

Julka D, Gill KD. 1996a. Altered calcium homeostasis: A possible mechanism of aluminum-induced neurotoxicity. Biochim Biophys Acta 13 15:47-54.

Julka D, Gill KD. 1996b. Involvement of altered cytoskeletal protein phosphorylation in aluminuminduced
CNS dysfunction. J Biochem Toxicol 11:227-233.

Julka D, Gill KD. 1996c. Effect of aluminum on regional brain antioxidant defense status in Wistar rats. Res Exp Med 196:187-194.

*Julka D, Vasishta RK, Gill KD. 1996. Distribution of aluminum in different brain regions and body organs of rat. Biol Trace ElemRes 52:181-192.

Kaaber K, Nielsen AO, Veien NK. 1992. Vaccination granulomas and aluminum allergy: Course and prognostic factors. Contact Dermatitis 26:304-306.

*Kabata-Pendias A, Pendias H, eds. 1984. Trace elements in soils and plants. Boca Raton, FL: CRC Press, Inc., 135-136.

*Kaehny WD, Hegg AP, Alfrey AC. 1977. Gastrointestinal absorption of aluminum from aluminumcontaining
antacids. N Engl J Med 296:1389-1390.

Kandiah J, Kies C. 1994. Aluminum concentrations in tissues of rats: effect of soft drink packaging. BioMetals 7:57-60.

Kanematsu N, Hara M, Kada T. 1980. Ret assay and mutagenicity studies on metal compounds. Mutat Res 77:109-116.

Kang N, Griffin D, Ellis H. 1992. The pathological effects of glove and condom dusting powders. J Appl Toxicol 12:443-449.

Karathanasis AD, Thompson YL, Evangelou VP. 1990. Temporal solubility trends of aluminum and iron leached from coal spoils and contaminated soil materials. J Environ Qual 19:389-395.

*Karlik SJ, Eichhorn GL, Crapper-McLachlan DR. 1980. Molecular interactions of aluminum with DNA. Neurotoxicology 1:83-88.

Kato H, Shibano M, Saito T, et al. 1994. Relationship between hemolytic activity and adsorption capacity of aluminum hydroxide and calcium phosphate as immunological adjuvants for biologicals. Microbial Immunol38:543-548.

Katyal R, Desigan B, Sodhi CP, et al. 1997. Oral aluminum administration and oxidative injury. Biol Trace ElemRes 57:125-130.

*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 22:7-9.

Kawachi I, Pearce N. 1991 . Aluminum in the drinking water-is it safe? Aust J Public Health 15 : 84-87.

*Keeler,R. 1991. ICP mass spectrometry shows its mettle. Res Dev 33:44-48.

*Kehoe RA, Cholak J, Story RV. 1940. A spectrochemical study of the normal ranges of concentration of certain trace metals in biological materials. J Nutr 19579-592.

*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.

*Khosla SN, Nand N, Khosla P. 1988. Aluminum phosphide poisoning. J Trop Med Hyg 91:196-198.

Kihira T, Yoshida S, Uebayashi Y, et al. 1994. Experimental model of motor neuron disease: Oral aluminum neurotoxicity. Biomed Res 15:27-36.

Kilburn KH, Warshaw RH. 1992. Irregular opacities in the lung, occupational asthma, and airways dysfunction in aluminum workers. Am J Ind Med 21:845-853.

Kilburn KH, Warshaw RH. 1993. Neurobehavioral testing of subjects exposed residentially to groundwater contaminated from an aluminum die-casting plant and local referents. J Toxicol Environ Health 39:483-496.

King EJ, Harrison CV, Mohanty GP, et al. 1958. The effect of aluminum and of aluminum containing 5 per cent. of quartz in the lungs of rats. J Pathol Bacterial 75:429-434.

*King SW, Savory J, Wills MR. 1981. The clinical biochemistry of aluminum CRC Crit Rev Clin Lab Sci 14:1-20.

*Kirschbaum BB, Schoolwerth AC. 1989. Acute aluminum toxicity associated with oral citrate and aluminum-containing antacids. Am J Med Sci 297:9-l 1.

*Kirschner EM. 1995. Production of top 50 chemicals increased substantially in 1994. Chem Eng News 74:16-22.

Kirsner JB. 1942. The effect of calcium carbonate, aluminum phosphate, and aluminum hydroxide on mineral excretion in man. J Clin Invest 22:47-52.

Klein GL. 1995. Aluminum in parenteral solutions revisited-again. Am J Clin Nutr 61:449-456.

Kloppel H, Fliedner A, Kordel W. 1997. Behaviour and ecotoxicology of aluminum in soil and water-Review of the scientific literature. Chemosphere 35:353-363.

*Klosterkotter W. 1960. Effects of ultramicroscopic gamma-aluminum oxide on rats and mice. AMA Arch Ind Health 2 1:458-472.

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.

*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.

Kongerud J. 1992. Respiratory disorders in aluminum potroom workers. Med Lav 83:414-417.

Kongerud J, Samuelsen SO. 1991 . A longitudinal study of respiratory symptoms in aluminum potroom workers. AmRev Respir Dis 144:10-16.

Kongerud J, Gronnesby JK, Magnus P. 1990. Respiratory symptoms and lung function of aluminum potroom workers. Stand J Work Environ Health 16:270-277.

Kongerud J, Boe J, Soyseth V, et al. 1994. Aluminum potroom asthma: The Norwegian experience. Eur Resp J 7:165-172.

*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. 1988. Aluminum and bone disorders with specific reference to aluminum contamination of infant nutrients. J Am Coll Nutr 7: 199-2 14.

*Koo WWK, Kaplan LA, Krug-Wispe SK. 1988. Aluminum contamination of infant formulas. J Parenter Enteral Nutr 12:170-173.

*Koo WWK Krug-Wispe SK, Succop P, et al. 1992. Sequential serum aluminum and urine aluminum: Creatinine radio and tissue aluminum loading in infants with fractures/rickets. Pediatrics 89:877-881.

*Kopp JF, Kroner RC. 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: US Department of the Interior, Federal Water Pollution Control Administration, Division of Pollution Surveillance.

*Kopp JF, McKee GD. 1978. Methods for chemical analysis of water and wastes, 1978. Cincinnati, OH: Environmental Monitoring and Support Lab. EPA/600/4-79/020.

*Kovalchik MT, Kaehny WD, Hegg AP, et al. 1978. Aluminum kinetics during hemodialysis. J Lab Clin Med 92:7 12-720.

*Kowalczyk GS, Gordon GE, Rheingrover SW. 1982. Identification of atmospheric particulate sources in Washington, D.C., 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, Raithel HJ, et al. 1997. [Early diagnosis of aluminum dust lung syndrome]. Arbeitsmed Sozialmed Umweltmed 32:203-207. (German).

*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 3rd, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures. In: Yang R, ed. Toxicology of chemical mixtures. New York: Academic Press, 399-437.

*Krishnaswamy R. 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). Report to US Bureau of Mines, Washington, DC, by NH Parker, PE and Associates, La Crescenta, CA. NTIS No. PB84-207091.

Kroschwitz JI, Howe-Grant M, Humphreys LJ. 1992a. Kirk-Othmer encyclopedia of chemical technology. Vol. 2. Fourth ed. New York, NY: John Wiley & Sons, 248-249.

Kroschwitz JI, Howe-Grant M, Humphreys LJ. 1992b. Kirk-Othmer encyclopedia of chemical technology. Vol. 6. Fourth ed. New York, NY: John Wiley & Sons, 405-423.

*Kroschwitz JI, Howe-Grant M. 1993. Kirk-Othmer encyclopedia of chemical technology. Vol. 7. Fourth ed. New York, NY: John Wiley & Sons, 602.

Krueger GL, Morris TK, Suskind RR, et al. 1984. The health effects of aluminum compounds in mammals. Crit Rev Toxicol 13: l-24.

Kubal G, Mason AB, Sadler PJ, et al. 1992. Uptake of Al 3'into the N-lobe of human serum transferrin. BiochemJ 285:711-714.

Kuroda Y, Kobayashi K, Ichikawa M, et al. 1995. Application of long-term cultured neurons in aging and neurological research: Aluminum neurotoxicity, synaptic degeneration and Alzheimer's disease. Gerontology 41(Suppl. 1):2-6.

Kyotomaa A, Nieminen S, Thuneberg P, et al. 1995. Accumulation of aluminum in hypogymnia physodes in the surroundings of a Finnish sulphite-cellulose factory. Water Air Soil Pollut 81:401-409.

*Lal B Gupta A, Gupta A, et al. 1993. Aluminum ingestion alters behaviour and some neurochemicals in rats.' Indian J Exp Bio13 1:30-35.

Lal1 SB, Sinha K, Mittra S, et al. 1997. An experimental study on cardiotoxicity of aluminum phosphide. Indian J Exp Biol 35:1060-1064.

*Landsberg JP, McDonald B, Watt F. 1992. Absence of aluminum in neuritic plaque cores in Alzheimer's disease. Nature 360:65-68.

*Lansdown AB. 1973. Production of epidermal damage in mammalian skins by some simple aluminum compounds. Br J Dermatol89:67-76.

*Lantzy RJ, MacKenzie FT. 1979. Atmospheric trace metals: Global cycles and assessment of man's impact. Geochim Cosmochim Acta 43:511-526.

Lauwerys RR. 1983. Industrial chemical exposure: Guidelines for biological monitoring. Davis, CA: Biomedical Publications.

Lawrence GB, David MB. 1997. Response of aluminum solubility to elevated nitrification in soil of a red spruce stand in eastern Maine. Environ Sci Technol 31:825-830.

LaZerte BD, van Loon G, Anderson B. 1997. Aluminum in water. In: Yokel RA, Golub M, eds. Research issues in aluminum toxicity. Washington, DC: Taylor & Francis, 17-45.

*Leblondel G, Allain P. 1980. Blood and brain aluminum concentrations in mice after intraperitoneal injection of different aluminum compounds. Res Commun Chem Patho1 Pharmacol27:579-586.

Lee DS, Garland JA, Fox AA. 1994. Atmospheric concentrations of trace elements in urban areas of the United Kingdom Atmos Environ 28:269 l-27 13.

*Lee RE Jr, Von Lehmden DJ. 1973. Trace metal pollution in the environment. J Air Pollut Control Assoc 23:853-857.

*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.

LehotzQ K, Gonda Z, Tatrai E. 1997. Learning and memory deficits induced by prenatal aluminum exposure in rat pups. Neurotoxicology 18:881.

*Letterman RD, Driscoll CT. 1988. Survey of residual aluminum in filtered water. J Am Water Works Assoc 80:154-158.

Letzel S, Schaller KH, Angerer J, et al. 1996. Biological monitoring of occupational aluminum powder exposure. Occup Hyg 3:27 l-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.

Levallois P, Battershill JH. 1995. Aluminum and Alzheimer's disease. Can Med Assoc J 152:467-469.

*Lewis C, Macia ES. 1980. Composition of size-fractionated aerosol in Charleston, West Virginia. Atmos Environ 14: 185- 194.

*Lewis RJ. 1993. Hawley's condensed chemical dictionary. 12th ed. New York, NY: Van Nostrand Reinhold Company.

*Lewis TE, ed. 1989. Introduction. In: Lewis TE, ed. Environmental chemistry and toxicology of aluminum Chelsea, MI: Lewis Publishers, Inc., l-2.

Li Y-M, Nakaya S, Kudo H, et al. 1991. Health survey of workers of an aluminum plant in China. 4. X-ray examinations of the skeletal system Fluoride 23-24:95-99.

*Lichte FE, Hopper S, Osborn TW. 1980. Determination of silicon and aluminum in biological matrices by inductively coupled plasma emission spectrometry. Anal Chem 52:120-124.

*Lide DR. 1997. CRC Handbook of chemistry and physics: A ready-reference book of chemical and physical data. 78th ed. Boca Raton, FL: CRC Press.

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 J-L, Leu M-L. 1996. Aluminum-containing agents may be toxic in predialysis chronic renal insufflciency patients. J Int Med 240:243-248.

Lin J-L, Kou -T, Leu M-L. 1996. Effect of long-termlow-dose aluminum-containing agents on hemoglobin synthesis in patients with chronic renal insufficiency. Nephron 74:33-38.

*Lione A. 1983. The prophylactic reduction of aluminum intake. Food Chem Toxicol 21: 103-109.

*Lione A. 1985a. Aluminum intake from non-prescription drugs and sucralfate. Gen Pharmacol 16:223-228.

*Lione A. 1985b. Aluminum toxicology and the aluminum-containing medications. Pharmacol Ther 29:255-285.

*Lione A, Allen PV, Smith JC. 1984. Aluminum coffee percolators as a source of dietary aluminum Food Chem Toxicol 22:265-268.

*Liss L, Thornton DJ. 1986. The rationale for aluminum absorption control in early stages of Alzheimer's disease. Neurobiol Aging 7:552-554.

*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.

Lithner G, Holm K, Borg H. 1995. Bioconcentration factors for metals in humic waters at different pH in the Ronnskar area (N. Sweden). Water Air Soil Pollut 85:785-790.

Liu JX, Nordberg GF. 1995. Nephrotoxicities of aluminum and/or cadmium-metallothionein in rats: Creatinine excretion and metabolism of selected essential metals. Pharmacol Toxicol 77: 155- 160.

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.

*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.

Llobet JM, Colomina MT, Sirvent JJ, et al. 1995. Reproductive toxicology of aluminum in male mice. Fundam Appl Toxicol 25:45-5 1.

*Locock, RA. 1971. Review of the antacids. Can Pharm J 104:86-89.

Lomonte C, Casucci C, Larenza C, et al. 1995. [A moderate overload of aluminum increase the consumption of erythropoietin]. Giornale Italian0 di Nefrologia 12:403-404. (Italian).

Lorieri D, Msenbeer H. 1997. Aluminum iron and manganese in near-surface waters of a tropical rainforest ecosystem Sci Total Environ 205: 13-23.

Lote CJ, Wood JA, Thewles A, et al. 1995. Renal filtration and excretion of aluminum in the rat: Dose-response relationships and effects of aluminum speciation. Hum Exp Toxicol 14:494-499.

*Lovell MA Ehmann WD, Markesbery WR.
Alzheimer's disease. Ann Neurol 33:36-42.
1993. Laser microprobe analysis of brain aluminum in

Lu JY, Chakrabarti CL, Back MH, et al. 1996. Speciation of some metals in river surface water, rain and snow, and the interactions of these metals with selected soil matrices. J Anal Atom Spectrom 11:1189-1201.

*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. Aluminumion in biological systems. Trends Biochem Sci 13:15-19.

Mackay IR, Oliphant RC, Laby B, et al. 1990. An immunologic and genetic study of asthma in workers in an aluminum smelter. J Occup Med 32:1022-1026.

*Madigosky SR, Alvarez-Hernandez X, Glass J. 199 1. 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.

Mahieu S, Calvo ML. 1998. Effect of chronic poisoning with aluminum on the renal handling of phosphate in the rat. Toxicol Lett 94:47-56.

Mahieu S, Calvo ML, Millen N, et al. 1998. Crecimiento y metabolismo del calcio en ratas sometidas a intoxication cronica con hidroxido de aluminio. Acta Physiol Pharmacol Ther Latinoam 48:32-40. (Spanish).

*Main J, Ward MK. 1992. Potentiation of aluminum absorption by effervescent analgesic tablets in a haemodialysis patient. Br Med J 304: 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 14:257-261.

*Makjanic J, McDonald B, Chen CPLH, et al. 1998. Absence of aluminum in neurofibrillary tangles in Alzheimer's disease. Neurosci Lett 240:123-125.

*Mandic 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.

Manzo L, Castoldi AF, Coccini T, et al. 1995. Mechanisms of neurotoxicity: Applications to human biomonitoring. Toxicol Lett 77:63-72.

Marcus DL, Wong S, Freedman ML. 1992. Dietary aluminum and Alzheimer's disease. J Nutr Elder 1255-61.

*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.

Marques HM. 1991. Kinetics of the release of aluminum from human serum dialuminum transferrin to citrate. J Inorg Biochem 41:187-193.

*Marquis JK. 1989. Neurotoxicity of aluminum In: Lewis TE, ed. Environmental chemistry and toxicology of aluminum Chelsea, MI: Lewis Publishers, Inc., 289-298.

*Martell AE, Mortekaitis 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.

*Martin RB. 1986. The chemistry of aluminum as related to biology and medicine. Clin Chem 32:1797-1806.

Martyn CN. 1992. The epidemiology of Alzheimer's disease in relation to aluminum In: Aluminum in biology and medicine. Chichester: John Wiley & Sons, 69-86.

*Martyn CN, Osmond C, Edwardson JA, et al. 1989. Geographical relation between Alzheimer's disease and aluminum in drinking water. Lancet 1:59-62.

*Martyn CN, Coggon DN, Inskip H, et al. 1997. Aluminum concentrations in drinking water and risk of Alzheimer's disease. Epidemiol 8:28 l-286.

*Marzin DR, Phi HV. 1985. Study of the mutagenicity of metal derivatives with *salmonellatyphimurium* TA102m Mutat Res 155:49-52.

Mayor GH, Bumatowska-Hledin MA. 1983. Impaired renal function and aluminummetabolism. 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 6:43-50.

Mazzaferro S, Coen G, Ballanti P, et al. 1992. Deferoxamine test and PTH serum levels are useful not to recognize but to exclude aluminum-related bone disease. Nephron 61: 151- 157.

*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 Sot Exp Biol Med 161:74-77.

*McDermott JR, Smith AI, Ward MK, et al. 1978. Brain-aluminum concentration in dialysis encephalopathy. Lancet 1:901-904.

*McDermott JR, Smith AI, Iqbal K, et al. 1979. Brain aluminum in aging and Alzheimer disease. Neurology 291809814.

McDonald B, Haszard R, Spence A, et al. 1996. A mortality study of Alzheimer's disease and aluminum exposure through inhalation of McIntyre powder in Cornish tin miners. Neurobiol Aging 17:s 122-S 123.

*McDonald DG, Wood CM, Rhem RG, et al. 199 1. Nature and time course of acclimation to aluminum in juvenile brook trout (salvelinusfontinalis). 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.

McGraw M, Bishop N, Jameson R, et al. 1986. Aluminum content of milk formulae and intravenous fluids used in infants. Lancet 1: 157.

*McKeever S WS, Moscovitch M, Townsend PD. 1995. Thermoluminescence dosimetry materials: Properties and uses. Kent, England: Nuclear Technology Publishing.

McLachlan DR, Fraser PE, Dalton AJ. 1992. Aluminum and the pathogenesis of Alzheimer's disease: A summary of the evidence. In: Aluminum in biology and medicine. Chichester: John Wiley & Sons, 87-108.

*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 46:401-405.

*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.

McMillan TM, Freemont AJ, Herxheimer A, et al. 1993. Camelford water poisoning accident: Serial neuropsychological assessments and further observations on bone aluminum Hum Exp Toxicol 12:37-42.

McNall AD, Fosmire GJ. 1996. Zinc status does not affect aluminum deposition in tissues of rats. Biol Trace Elem Res 53:7-18.

*Meiklejohn A, Jones WW. 1948. The effect of the used of calcined alumina in china biscuit placing on the health of the workmen. J Ind Hyg Toxicol 30: 160- 165.

*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 14:229-23 1.

Meiri H, Banin E, Roll M. 1991. Aluminum ingestion-Is it related to dementia? Rev Environ Health 9:191-205.

Meiri H, Banin E, Roll M, et al. 1993. Toxic effects of aluminum on nerve cells and synaptic transmission. Prog Neurobiol40: 89- 121.

*Mera SL. 1996. Biomedical comment. Alzheimer's disease: genetic or environment? Br J Biomed Sci 53:91-92.

Merino A, Macias F, Garcia-Rodeja E. 1998. Aluminum dynamics in experimentally acidified soils from a humid-temperate region of South Europe. Chemosphere 36:1137-l 142.

Meyer OA, Tilson HA, Byrd WC, et al. 1979. A method for the routine assessment of fore- and hindlimb grip strength of rats and mice. Neurobehav Toxicol 1:233-236.

*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.

Milham SJ. 1993. Unusual sex ratio of births to carbon setter fathers. Am J Ind Med 23:829-831.

*Milham S Jr. 1979. Mortality in aluminum reduction plant workers. J Occup Med 21:475-480.

Miller EK, Huntington TG, Johnson AH, et al. 1992. Plant and environment interactions-aluminum in soil solutions from a subalpine spruce-fir forest at Whiteface Mountain, New York. J Environ Qual 21:345-352.

*Miller RG, Kopfler FC, Kelty KC, et al. 1984. The occurrence of aluminum in drinking water. J Am Water Works Assoc 76:84-91.

Minami T, Ichii M, Tohno Y, et al. 1996. Age-dependent aluminum accumulation in the human aorta and cerebral artery. Biol Trace Elem Res 55:199-205.

*Misawa T, Shigeta S. 1992. Behavioral effects of repeated aluminum administration in the rat. Tokai J Exp Clin Med 17:155-159.

Misawa T, Shigeta S. 1993. Effects of prenatal aluminum treatment on development and behavior in the rat. J Toxicol Sci 18:43-48.

Mitani K. 1992. Relationship between neurological diseases due to aluminum load, especially amyotrophic lateral sclerosis, and magnesium status. Magnes Res 5:203-2 13.

*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.

Mjoberg B, Hellquist E, Mallmin H, et al. 1997. Aluminum Alzheimer's disease and bone fragility. Acta Orthop Stand 68:511-514.

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.

*Monteagudo FSE, Isaacson LC, Wilson G, et al. 1988. Aluminum excretion by the distal tubule of the pig kidney. Nephron 49:245-250.

Mookherji S, Floyd M. 1991 . The effect of aluminum on growth of and nitrogen fixation in vegetable soybean germplasm. Plant Soil 136:25-29.

*Moomaw JC, Nakamura MT, Sherman GD. 1959. Aluminum in some Hawaiian plants. Pat Sci 13:335-341.

Moon J, Davison A, Bandy B. 1992. Vitamin D and aluminum absorption. Can Med Assoc J 147:1308,1313.

Moore JG, Coburn JW, Sanders MC, et al. 1995. Effects of sucralfate and ranitidine on aluminum concentrations in elderly volunteers. Pharmacotherapy 15:742-746.

Moos T. 1995. Age-dependent uptake and retrograde axonal transport of exogenous albumin and transferrin in rat motor neurons. Brain Res 672:14-23.

Moreno A, Dominquez P, Dominquez C, et al. 1991. High serum aluminum levels and acute reversible encephalopathy in a 4-year-old boy with acute renal failure. Eur J Pediatr 150:5 13-5 14.

Morie T, Iwamoto M, Harada N, et al. 1996. Urinary excretion of aluminum: Effects of aging and diurnal variation. Arch Gerontol Geriatr 22:287-295.

Morrisey JF, Barreras RF. 1974. Antacid therapy. N Engl J Med 290:550-554.

Morissey J, Slatopolsky E. 1986. The effect of aluminum on parathyroid hormone secretion. Kidney Int 29S:41-48.

Morre PB, Edwardson JA, Ferrier IN, et al. 1997. Gastrointestinal absorption of aluminum is increased in Down's syndrome. Biol Psychiatry 41:488-492.

*Morrow PE. 1988. Possible mechanisms to explain dust overloading of the lungs. Fund Appl Toxicol 10:369-384.

*Morrow PE. 1992. Dust overloading of the lungs: update and appraisal. Toxicol Appl Pharmacol 113: 1-12.

*Morselli PL, France-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 Sot Trans 14:916-917.

Moshtaghie AA, Taher M, Fazilati M, et al. 1996. Aluminum toxicity and changes in serum parameters related to liver function in rats. Clin Chem Enzymol Commun 7: 187- 192.

*Meyers JL, Ranweiler LE, Hopf SB, et al. 1977. Evaluation of particulate trace species in Southwest desert atmosphere. Environ Sci Technol 11:789-795.

Mui S, Briggs M, Chung H, et al. 1996. A newly identified polymorphism in the apolipoprotein E enhancer gene region is associated with Alzheimer's disease and strongly with the E 4 allele. Neurology 47:196-201.

Mukerjee S, Ellenson WD, Lewis RG, et al. 1997. An environmental scoping study in the lower Rio Grande Valley of Texas - 3. Residential microenvironmental monitoring for air, house dust, and soil. Environ Int 23:657-673.

*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 42:253-261.

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 34:79-87.

*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 39:2 11-219.

*Muller JP, Steinegger A, Shlatter C. 1993b. Contribution of aluminum from packaging materials and cooking utensils to the daily aluminum intake. Z Lebensm Unters Forsch 197:332-341.

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.

Mundy WR, Freudenrich TM, Kodavanti PRS. 1997. Aluminum potentiates glutamate-induced calcium accumulation and iron-induced oxygen free radical formation in primary neuronal cultures. Mol Chem Neuropathol32:41-56.

Munoz DG. 1994. Aluminum and Alzheimer's disease. Can Med Assoc J 151:268-271.

*Mur JM, Moulin JJ, Meyer-Bisch C, et al. 1987. Mortality of aluminum reduction plant workers in France. Int J Epidemiol 16:257-264.

Murungi JI, Robinson JW. 1992. Uptake and accumulation of aluminum by fish -the modifying effect of added ions. J Environ Sci Health Part A A27:713-719.

*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 37:367-372.

*Mussi I, Calzaferri G, Buratti M, et al. 1984. Behaviour of plasma and urinary aluminumlevels in occupationally exposed subjects. Int Arch Occup Environ Health 54: 155-l 61.

Nabrzyski M, Gajewska R. 1995. Aluminum and fluoride in hospital daily diets and in teas. Z Lebensm Unters Forsch 201:307-310.

Nagy E, Jobst K. 1994a. Aluminum dissolved from kitchen utensils. Bull Environ Contam Toxicol 52:396-399.

Nagy E, Jobst K. 1994b. The kinetics of aluminum-containing antacid absorption in man. Eur J Clin ChemClinBiochem 32:119-121.

*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 34588593.

NAS. 1982. Drinking water and health: Volume 4. Washington, DC: National Academy Press, 155-167.

*NAS/NRC. 1989. Biologic markers in reproductive toxicology. Washington, DC: National Academy of Sciences, National Research Council, National Academy Press.

Nathan E, Pedersen SE. 1980. Dialysis encephalopathy in a non-dialysed uraemic boy treated with aluminumhydroxide orally. Acta Paediatr Stand 69:793-796.

*NATICH. 1988. National Air Toxics Information Clearinghouse. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards.

*NATICH. 1992. National Air Toxics Information Clearinghouse. Report on state, local, and EPA air toxics activities. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. December 1992.

Nayak P, Chtterjee AK. 1998. Impact of protein malnutrition on subcellular nucleic acid and protein status of brain of aluminum-exposed rats. J Toxicol Sci 23: 1-14.

Naylor GJ, Sheperd B, Treliving L, et al. 1990. Tissue aluminum concentrations stability over time, relationship to age, and dietary intake. Biol Psychiatry 27:884-890.

Neiva TJC, Fries DM, Monteiro HP, et al. 1997. Aluminum induces lipid peroxidation and aggregation of human blood platelets. Braz J Med Biol Res 30:599-604.

Nellessen JE, Fletcher JS. 1993. Assessment of published literature on the uptake, accumulation, and translocation of heavy metals by vascular plants. Chemosphere 27: 1669- 1680.

*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. [letter]. Lancet 338:390.

*NFPA. 1994. Fire protection guide to hazardous materials. 1 lth edition. Quincy, MA: National Fire Protection Association.

Nicar MJ, McIntire DD, Pak LK. 1992. Brain and bone aluminum A comparison of aluminum intake in rats. Environ Toxicol Chem 11:1331-1336.

Nicholls DMcE, Speares GM, Asina S, et al. 1995. Brain mRNA from infants of aluminum-exposed lactating rabbits. Int J Biochem Cell Biol27:365-370.

*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 3:29-81.

Nielsen J, Dahlqvist M, Welinder H, et al. 1993. Small airways function in aluminum and stainless steel welders. Int Arch Occup Environ Health 65: 101 - 105.

NIOSH. 1976. National occupational hazard survey. Cincinnati, Ohio: Department of Health and Human Services, National Institute for Occupational Safety and Health.

NIOSH. 1984a. National occupational exposure survey. Cincinnati, Ohio: Department of Health and Human Services, National Institute for Occupational Safety and Health.

*NIOSH. 1984b. Aluminum and compounds: Methods 7013 and 7300. Department of Health and Human Services, National Institute for Occupational Safety and Health. NIOSH manual V5 173-1.

*NIOSH. 1988. National occupational exposure survey field guidelines. Cincinnati, Ohio: Department of Health and Human Services, National Institute for Occupational Safety and Health. Publication no. 88-106.

*NIOSH. 1991. National occupational exposure survey matrix. Cincinnati, Ohio: Department of Health and Human Services, National Institute for Occupational Safety and Health. December 11, 1996.

*NIOSH. 1992. NIOSH Recommendations for occupational safety and health--compendium of policy documents and statements. Cincinnati, Ohio: Department of Health and Human Services, National Institute for Occupational Safety and Health. Publication No. 92-100.

Nolan CR, DeGoes JJ, Alfrey AC. 1994. Aluminum and lead absorption from dietary sources in women ingesting calcium citrate. South Med J 87:894-898.

Nordberg GF. 1990. Human health effects of metals in drinking water: Relationship to cultural acidification. Environ Toxicol Chem 9:887-894.

Norseth T. 1979. Aluminum In: Friberg L, Nordberg GR, Vouk VB, eds. Handbook on the toxicology of metals. New York, NY: Elsevier North Holland, 275-281.

*Norton SA. 197 1. Geochemical cycles involving flora, lake water, and bottom sediments. PB No. 206197.

Nowak P, Brus R, Szkilnik R, et al. 1997. Central dopaminergic reactivity in rats after a long-term consumption of aluminum sulfate in their drinking water. Pharmacol Rev Commun 9: 123- 131.

*NRC. 1982. Drinking water and health. Vol. 4. Washington, DC: National Academy of Sciences, National Research Council, National Academy Press, 155-167.

*NRC. 1993. National Research Council. Pesticides in the diets of infants and children. Washington, DC: National Academy Press.

*NRC. 1993. National Research Council. Pesticides in the diets of infants and children. Washington, DC: National Academy Press.

*NRC. 1995. National Research Council. Nitrate and nitrite in drinking water. Washington, DC: National Academy Press. NTIS No. PB95-267092.

*Nyholm NE. 198 1. 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.

Oganesyan GA, Titkov ES. 1995. [Study of the long-term effects of small concentrations of aluminum on the central nervous system of white rats and a determination of the potential danger of the effects of these concentrations on humans]. Zh Evol Biokhim Fiziol 31:483-488. (Russian).

*OHM/TADS. 1989. Oil and Hazardous Materials Technical Assistance Data System Washington, DC: U.S. Environmental Protection Agency, National Institute of Health.

*Öman L-O, Martin RB. 1994. Citrate as the main small molecule binding A13+ in serum Clin Chem 40598-601.

Okuizumi K, Onodera 0, Seki K, et al. 1996. Lack of association of very low density lipoprotein receptor gene polymorphism with Caucasian Alzheimer's disease. Ann Neurol 40:251-254.

O'Mahony D, Denton J, Templar J, et al. 1995. Bone aluminum content in Alzheimer's disease. Dementia 6169-72.

*Ondov JM, Zoller WH, Gordon GE. 1982. Trace element emissions of aerosols from motor vehicles. Environ Sci Technol 16:318-328.

*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 23:305-312.

*Oneda S, Takasaki T, Kurowaki K, et al. 1994. Chronic toxicity and tumorigenicity study of aluminum potassium sulfate in B6C3Fl mice. In Vivo 8:271-278.

Orihuela D, Carnovale CE, Monti JA, et al. 1996. Sex-related differences in the effect of aluminum on calcium transport in the small intestine of the rat. Toxicol Lett 85: 165- 171.

*OSHA. 1974. U. S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000.

OSHA. 1982. U. S. Department of Labor. Occupational Safety and Health Administration. Federal Register 47:30420.

*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 42:1296-1300.

*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 see-ip-ms. Food Chem Toxicol 32:697-705.

Owen PJ, Miles DPB. 1995. A review of hospital discharge rates in a population around Camelford in North Cornwall up to the fifth anniversary of an episode of aluminum sulphate absorption. J Public Health Med 17:200-204.

Paik S R, Lee J-H, Kim D-H, et al. 1997. Aluminum-induced structural alterations of the precursor of the non-alphabeta component of Alzheimer's disease amyloid. Arch Biochem Biophys 344:325-334.

Panchalingam K, Sachedina S, Pettegrew JW, et al. 1991. Al-ATP as an intracellular carrier of Al(II1) ion. Int J Biochem 23:1453-1469.

Park H-S, Uh S-T, Park C-S. 1996. Increased neutrophil chemotactic activity is noted in aluminuminduced
occupational asthma. Korean J Intern Med 11:69-73.

Parkinson IS, Ward MK, Feest TG, et al. 1979. Fractioning dialysis osteodystrophy and dialysis encephalopathy: An epidemiological survey. Lancet 1:406-409.

Partridge NA, Regnier FE, White JL, et al. 1989. Influence of dietary constituents on intestinal absorption of aluminum Kidney Int 35:1413-1417.

*Pastor E, de Pablos F, Ariza JLG. 1987. Determination of nanogram amounts of aluminum and indium with 4,4'-oxalybis(hydrazonomethyl)diresorcinol. Analyst 112: 1041- 1045.

*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.

Pearson RJC, Battigelli MC, Gamble JT. 1993. Mortality from working in the aluminum reduction industry. Environ Res 61: 19-24.

Pendlebury WW, Beal MF, Kowall NW, et al. 1988. Neuropathologic, neurochemical and immunocytochemical characteristics of aluminum-induced neurofilamentous degeneration. Neurotoxicology 9:503-510.

Peng J-HF, Xu Z-C, Xu Z-X, et al. 1992. Aluminum-induced acute cholinergic neurotoxicity in rat. Mol Chem Neuropathol 17:79-89.

*Pennington JAT. 1987. Aluminumcontent of foods and diets. Food Addit Contam 5:161-232.

*Pennington JAT, Schoen SA. 1995. Estimates of dietary exposure to aluminum Food Addit Contam 12:119-128.

Pennington JAT, Jones JM, Vanderveen JE. 1987. Aluminum in total diet study foods and diets. [Abstract]. Fed Proc 46:1002.

Perez-Tur J, Froelich S, Prihar G, et al. 1995. A mutation in Alzheimer's disease destroying a splice acceptor site in the presenilin-1 gene. NeuroReport 7:297-301.

Pericak-Vance MA, Haines JL. 1995. Genetic susceptibility to Alzheimer disease. Trends Genet 11:504-508.

*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 aluminuminto central nervous system along nasal-olfactory pathways. Lancet 1:1028.

*Perl DP Good PF. 1988. Aluminum environment and central nervous-system disease. Environ Technol Lett 9:901-906.

Perl DP, Good PF. 1991. Aluminum Alzheimer's disease, and the olfactory system Ann N Y Acad Sci 640:8-13.

*Perl DP, Gajdusek DC, Garruto RM, et al. 1982. Intraneuronal aluminum accumulation in amyotrophic lateral sclerosis and Parkinsonism-dementia of Guam Science 217:1053-1055.

Petit TL, Biederman GB, Jonas P, et al. 1985. Neurobehavioral development following aluminum administration in infant rabbits. Exp Neurol 88:640-651.

*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: 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 52:396-403.

*Pigott GH, Gaskell BA, Ishmael J. 1981. Effects of long terminhalation of alumina fibres in rats. Br J Exp Pathol 62:323-331.

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 0, et al. 1992. Role of aluminum in skin reactions after diphtheriatetanus-pertussis-poliomyelitis vaccination: An experimental study in rabbits. Toxicology 73:117-125.

Pineau A, Guillard 0, Huguet F, et al. 1993. An evaluation of the biological significance of aluminum in plasma and hair of patients on long-termhemodialysis. Eur J Pharmacol 228:263-268.

*Pivnick EK, Kerr NC, Kaufman RA, et al. 1995. Rickets secondary to phosphate depletion. Clin Pediatr 34:73-78.

*Plankey BJ, Patterson HH. 1987. Kinetics of aluminum-fulvic acid complexation in acidic waters, Environ Sci Technol2 1:595-601.

Platt B, Carpenter DO, Busselberg D, et al. 1995. Aluminum impairs hippocampal long-term potentiation in rats in vitro and in vivo. Exp Nemo1 134:73-86.

*Poetzl K. 1970. Inorganic chemical analyses of nonpolluted aerosols sample at 1800 meters altitude. J Geophys Res 75:2347-2352.

*Polinsky MS, Gruskin AB. 1984. Aluminum toxicity in children with chronic renal failure. J Pediatr 1(X5:758-761.

Poole KG, Elkin BT, Bethke RW. 1998. Organochlorine and heavy metal contaminants in wild mink in western Northwest Territories, Canada. Arch Environ Contam Toxicol 34:406-413.

*Posner E, Kennedy MCS. 1967. A further study of china biscuit placers in Stoke-on-Trent. Br J Ind Med 24:133-142.

Postek KM, Driscoll CT, Kahl JS, et al. 1995. Changes in the concentrations and speciation of aluminum in response to an experimental addition of ammonium sulfate to the Bear Brook watershed, Maine, U.S.A. Water Air Soil Pollut 85:1733-1738.

Poulos BK, Perazzolo M, Lee MY, et al. 1996. Oral aluminum administration during pregnancy and lactation produces gastric and renal lesions in rat mothers and delay in CNS development in their pups. Mol Chem Neuropathol29:15-25.

Poulsen OM, Christensen JM, Sabbioni E, et al. 1994. Trace element reference values in tissues from inhabitants of the European community. 5. Review of trace elements in blood, serum and urine and critical evaluation of reference values for the Danish population. Sci Total Environ 141: 197-215.

Powell JJ, Thompson RPH. 1990. Aluminum deposition in bone after contamination of drinking water supply. Lancet 336888.

Powell JJ, Greenfield SM, Parkes HG, et al. 1993. Gastro-intestinal availability of aluminum from tea. Food Chem Toxicol 31:449-454.

*Priest ND. 1993. Satellite symposium on 'Alzheimer's disease and dietary aluminum. Proc Nutr Sot 52:231-240.

*Priest ND, Newton D, Day JP, et al. 1995. Human metabolism of aluminum-26 and gallium-67 as citrates. Hum Exp Toxicol 14:287-293.

*Priest ND, Talbot RJ, Austin JG, et al. 1996. The bioavailability of ^{26}AI-IabeIled aluminum citrate and aluminum hydroxide in volunteers. BioMetals 9:22 1-224.

Priest ND, Talbot RJ, Newton D, et al. 1998. Uptake by man of aluminum in a public water supply. Hum Exp Toxicol 17:296-301.

*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. Jnfluence of calcium on aluminum accumulation by the rat jejunal slice. Res Commun Chem Patho1 Pharmacol59:79-92.

Quarterly B, Essehnont G, Taylor A, et al. 1993. Effect of oral aluminum citrate on short-term tissue distribution of aluminum Food Chem Toxicol 31:543-548.

Quatrale RP. 1985. Mechanism of antiperspirant action. Cosmet Toiletries 100:23-26.

*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 1861-80.

Quintela MJ, Gallego M, Valcarcel M. 1993. Flow injection spectrophotometric method for the speciation of aluminum in river and tap waters. Analyst 118:1199-1203.

*Qureshi N, Malmberg RH. 1985. Reducing aluminum residuals in finished water. J Am Water Works Assoc 77:101-108.

Raab D, Stumm W. 1993. Effect of acid deposition on the displacement of Al(III) in soils. Water Air Soil Pollut 68:199-212.

*Radiation Safety Guide. 1999. Occupational radiation exposure monitoring - External monitoring. http://www.nih.gov/od/ors/ds/rsb/rsguide/orem.htm

*Radiation Safety Newsletter. 1998. http://www.ors.gatech.edu/News9804.htm. June 1999.

Radunovic A, Delves HT, Bradbury MWB. 1998. Uptake of aluminum and gallium into tissues of the rat. Influence of antibody against the transferrin receptor. Biol Trace Elem Res 62:51-64.

*Rahman H, Skillen AW, Channon SM, et al. 1985. Methods for studying the binding of aluminum by serumprotein. ClinChem31:1969-1973.

*Rahn KA. 197 1. Sources of trace elements in aerosols - approach to clean air. US. Atomic Energy Commission, NTIS No. COO-1705-9.

Rajwanshi P, Singh V, Gupta MK, et al. 1997. Studies on aluminum leaching from cookware in tea and coffee and estimation of aluminum content in toothpaste, baking powder and paan masala. Sci Total Environ 193:243-249.

Rankin J, Sedowofia K, Clayton R, et al. 1993. Behavioural effects of gestational exposure to aluminum Ann 1st Super Sanita 29:147-152.

Rao GV, Rao KSJ. 1992. Evidence for a hydroxy-aluminum polymer(AL 13) in synaptosomes. FEBS Lett 311:49-50.

Rao KSJ. 1992. Effect of aluminum(AL) on the brain cells of the rat. Biochem Int 28:51-56.

Rao KSJ, Divakar S. 1993. Spectroscopic studies on the effects of aluminum ion on calf-thymus DNA. Bull Environ Contam Toxico1 50:92-99.

Rao KSJ, Rao GV. 1994. The characterization of aluminum-alanine complex. Mol Cell Biochem 137:61-64.

Rao VS, Cupples LA, Van Duijn CM, et al. 1996. Evidence for major gene inheritance of Alzheimer disease in families of patients with and without apolipoprotein E4. Am J Hum Genet 59:664-675.

*Reeker 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 8786-100.

Reimann C, De Caritat P, Halleraker JH, et al. 1997. Rainwater composition in eight arctic catchments in Northern Europe (Finland, Norway and Russia). Atmos Environ 31: 159-170.

Reusche E, Seydel U. 1993. Dialysis-associated encephalopathy: Light and electron microscopic morphology and topography with evidence of aluminum by laser microprobe mass analysis. Acta Neuropathol 86:249-258.

Rice DC. 1990. Lead-induced behavioral impairment on a spatial discrimination reversal task in monkeys exposed during different periods of development. Toxicol Appl Pharmacol 106:327-333.

*Riddell AR. 1948. Pulmonary changes encountered in employees engaged in the manufacture of alumina abrasives. Occup Med 5:710-717.

Rifat SL. 1993. Alzheimer's disease and environmental aluminum Age Ageing 22:476-477.

*Rifat SL, Eastwood MR, Crapper-McLachlan DR, et al. 1990. Effect of exposure of miners to aluminum powder. Lancet 336:1162-l 165.

Roberts NB, Clough A, Bellia JP, et al. 1998. Increased absorption of aluminum from a normal dietary intake in dementia. J Inorg Biochem 69:171-176.

Robinson NR, De Sousa MA, Itzhaki RF. 1993. Aluminum and Alzheimer's disease: Electrophoresis of proteins from aluminum-treated neuroblastoma cells. Biochem Sot Trans 21:322S-3233.

*Rockette HE, Arena VC. 1983. Mortality studies of aluminum reduction plant workers: Potroom and carbon department. J Occup Med 25:549-557.

Rodushkin I, Moiseenko T, Kudravsjeva L. 1995a. Aluminum in the surface waters of the Kola Peninsula, Russia. Sci Total Environ 163:55-59.

Rodushkin IV, Moiseenko TI, Kudryavtseva LP. 1995b. Changes in trace element speciation in Kola Morth surface waters during snow melt. Water Air Soil Pollut 85:731-736.

Rollin HB, Theodorou P, Kilroe-Smith TA. 1991. Deposition of aluminum in tissues of rabbits exposed to inhalation of low concentrations of AL203 dust. Br J Ind Med 48:389-391.

Romanski SA, McCarthy JT, Kluge K, et al. 1993. Detection of subtle aluminum-related renal osteodystrophy. Mayo Clin Proc 68:419-426.

Ronneberg A, Langmark F. 1992. Epidemiologic evidence of cancer in aluminum reduction plant workers. Am J Ind Med 22:573-590.

Ross JS, Smith NP, White IR. 1991. Role of aluminum sensitivity in delayed persistent immunisation reactions. J Clin Patho1 44:876-878.

*Rosseland BO, Eidhuset TD, Staurnes M. 1990. Environmental effects of aluminum Environ GeochemHealth 12:17-27.

Rottiers DV. 1993. Elemental composition of a migratory and a land-locked strain of Atlantic salmon sahno salar. Comp Biochem Physiol 104A:93-100.

Rowland A, Grainger R, Smith RS, et al. 1990. Water contamination in North Cornwall: A retrospective cohort study into the acute and short-term effects of the aluminum sulphate incident in July 1988. J R Sot Health 110:166-172.

Roy AK, Talukder G, Sharma A. 1991. Similar effects in vivo of two aluminum salts on the liver, kidney, bone, and brain of rattus norvegicus. Bull Environ Contam Toxico1 47:288-295.

Roy M, Couillard D. 1998. Metal leaching following sludge application to a deciduous forest soil. Water Res 32:1642-1652.

Roychowdhury M. 1993. A review of safety and health hazards of metalorganic compounds. Am Ind Hyg Assoc J 54:607-614.

*RTECS. 1989. Registry of Toxic Effects and Chemical Substances. National Library of Medicine, Bethesda, MD.

Rudman D, Dedonis JL, Fountain MT, et al. 1980. Hypocitraturia in patients with gastrointestinal malabsorption. N Engl J Med 303 :657-661.

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: 129- 135.

Sahin G, Aydin A, Isimer A, et al. 1995a. Aluminum content of infant formulas used in Turkey. Biol Trace Elem Res 50:87-96.

*Sahin G, Taskin T, Benli K, et al. 1995b. Impairment of motor coordination in mice after ingestion of aluminum chloride. Biol Trace Elem Res 50:79-85.

*St. George-Hyslop P. 1995. Genetic determinants of Alzheimer disease. Etiology and Pathogenesis of Down Syndrome 139-145.

St. Louis VL. 1993. Element concentrations in chironomids and their abundance in the littoral zone of acidified lakes in Northwestern Ontario. Can J Fish Aquat Sci 50:953-963.

Sakhaee K, Wabner CL, Zerwekh JE, et al. 1993. Calcium citrate without aluminum antacids does not cause aluminum retention in patients with functioning kidneys. Bone Mineral 20:87-97.

*Salib E, Hillier V. 1996. A case-control study of Alzheimer's disease and aluminum occupation. Br J Psychiatry 168:244-249.

Salusky IB, Coburn JW, Nelson P, et al. 1990. Prospective evaluation of aluminumloading from formula in infants with uremia. J Pediatr 116:726-729.

Salusky IB, Foley J, Nelson P, et al. 1991. Aluminum accumulation during treatment with aluminum hydroxide and dialysis in children and young adults with chronic renal disease. N Engl J Med 324:527-531.

San LN, Uysal H, Gokbel H, et al. 1998. Pulmonary function of workers in the aluminum industry. Am J Ind Med 33:305-307.

*Sanchez DJ, Gomez M, Llobet JM, et al. 1997. Effects of aluminum on the mineral metabolism of rats in relation to age. Pharmacol Toxicol 80:11-17.

SANSS. 1989. Structure and Nomenclature Search System Chemical Information Systems, Inc.

*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 65:53-55.

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.

Santucci D, Rankin J, Laviola G, et al. 1995. Eight-arm radial maze performance and hippocampal nerve growth factor levels in adult C57B 1/65 mice following prenatal exposure to aluminum [Abstract]. Behavioral brain research in naturalistic and semi-naturalistic settings (NATO AS1 series D, No. 82).

Sanz P, Amoros E, Prat A, et al. 1992. Aluminum exposure in children associated with industrial waste. Lancet 339:1488-1489.

*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 2:177-184.

Sarin S, Gupta V, Gill KD. 1997a. Alterations in lipid composition and neuronal injury in primates following chronic aluminum exposure. Biol Trace Elem Res 59: 133-143.

Sarin S , Julka D, Gill KD. 1997b. Regional alterations in calcium homeostasis in the primate brain following chronic aluminum exposure. Mol Cell Biochem 168:95-100.

Sarr AB, Mayura K, Kubena LF, et al. 1995. Effects of phyllosilicate clay on the metabolic profile of aflatoxin Bl in Fischer-344 rats. Toxicol Lett 75:145-151.

*Saunders FM. 1988. Heavy metal impact on disposal and reclamation of aluminum-anodizing residues. Environ Technol Lett 9:945-956.

Savory J, Garruto RM. 1998. Aluminum, tau protein, and Alzheimer's disease: An important link? Nutrition 14:313-314.

*Savory J, Wills MR. 1986. Analytical methods for aluminum measurement. Kidney Int 29(Supp):S24-s27.

Savory J, Exley C, Forbes WF, et al. 1996. Can the controversy of the role of aluminumin Alzheimer's disease be resolved? What are the suggested approaches to this controversy and methodological issues to be considered? J Toxicol Environ Health 48:615-635.

*Sax NI, Lewis RJ Sr, eds. 1987. Hawley's condensed chemical dictionary. 11th ed. New York, NY: Van Nostrand Reinhold Co., 42-51, 1248-1249.

*Sax NI, Lewis RJ Sr, eds. 1989. Dangerous properties of industrial materials. Vo12. 7th ed. New York, NY: Van Nostrand Reinhold. 134-141.

Sayer MDJ, Reader JP, Dalziel TRK, et al. 1991. Mineral content and blood parameters of dying brown trout (salmo trutta 1.) exposed to acid and aluminum in soft water. Comp Biochem Physiol 99C:345-348.

*Schaller KH, Valentin H. 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, 20-30. NTIS No. PB86-229242.

*Schellenberg GD. 1995a. Genetic dissection of Alzheimer's disease, a heterogeneous disorder. Proc Natl Acad Sci U S A 92:8552-8559.

*Schellenberg GD. 199Sb. Progress in Alzheimer's disease genetics. Curr Opin Neurol 8:262-267.

*Schenck RU, Bjorksten J, Yeager L. 1989. Composition and consequences of aluminumin water, beverages and other ingestibles. In: Lewis TE, ed. Environmental chemistry and toxicology of aluminum Chelsea, MI: Lewis Publishers, Inc, 247-269.

Schetinger MR, Wyse ATS, Da Silva LB, et al. 1995. Effects of aluminum chloride on the kinetics of rat cortex synaptosomal ATP diphosphohydrolase (EC 3.6.1 S). Biol Trace Elem Res 50:209-2 19.

Scheuhammer AM. 1991 a. Acidification-related changes in the biogeochemistry and ecotoxicology of mercury, cadmium, lead and aluminum: Overview. Environ Pollut 71:87-90.

Scheuhammer AM. 1991b. Effects of acidification on the availability of toxic metals and calcium to wild birds and mammals. Environ Pollut 7 1:329-375.

S&latter C. 1992. Biomedical aspects of aluminum. Med Lav 83:470-474.

* SchlettweinGsell D, MommsenStraub S. 1973. Trace elements in food. XII. Aluminum International Journal for Vitamin and Nutrition Research 43(2): 25 1263.

*Schmid K, Angerer 3, 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 163:147-151.

*Schiinholzer 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 92379-383.

Schott EJ, Gardner RC. 1997. Aluminum-sensitive mutants of saccharomyces cerecisiae. Mol Gen Genet 254:63-72.

*Schroeder HA, Mitchener M. 1975a. Life-term studies in rats: effects of aluminum, barium beryllium and tungsten. J Nutr 105:421-427.

*Schroeder HA, Mitchener M. 1975b. Life-term effects of mercury, methyl, mercury, and nine other trace metals on mice. J Nutr 105:452-458.

Schroeder TM, Caspers ML. 1996. Kinetics of aluminum-induced inhibition of sigma-aminolevulinic acid dehydratase in vitro. Biochem Pharmacol52:927-931.

*Schupf N, Silverman W, Zigman WB, et al. 1989. Aluminum and Alzheimer's disease. Lancet 1:267-269.

Schwarz Y, Kivity S, Fischbein A, et al. 1998. Evaluation of workers exposed to dust containing hard metals and aluminum oxide. Am J Ind Med 34:177-182.

Sedman A. 1992. Aluminum toxicity in childhood. Pediatr Nephrol 6:383-393.

*Sedman AB, Klein GL, Merritt RJ, et al. 1985. Evidence of aluminumloading in infants receiving intravenous therapy. N Engl J Med 312:1337-1342.

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 79:86-92.

Seiler HG, Sigel H, eds. 1988. Handbook on toxicity of inorganic compounds. New York, NY: Marcel Dekker, Inc., 33-43.

Selkoe DJ. 1996. Atnyloid beta-protein and the genetics of Alzheimer's disease. J Biol Chem 271:18295-18298.

*Sennett P. 1993. Clay (uses). In: Kroschwitz I, Howe-Grant M, eds. Kirk-Othmer encyclopedia of chemical technology. New York: John Wiley & Sons, 405-423.

*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.

*Shacklette HT, Boerngen JG. 1984. Element concentrations in soils and other surficial materials of the conterminous United States. United States Geological Survey Professional Paper, 1270.

Shafer TJ, Mundy WR. 1995. Effects of aluminum on neuronal signal transduction: Mechanisms underlying disruption of phosphoinositide hydrolysis. Gen Pharmacol 26:889-895.

Sharp CA, Perks J, Worsfold M, et al. 1993. Plasma aluminum in a reference population: The effects of antacid consumption and its influence on biochemical indices of bone formation. Eur J Clin Invest 23:554-560.

*Shaver CG. 1948. Pulmonary changes encountered in employees engaged in the manufacture of alumina abrasives. Occup Med 5:7 18-728.

Shaver CG, Riddell AR. 1947. Lung changes associated with the manufacture of alumina abrasives. J Ind Hyg Toxicol 29:145-157.

Shea TB. 1995. Calcium modulates aluminum neurotoxicity and interaction with neurofilaments. Mol ChemNeuropathol 24:151-163.

Shea TB, Husain T, 1995. Inhibition of proteolysis enhances aluminum-induced perikaryal neurofilament accumulation but does not enhance tau accumulation. Mol Chem Neuropatho126: 195-211.

Shea TB, Beermann ML, Wang F-S. 1995. Relative susceptibility of cytoskeleton-associated and soluble neurotilament subunits to aluminum exposure in intact cells. Mol Chem Neuropathol24:203-219.

*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.

*Sherrard DJ, Andress DL. 1989. Aluminum-related osteodystrophy. Adv Intern Med 34:307-324.

Shi B, Chou K, Haug A. 1993. Aluminum impacts elements of the phosphoinositide signalling pathway in neuroblastoma cells. Mol Cell Biochem 121:109-118.

Shin RW, Lee VMY, Trojanowski JQ. 1995. Neurofibrillary pathology and aluminum in Alzheimer's disease. Histol Histopathol 10:969-978.

*Shore D, Wyatt RJ. 1983. Aluminum and Alzheimer's disease. J Nerv Ment Dis 171:553-558.

Shultz AM, Begemann MH, Schmidt DA, et al. 1993. Longitudinal trends in pH and aluminum chemistry of the Coxing Kill, Ulster County, New York. Water Air Soil Pollut 69:113-125.

Shuman LM, Wilson DO, Ramseur EL. 1991. Testing aluminum-chelate equilibria models using sorghum root growth as a bioassay for aluminum Water Air Soil Pollut 57-58:149-158.

Sieber WKJ, Sundin DS, Frazier TM, et al. 1991. Development, use and availability of a job exposure matrix based on national occupational hazard survey data. Am J Ind Med 20:163-174.

*Sim M, Dick R, Russo J, et al. 1997. Are aluminum potroom workers at increased risk of neurological disorders? Occup Environ Med 54:229-235.

Simmer K. 1993. Aluminum and infants. J Pediatr Child Health 29:80-81,

*Simmer K, Fudge A, Teubner J, et al. 1990. Aluminum concentrations in infant formulae. J Paediatr Child Health 26:9-11.

*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.

*Singer SM, Chambers CB, Newfry GA, et al. 1997. Tau in aluminum-induced neurotibrillary tangles. Neurotoxicology 1863-76.

Singh RB. 1994. Aluminumphosphide poisoning. J Assoc Physicians lndia 42:844-845.

Singh S, Singh D, Wig N, et al. 1996. Aluminum phosphide ingestion - a clinico-pathologic study. Clin Toxicol 34:703-706.

Sjögren B, Elinder CG. 1992. Proposal of a dose-response relationship between aluminum welding fume exposure and effect on the central nervous system Med Lav 83:484-488.

*Sjögren B, Lidums V, Hakansson M, et al. 1985. Exposure and urinary excretion of aluminum during welding. Stand J Work Environ Health 11:39-43.

Sjögren B, Gustavsson P, Hogstedt C. 1990. Neuropsychiatric symptoms among welders exposed to neurotoxic metals. Br J Ind Med 47:704-707.

*Sjögren B, Elinder C-G, Lidums V, et al. 1988. Uptake and urinary excretion of aluminum among welders. Int Arch Occup Environ Health 60:77-79.

*Sjögren B, Ljunggren KG, Almkvist 0, et al. 1996. A follow-up study of five cases of aluminosis. Int Arch Occup Environ Health 68: 16 l- 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 22:391-397.

*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 56:33 I-336.

*Slanina P, Frech W, Ekstrom L-G, et al. 1986. Dietary citric acid enhances absorption of aluminum in antacids. Clin Chem 32/33:539-541.

Smith CM, Wang X, Hu H, et al. 1994. A polymorphism in the aminolevulinic acid dehydratase gene may modify the pharmacokinetics and toxicity of lead. Environ Health Perspect 103:248-253.

*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: 189-l 93.

Somova LI, Missankov A, Khan MS. 1997. Chronic aluminum intoxication in rats: Dose-dependent morphological changes. Methods Find Exp Clin Pharmacol 19:599-604.

*Sorenson JRJ, Campbell IR, Tepper LB, et al. 1974. Aluminum in the environment and human health. Environ Health Perspect 8:3-95.

Soyseth V, Kongerud J. 1992. Prevalence of respiratory disorders among aluminum potroom workers in relation to exposure to fluoride. Br J Ind Med 49:125-130.

Soyseth V, Kongerud J, Kjuus H, et al. 1994. Bronchial responsiveness and decline in FEV in aluminum potroom workers. Eur Resp J 7888894.

Soyseth V, Boe J, Kongerud J. 1997. Relation between decline in FEV and exposure to dust and tobacco smoke in aluminum potroom workers. Occup Environ Med 54:27-3 1.

Sparling DW. 1990. Acid precipitation and food quality: Inhibition of growth and survival in black ducks and mallards by dietary aluminum calcium and phosphorus. Arch Environ Contam Toxicol 19:457-463.

Sparling DW. 1991. Acid precipitation and food quality: Effects of dietary Al, Ca, and P on bone and liver characteristics in American black ducks and mallards. Arch Environ ContamToxicol 21:281-288.

*Sparling DW, Lowe TP. 1996. Environmental hazards of aluminum to plants, invertebrates, fish, and wildlife. Rev Environ Contam Toxicol 145:1-127.

Sparling DW, Lowe TP, Campbell PGC. 1997. Ecotoxicology of aluminum to fish and wildlife. In: Yokel RA, Golub MS, eds. Research issues in aluminum toxicity. Washington, DC: Taylor & Francis, 47-68.

*Spencer H, Kramer L, Norris C, et al. 1980. Effect of aluminum on fluoride and calcium metabolism in man. Trace Subst Environ Health 14:94-102.

Spencer H, Osis D, Lender M. 1981. Studies of fluoride metabolism in man: A review and report of original data. Sci Total Environ 17:1-12.

Spicer CW, Buxton BE, Holdren MW, et al. 1996. Variability of hazardous air pollutants in an urban area. Atmos Environ 30:3443-33456.

Spinelli JJ, Band PR, Svirchev LM, et al. 1991, Mortality and cancer incidence in aluminum reduction plant workers. J Occup Med 33:1150-1 155.

*SRI. 1988. Stanford Research Institute International. Directory of chemical producers: United States of America. Menlo Park. CA: SRI International.

*SRI. 1990. Stanford Research Institute International. Directory of chemical producers: United States of America. Menlo Park, CA: SRI International.

*SRI. 1992. Stanford Research Institute International. Directory of chemical producers: United States of America. Menlo Park, CA: SRI International.

*SRI. 1994. Stanford Research Institute International. Directory of chemical producers: United States of America. Menlo Park. CA: SRI International.

*SRI. 1995. Stanford Research Institute International. Directory of chemical producers: United States of America. Menlo Park, CA: SRI International.

Stables GI, Forsyth A, Lever RS. 1996. Patch testing in children. Contact Dermatitis 34:341-344.

Starmer GA, McLean S, Thomas J. 1971. Analgesic potency and acute toxicity of substituted anilides and benzamides. Toxicol Appl Pharmacol 19:20-28.

Staley JT, Haupin W. 1992. Aluminum and aluminum alloys. In: Kroschwitz JI, Howe-Grant M, eds. Kirk-Othmer encyclopedia of chemical technology. New York: John Wiley & Sons, 248-249.

*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.

*Stevens RK, Dzubay TG, Russwurm G, et al. 1978. Sampling and analysis of atmospheric sulfates and related species. Atmos Environ 12:55-68.

Still CN, Kelley P. 1980. On the incidence of primary degenerative dementia vs. water fluoride content in South Carolina. Neurotoxicology 1:125-131.

*Stitch SR. 1957. Trace elements in human tissue. I. A semi-quantitative spectrographic survey. Biochem J 67:97-109.

Stockhausen HB, S&rod 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.

*Stokinger HE. 1981. The metals. In: Clayton CD, Clayton FE, eds. Patty's industrial hygiene and toxicology. New York, NY: John Wiley Sons, 1493-1505.

Stollery BT, Broadbent DE, Banks HA, et al. 1991. Short term prospective study of cognitive functioning in lead workers. Br J Ind Med 48:739-749.

*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 Pharmacol49:7 l-76.

Storey E, Masters CL. 1995. Amylod, aluminum and the aetiology of Alzheimer's disease. Med J Aust 163:256-259.

Strong MJ, Garruto RM. 1991. Chronic aluminum-induced motor neuron degeneration: Clinical, neuropathological and molecular biological aspects. Can J Neurol Sci 18:428-431.

Strong MJ, Gaytan-Garcia S, Jakowec DM. 1995. Reversibility of neurotilamentous inclusion formation following repeated sublethal intracisternal inoculums of AlCl, in New Zealand white rabbits. Acta Neuropathol 90:57-67.

*Strong MJ, Garruto RM, Joshi JG, et al. 1996. Can the mechanisms of aluminum neurotoxicity be integrated into a unified scheme.7 J Toxicol Environ Health 48:599-613.

Struys-Ponsar C, Kerkhofs A, Gauthier A, et al. 1997. Effects of aluminum exposure on behavioral parameters in the rat. Pharmacol Biochem Behav 56:643-648.

Subra J-F, Krari N, Tirot P, et al. 1991. Aluminum determination in the skin of patients with and without end-stage renal failure. Nephron 58:170-173.

Sunderman FW, Lau TJ, Cralley LJ. 1974. Inhibitory effect of manganese upon muscle tumorigenesis by nickel subsultide. Cancer Res 34:92-95.

*Sung W. 1985. Residual aluminum in potable water. Technical completion report. University of New Hampshire, Water Resource Research Center, Durham NH. Project Number G856-05. NTIS No. PB85-214963.

Sutherland JE, Greger JL. 1998. Kinetics of aluminum disposition after ingestion of low to moderate pharmacological doses of aluminum Toxicology 126: 115- 125.

Sutherland JE, Radzanowski GM, Greger JL. 1996. Bile is an important route of elimination of ingested aluminumby conscious male Sprague-Dawley rats. Toxicology 109:101-109.

*Sung W. 1984. Residual aluminum in potable water. Technical completion report. Durham NH: University of New Hampshire, Water Resource Research Center. Project Number G85605. NTIS no. PB85214963.

*Sweet CW Vermette SJ. 1993. Sources of toxic trace elements in urban air in Illinois. Environ Sci Technol27:2502-2510.

*Swensson A, Nordenfelt 0, Forssman S, et al. 1962. Aluminum dust pneumoconiosis: A clinical study. Int Arch Gewerbepathol Gewerbehyg 19:131-148.

Tahan JE, Sanchez JM, Granadillo VA, et al. 1995. Concentration of total Al, Cr, Cu, Fe, Hg, Na, Pb, and Zn in commercial canned seafood determined by atomic spectrometric means after mineralization by microwave heating. J Agric Food Chem43:910-915.

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.

Tan K, Keltjens WG. 1990a. Interaction between aluminum and phosphorus in sorghum plants. 2. Studies with the aluminum tolerant sorghum genotype SC0283. Plant Soil 124:25-32.

Tan K, Keltjens WG. 1990b. Interaction between aluminum and phosphorus in sorghum plants. 1. Studies with the aluminum sensitive sorghumgenotype TAM428. Plant Soil 124:15-23.

*Tapparo A, Bombi GG. 1990. Ion chromatographic determination of trace amounts of aluminum with on-line preconcentration and spectrophotometric detection. Clin Chim Acta 238:279-284.

Tatsumi M, Mu C-J, Liang F, et al. 1990-1991. Health survey of workers of an aluminum plant in China. 3. Respiratory symptoms and ventilatory functions. Fluoride 23-24:90-94.

Taylor A, Walker AW. 1992. Measurement of aluminum in clinical samples. Ann Clin Biochem 29:377-389.

*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, Ferrier IN, McLaughlin IJ, et al. 1992. Gastrointestinal absorption of aluminum in Alzheimer's disease: Response to aluminum citrate. Age Ageing 21:8 1-90.

Taylor GA, Newens AJ, Edwardson JA, et al. 1995. Alzheimer's disease and the relationship between silicon and aluminum in water supplies in northern England. J Epidemiol Commun Health 49:323-328.

Taylor GA, Moore PB, Ferrier IN, et al. 1998. Gastrointestinal absorption of aluminum and citrate in man. J Inorg Biochem 69: 165 169.

Tennakone BK, Wickramanayake S. 1987. Aluminumleaching fromcooking utensils. Nature 325:202.

Tennakone BK, Wickramanayake S, Fernando CAN. 1988. Aluminum contamination from fluoride assisted dissolution of metallic aluminum Environ Pollut 49:133-143.

*Teraoka H. 1981 . Distribution of 24 elements in the internal organs of normal males and the metallic workers in Japan. Arch Environ Health 36:155-165.

*Testolin G, Erba D, Ciappellano S, et al. 1996. Influence of organic acids on aluminum absorption and storage in rat tissues. Food Addit Contam 13:21-27.

*Theriault G, Cordier S, Tremblay C, et al. 1984a. Bladder cancer in the aluminum industry. Lancet 1:947-950.

Theriault G, Cordier S, Harvey R. 1984b. Skin telangiectases in workers at an aluminum plant. N Engl J Med 303:1278-1281.

Theriault GP, Tremblay CG, Armstrong BG. 1990. Bladder cancer screening among primary aluminum production workers in Quebec. J Occup Med 32:869-872.

*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 6:197-209.

*Thorne BM, Donohoe T, Lin K-N, et al. 1986. Aluminum ingestion and behavior in the Long-Evans rat. Physiol Behav 36:63-67.

*Thorne BM, Cook A, Donohoe T, et al. 1987. Aluminum toxicity and behavior in the weanling Long-Evans rat. Bull Pyschon Sot 25:129-132.

*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.

*Tipton I, Stewart PL, Martin PG. 1966. Trace elements in diets and excreta. Health Phys 12:1683-1689.

Titkov ES, Oganesyan GA. 1995. [Study of the chronic effect of large doses of aluminum on the nervous and cardiac activity of rats with intramuscular injection]. Zh Evol Biokhim Fizio13 152-58. (Russian).

Toimela TA, Tahti H. 1995. Effects of mercury, methylmercury and aluminum on glial fibrillary acidic protein expression in rat cerebellar astrocyte cultures. Toxico1 in Vitro 9:3 17-325.

Tokutake S. 1997. Accumulation of aluminum and silicon in lipofnscin granules suggests retardation of blood-brain barrier function by aging. Ann N Y Acad Sci 826:5 10-512.

Townsend MC, Enterline PE, Sussman NB, et al. 1985. Pulmonary function in relation to total dust exposure at a bauxite refinery and alumina-based chemical products plant. Am Rev Respir Dis 132:1174-l 180.

Tremblay C, Armstrong, Theriault G, et al. 1995. Estimation of risk of developing bladder cancer among workers exposed to coal tar pitch volatiles in the primary aluminum industry. Am J lnd Med 27:335-348.

TRI. 1989. Toxic Release Inventory. Office of Toxic Substance. U.S. Environmental Protection Agency. Washington, DC.

TR194. 1996. Toxic Release Inventory. Office of Pollution Prevention. U.S. Environmental Protection Agency, Washington, DC.

*TR196. 1998. Toxic Release Inventory. Office of Pollution Prevention. U.S. Environmental Protection Agency. Washington, DC.

*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.

Trimmer E. 1994. Aluminum and Alzheimer's disease in Finchley, North London. Lancet 344:486.

Trocine RP, Trefry JH. 1996, Metal concentrations in sediment, water and clams from the Indian River Lagoon, Florida. Mar Pollut Bull 32:754-759.

*Tsou VM, Young RM, Hart MH. 199 1. Elevated plasma aluminum levels in normal infants receiving antacids containing aluminum Pediatrics 87 : 148- 151.

Turnquest EM, Hallenbeck WH. 1991. Blood aluminum levels as a function of aluminum intake from drinking water. Bull Environ Contam Toxico1 46:554-560.

Tzanno-Martins C, Azevedo LS, Tanji M, et al. 1995. The role of experimental aluminum intoxication in allogeneic immunoresponse. Transpl Int 8:396-398.

Tzanno-Martins C, Azevedo LS, Orii N, et al. 1996. The role of experimental chronic renal failure and aluminum intoxication in cellular immune response. Nephrol Dial Transplant 11:474-480.

*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.

Umeda M, Tsurusaki K, Kamikawa S, et al. 1990. Red blood cell aluminum in patients with renal failure and effect of desferrioxamine infusion. Blood Purif 8:295-300.

*Underwood JR, ed. 1977. 1, Aluminum: Trace elements in human and animal nutrition. 4th ed. New York Academic Press, 430-433.

Urano N, Yano E, Evans PH. 199 1. Reactive oxygen metabolites produced by the carcinogenic fibrous mineral erionite. Environ Res 54:74-81.

*USGS. 1972. Environmental geochemistry. Geochemical survey of Missouri: Plans and progress for fifth six-month period (July-Dec. 197 1). U.S. Geological Survey, Branch of Regional Geochemistry. Open-file report 92,102.

*USGS. 1996. Aluminum In: Minerals yearbook: Volume I - metals and minerals.

*USGS. 1997a. Aluminum http://minerals.er.usgs.gov/minerals/pubs/commodity/aluminum/index.html.

*USGS. 1997b. Aluminum http://minerals.usgs.gov/minerals/pubs/commodity/aluminum/050497.pdf.

*USGS. 1998. Aluminum http://minerals.usgs.gov/minerals/pubslcommodity/aluminum/050398.pdf.

*USGS. 1999. Aluminum http://minerals.usgs.gov/minerals/pubs/commodity/aluminum/050399.pdf.

*Valkonen S , Aitio A. 1997. Analysis of aluminum in serum and urine for the biomonitoring of occupational exposure. Sci Total Environ 199:103-110.

Van Broeckhoven CL. 1995. Molecular genetics of Alzheimer's disease: identification of genes and gene mutations. Eur Neurol 35:8-19.

Vandenplas 0, Delwiche JP, Vanbilsen ML, et al. 1998. Occupational asthma caused by aluminum welding. Eur Resp J 11:1182-1184.

van der Voet G. 1992. Intestinal absorption of aluminum In: Aluminum in biology and medicine. Chichester: John Wiley & Sons, Inc., 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 90:190-197.

*van der Voet GB, de Wolff FA. 1998. Intestinal absorption of aluminum: effect of sodium and calcium Arch Toxicol 72:110-114.

*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 de Vyver FL, De Broe ME. 1985. Aluminum in tissues. Clin Nephrol 24:537-557.

*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 66:216-222.

van Rensburg SJ, Carstens ME, Potocnik FCV, et al. 1995. Transferrin C2 and Alzheimer's disease: Another piece of the puzzle found? Med Hypotheses 44:268-272.

van Rensburg SJ, Daniels WMU, Potocnik FCV, et al. 1997. A new model for the pathophysiology of Alzheimer's disease. S Afr Med J 87:1111-1115.

Van Wijnen JH, Clausing P, Brunekreef B. 1990. Estimated soil ingestion by children. Environ Res 51:147-162.

*Varner JA, Huie C, Horvath W, et al. 1993. Chronic AlF3 administration: II. Selected histological observations. Neurosci Res Comrnun 13:99-104.

*Varner JA, Horvath WJ, Huie CW, et al. 1994. Chronic aluminum fluoride administration. 1. Behavioral observations. Behav Neural Biol 61:233-241.

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 784:284-298.

Vasconcelos MTSD, Machado AASC, Silva Laquipai PAP. 1996. Metals and fluoride from electric arc welding fume in real tasks: Part 1 -correlations between the levels of the different pollutants. Occup Hyg 3:311-329.

*Veien NK, Hattel T, Justesen 0, et al. 1986. Aluminum allergy. Contact Dermatitis 15:295-297.

*Venugopal B, Luckey TD, eds. 1978. Metal toxicity in mammals. Vol 2. New York, NY: Plenum Press, 104-112.

Verity MA. 1993. Environmental neurotoxicity of chemicals and radiation. Curr Opin Neurol Neurosurg 6:437-442.

Verstraeten SV, Golub MS, Keen CL, et al. 1997. Myelin is a preferred target of aluminum-mediated oxidative damage. Arch Biochem Biophys 344:289-294.

*Vieira I, Sonnier M, Cresteil T. 1996. Developmental expression of CYP2El in the human liver: hypermethylation control of gene expression during the neonatal period. Eur J Biochem 238:476-483.

*Vogt KA, Dahlgren R, Ugolini F, et al. 1987. Aluminum iron, calcium magnesium potassium manganese, copper, zinc, and phosphorus in above and below ground biomass: II. Pools and circulation in a subalpine *abies amabilis* stand. Biogeochem 4:295-3 11.

Voisin C, Fisekci F, Buclez B, et al. 1996. Mineralogical analysis of the respiratory tract in aluminum oxide-exposed workers. Eur Resp J9: 1874-1879.

Voroniuc 0, Mancas G, Gavt V, et al. 1997. Neurotoxic effects of aluminum from drinking water. Neurotoxicology 18: 1092.

Vukicevic S. 1992. Letter to the editor. Bone 13:119.

*Vuori K-M, Witick A, Jokela S. 1990. Accumulation of aluminum infintinalis dalecarlica br. eur. in a brownwater river in western Europe. Aqua Fenn 20:203-204.

Vuorinen M, Vuorinen PJ, Hoikka J, et al. 1993. Lethal and sublethal threshold values of aluminum and acidity to pike (esox lucius), whitefish (coregonus lavaretus pallasi), pike perch (stizostedion lucioperca) and roach (rutilus rutilus) yolk-sac fry. Sci Total Environ Suppl:953-967.

Wakayama I, Nerurkar VR, Strong MJ, et al. 1996. Comparative study of chronic aluminum-induced neurofilamentous aggregates with intracytoplasmic inclusions of amyotrophic lateral sclerosis. Acta Neuropathol92:545-554.

*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 105:1297-1299.

Walker VR, Sutton RAL, Meirav 0, et al. 1994. Tissue disposition of 26aluminum in rats measured by accelerator mass spectrometry. Clin Invest Med 17:420-425.

*Walker WJ, Cronan CS, Patterson HH. 1988. A kinetic-study of aluminum adsorption by aluminosilicate clay-minerals. Geochim Cosmochim Acta 52:55-62.

Wallace WE, Harrison J, Keane MJ, et al. 1990. Clay occlusion of respirable quartz particles detected by low voltage scanning electron microscopy-X-ray analysis. Ann O&up Hyg 34:195-204.

Walsh CT, Neville MC. 1994. Effects of xenobiotics on milk secretion and composition. J Nutr Biochem 5:418-441.

*Walton J, Tuniz C, Fink D, et al. 1995. Uptake of trace amounts of aluminum into the brain from drinking water. Neurotoxicology 16:187-190.

*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.

*Ward NI. 1989. Environmental contamination of aluminum and other elements in North Cornwall as a result of the Lower-moor water treatment works incident. In: Vernet J-P, ed. Heavy metals in the environment. Edinburgh: CEP Consultants, 118- 12 1.

Watanabe S, Dawes C. 1988. The effect of pH and fluoride on leaching of aluminum fromkitchen utensils. Fluoride 21:58-59.

*Wawschinek 0, Petek W, Lang J, et al. 1982. The determination of aluminum in human plasma. Mikrochim Acta 1:335-339.

*Weast RC, Lide DR, Astle MJ, et al. 1989. CRC handbook of chemistry and physics. 70th ed. Boca Raton, FL: CRC Press, Inc.

*Weberg R, Berstad A. 1986. Gastrointestinal absorption of aluminum from single doses of aluminum containing antacids in man. Eur J Clin Invest 16:428-432.

Weberg R, Berstad A, Ladehaug B, et al. 1986. Are aluminum containing antacids during pregnancy safe? Acta Pharmacol Toxicol (Copenh) 59:63-65.

*Wedrychowski A, Schmidt WN, Hnilica LS. 1986. The in-vivo cross-linking of proteins and DNA by heavy metals. J Biol Chem 261:3370.

*Weintraub R, Hams G, Meerkin M, et al. 1986. High aluminum content of infant milk formulas. Arch Dis Child 61:914-916.

*Weiss G, ed. 1986. Hazardous chemicals data book. 2nd ed. Park Ridge, NJ: Noyes Data Corporation, 65-68.

Wennberg A. 1994. Neurotoxic effects of selected metals. Stand J Work Environ Health 20:65-71.

Werber MM, Peyser YM, Muhlrad A. 1992. Characterization of stable beryllium fluoride, aluminum fluoride, and vanadate containing myosin subfragment 1 -Nucleotide complexes. Biochemistry 3 1:7 190-7197.

*West JR Smith HW, Chasis H. 1948. Glomerular filtration rate, effective renal blood flow, and maximal mbular 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 63:97-103.

Whalley LJ, McGonigal G, Thomas B. 1992. Aluminum and dementia. Lancet 339:1235-1236.

*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.

Whitehead MW, Farrar G, Christie GL, et al. 1997. Mechanisms of aluminum absorption in rats. Am J Clin Nutr 65:1446-1452.

Whitten MG, Ritchie GSP. 1991. Soil tests for aluminum toxicity in the presence of organic matter: Laboratory development and assessment. Commun Soil Sci Plant Anal 22:343-368.

*WHO. 1984. Guidelines for drinking-water quality. Volume 1: Recommendations. Lyon, France: World Health Organization.

*Widdowson EM, Dickerson JWT. 1964. Chapter 17: Chemical composition of the body. In: Comar CL, Bronner F, eds. Mineral metabolism: An advanced treatise. Volume II: The elements Part A. New York: 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 33:47-53.

*Wigle DT. 1977. Bladder cancer: Possible new high-risk occupation [letter]. Lancet 2:83-84.

Wilhelm M, Ohnesorge FK. 1990. Influence of storage conditions on aluminum concentrations in serum dialysis fluid, urine, and tap water. J Anal Toxicol 14:206-210.

*Wilhelm M, Jager DE, Ohnesorge FK. 1990. Aluminum toxicokinetics. Pharmacol Toxicol 66:4-9.

Wilhelm M, Zhang XJ, Hafner D, et al. 1992. Single-dose toxicokinetics of aluminum in the rat. Arch Toxicol 66:700-705.

*Wilkinson KJ, Campell PGC. 1993. Aluminum bioconcentration at the gills surface of juvenile Atlantic salmon in acidic media. Environ Toxicol Chem 12:2083-2095.

Wilkinson KJ, Bertsch PM, Jagoe CH, et al. 1993. Surface complexation of aluminum on isolated fish gill cells. Environ Sci Technol 27:1132-1138.

*Wills MR, Savory J. 1989. Aluminum and chronic renal failure: Sources, absorption, transport, and toxicity. CRC Crit Rev Clin Lab Sci 27:59-107.

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 23:1-16.

Winship KA. 1993. Toxicity of aluminum: A historical review, Part 2. Adverse Drug React Toxicol Rev 12:177-211.

Wisniewski HM, Wen GY. 1992. Aluminum and Alzheimer's disease. In: Aluminum in biology and medicine. Chichester: John Wiley & Sons, 142-164.

Wisniewski HM, Sturman JA, Shek JW. 1980. Aluminum chloride induced neurofibrillary changes in the developing rabbit: A chronic animal model. Ann Neurol 8:479-490.

Wisniewski HM, Sturman JA, Shek JW, et al. 1985. Aluminum and the central nervous system J Environ Pathol Toxicol Oncol 6:1-8.

Wober C, Dal-Bianco P, Hufgard J, et al. 1992. [Aetiology of Alzheimer's disease]. Nervenarzt 63:74-8 1. (German).

Wolff BG, Phillips RE. 1990. Effects of dietary aluminum on reproduction in Japanese quail coturnix coturnix japonica. Water Air Soil Pollut 50:293-299.

*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 4711593-1603.

*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 22:695-698.

Woodward-Knight L, Fudge A, Teubner J, et al. 1992. Aluminum absorption and antacid therapy in infancy. J Paediatr Child Health 28:257-259.

*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 120:809-815.

Xie X, Yokel RA, Markesbery WR. 1994. Application of electron energy loss spectroscopy and electron spectroscopic imaging to aluminum determination in biological tissue. Biol Trace Elem Res 40:39-48.

*Xu N, Majidi V, Markesbery WR, et al. 1992a. Brain aluminum iti Alzheimer's disease using an improved GFAAS method. Neurotoxicology 13:735-744.

*Xu Z-C, Tang J-ping, Xu Z-X, et al. 1992b. Kinetics of aluminum in rats IV: Blood and cerebrospinal fluid kinetics. Toxicol Lett 63:7-12.

Yano I, Yoshida S, Uebayashi Y, et al. 1989. Degenerative changes in the central nervous system of Japanese monkeys induced by oral administration of aluminum salt. Biomed Res 10:33-41.

Yasui M, Yase Y, Ota K, et al. 1991. Aluminum deposition in the central nervous system of patients with amyotrophic lateral sclerosis from the Kii peninsula of Japan. Neurotoxicology 12:615-620.

Yen-Koo HC. 1992. The effect of aluminum on conditioned avoidance response (CAR) in mice. Toxicol Ind Health 8: l-7.

Yi S-M, Sofuoglu SC, Holsen TM, et al. 1996. Atmospheric mass and metal size distributions measured around Lake Michigan. In: Measurements of toxic relationships between air pollutants. Pittsburgh, PA: Air & Waste Management Association, 369-378.

*Yokel RA. 1985. Toxicity of gestational aluminum exposure to the maternal rabbit and offspring. Toxicol Appl Pharmacol 79:121-133.

*Yokel RA. 1987. Toxicity of aluminum exposure to the neonatal and immature rabbit. Fundam Appl Toxicol 9:795-806.

Yokel RA. 1989. Aluminum produces age related behavioral toxicity in the rabbit. Neurotoxicol Teratol 11:237-242.

Yokel RA. 1994. Aluminum chelation: Chemistry, clinical, and experimental studies and the search for alternatives to desferrioxamine. J Toxicol Environ Health 41: 131-17 4.

*Yokel RA, McNamara PJ. 1985. Aluminum bioavailability and disposition in adult and immature rabbits. Toxicol Appl Pharmacol 77:344-352.

*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 95:32-43.

*Yokel RA, McNamara PJ. 1989. Elevated aluminum persists in serum and tissues of rabbits after a 6-hour infusion. Toxicol Appl Pharmacol 99:133-138.

Yokel RA, Lidums V, McNamara PJ, et al. 1991. Aluminum distribution into brain and liver of rats and rabbits following intravenous aluminum lactate or citrate: A microdialysis study. Toxicol Appl Pharmacol 107:153-163.

Yoshida S, Gershwin ME, Keen CL, et al. 1989. The influence of aluminum on resistance to Zisteria monocytogenes in Swiss-Webster mice. Int Arch Allergy Appl Immunol 89:404-409.

Yoshida S, Yano I, Wakayama I, et al. 1990. Morphometric analysis of neurodegenerative changes induced by low calcium-magnesium and excessive aluminum intake. Biomed Res 11:11-18.

*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.

Yukihiro S, Okada S, Takeuchi K, et al. 1995. Experimental osteodystrophy of chronic renal failure induced by aluminum- and ferric-nitrilotriacetate in Wistar rats. Patho1 Int 45:19-25.

Zafar TA, Weaver CM, Martin BR, et al. 1997. Aluminum (A126) metabolism in rats. Proc Sot Exp Biol Med 216:81-85.

Zaman K, Zaman A, Batcabe J. 1993a. Hematological effects of aluminum on living organisms. Comp Biochem Physiol 106C:285-293.

Zaman K, Zaman W, Dabrowski Z, et al. 1993b. Inhibition of delta aminolevulinic acid dehydratase activity by aluminum Comp Biochem Physiol 104C:269-273.

Zaman K, Zaman W, Siddique H. 1993c. Hematological and enzymatic results of aluminum intoxication in rats. Comp Biochem Physiol 105C:73-76.

Zapatero MD, Garcia de Jalon A, Pascual F, et al. 1995. Serum aluminumlevels in Alzheimer's disease and other senile dementias. Biol Trace Elem Res 47:235-240.

*Zatta PF. 1995. Aluminum binds to the hyperphosphorylated tau in Alzheimer's disease: A hypothesis. Med Hypotheses 44:169-172.

Zatta P, Favarato M, Nicolini M. 1993. Deposition of aluminum in brain tissues of rats exposed to inhalation of aluminum acetylacetonate. NeuroReport 4:1119-1122.

Zhang M, Alva AK, Li YC, et al. 1997. Fractionation of iron, manganese, aluminum and phosphorus in selected sandy soils under citrus production. Soil Sci Sot Am J 61:794-801.

Zhao S-J, Li H, Jiang Y, et al. 1996. [Subtype-specific antibodies for muscarinic receptors in measuring brain muscarinic receptor content in aluminum chloride intoxicated mice]. Chin J Pharmacol Toxicol 10:215-218. (Chinese).

Zhou CY, Wu J, Chi H, et al. 1996. The behaviour of leached aluminumin tea infusions. Sci Total Environ 177:9-16.

*Ziegler EE, Edwards BB, Jensen RL et al. 1978. Absorption and retention of lead by infants. Pediatr Res 12:29-34.

Zsiros V, Rojik I, Kovacs T, et al. 1997. Comparative morphological and physiological aspects of aluminum actions on central neurons and neuronal synapses of invertebrate and vertebrate animals. Neurotoxicology 18:1092.

9. GLOSSARY

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

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

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

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

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

Benchmark Dose (BMD)-is 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-is 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-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.

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

Carcinogen-A chemical capable of inducing cancer.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Immunological Effects-are functional changes in the immune response.

9.GLOSSARY

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

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

In Viva-Occurring within the living organism.

Lethal Concentration$_{(50)}$ (LC_{LO})-The 1 owest concentration of a chemical in air which has been reported to have caused death in humans or animals.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Permissible Exposure Limit (PEL)-An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an g-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-is the science of quantitatively predicting the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

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

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

Physiologically Based Pharmacokinetic (PBPK) Model-is 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 4such 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 PgfL for water, mg/kg/day for food, and $\mu g/m^3$ for air).

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

Reference Concentration (RfC)-An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)-An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the No-Observed-Adverse-Effect Level (NOAEL- from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

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

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

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 casual factors that can be ascertained from existing records and/or examining survivors of the cohort.

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

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

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

Short-Term Exposure Limit (STEL)-The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 mm

between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

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

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

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

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

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

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

Uncertainty Factor (UF)-A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using Lowest-Observed-Adverse-Effect Level (LOAEL) data rather than No-Observed-Adverse-Effect Level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

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

APPENDIX A

ATSDR MINIMAL RISK LEVEL AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99-4991, requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

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

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

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEETS

Chemical name:	Aluminum
CAS number(s) :	7429-90-5
Date:	May 24, 1999
Profile status:	Final
Route:	[ ] Inhalation [X] Oral
Duration:	[ ] Acute [X] Intermediate [ ] Chronic
Key to figure:	24
Species:	Mouse

MRL: 2.0 [Xl mg/kg/day [] ppm [ ] mg/m^3

Reference: Golub MS, Donald JM, Gershwin ME, Keen CL. 1989. Effects of aluminum ingestion on spontaneous motor activity of mice. Neurotoxicol Teratol. 11: 231-235.

Experimental design: Spontaneous Motor activity was studied in groups of 15 female Swiss-Webster mice that were exposed to an average of 25, 500 or 1000 1-1 g Al/g (ppm) as aluminum lactate in a semipurified diet for 6 weeks. Reported average intake levels were 3, 62 and 130 mg Al/kg-day in the control (25 ppm), low-dose and high-dose groups, respectively. Subsequent to completion of the study a pair-fed control group was added when differences in food intake were noted. The pair-fed group was treated identically except that food provided was equated on a per cage basis with that eaten by mice in the 130 mg/kg/day group. No mice were exposed to lactate alone. Food intake, body weight and signs of toxicity (irritability, respiratory discharge, eye discharge, fur loss, abnormal paw placement, abnormal gait, hindlimb splaying, hindlimb dragging, opisthotonos, paralysis, and seizures) were evaluated at 3-day intervals throughout the exposure period. Motor activity levels were measured during a 24-hour session during week 5 using an automated method which distinguished between locomotor activity (horizontal) and rearing and feeding movements (vertical). No other types of neurobehavioral tests were performed. All mice were killed at the end of the 6-week feeding period for measurement of aluminum in bone (tibia), liver and brain.

Effects noted in study and corresponding doses: No statistically significant changes in group mean food intake or body weight gain occurred at either dose level, although the treated groups demonstrated a cyclic pattern of food intake, and the 130 mg Al/kg-day and pair-fed control groups gained less weight than the control and low-dose groups over the course of the study. No neurotoxic signs were observed in any group, but there was a dose-dependent increase in localized fur loss. Total activity was significantly decreased (20%, $p < 0.05$) at 130 mg Al/kg-day, with vertical movement (primarily rearing and feeding) more affected than horizontal movement (primarily locomotion). Mice in the 130 mg Al/kg-day group were less active than controls during the diurnal period of peak activity, and their activity periods were also somewhat shorter (130 versus 200 minutes), but there was no shift in the diurnal activity cycle or any prolonged periods of inactivity. Activity in the 65 mg Al/kg-day and pair-fed groups did not differ significantly from controls. Tissue levels of aluminum were significantly increased at 130 mg Al/kg-day in liver and bone, but not in brain.

Dose and end point used for MRL derivation:,

The low dose, 62 mg Al/kg-day, is a NOAEL for neurotoxicity and the most appropriate basis for MRL derivation.

[X] NOAEL [ ] LOAEL

Uncertaintv factors used in MRL derivation:
[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

No (doses corresponding to food ppm levels were reported by investigators)

Was a conversion used from intermittent to continuous exposure?

NA

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

NA

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

Neurotoxicity is well-documented effect of aluminum in orally-exposed in mice and rats. Neurobehavioral deficits have been observed in animals exposed for intermediate durations, as well as in weanlings and young animals exposed by gestation, combined gestation and lactation, combined gestation and lactation followed by postweaning ingestion, or postweaning ingestion alone. The lowest reliable effect levels (i.e., NOAELs and LOAELs that accounted for contribution of aluminum from the base diet) are in mice. Data supporting the critical NOAEL are not available, however, the LOAEL from the MRL study is supported by observations of the same neurotoxic effect (reduced spontaneous motor activity) in adult mice exposed to higher doses as aluminum chloride for 49 days or aluminum lactate for 90 days (Golub et al. 1992b, Oteiza et al. 1993); other effects in these studies included decreased grip strength and startle responsiveness. Additionally, neurodevelopmental effects occurred in mice at doses similar to the LOAEL for decreased motor activity. A LOAEL of 155 mg Al/kg-day is identified for neurotoxicity in the offspring of mice exposed to dietary aluminum lactate during gestation and lactation and tested as weanlings or adults (Donald et al. 1989; Golub et al. 1995). Effects observed at the neurodevelopmental LOAEL included increased fore- and hindlimb grip strengths, landing foot splay, and latency to remove tail from hot water in offspring tested as weanlings (Donald et al. 1989), and decreased grip strength, decreased air-puff startle response, and improved performance during operant training in offspring tested as adults (Golub et al. 1995). Lower dose levels were not tested in these studies, precluding determination of a NOAEL for neurodevelopmental toxicity.

Agency Contact (Chemical Manager): Sam Keith

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 proftie that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Signikant Exposure (LSE)

Tables (2-l) 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse- Effect Levels (NOAELs), Lowest-Observed- Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrat.e the application of these tables and figures. Representative examples of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-l

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1,2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

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

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL(also see the 2 "18r" data points in Figure 2-1).

(5) Species The test species, whether animal or human, are identified in this column. Section2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAFLs and LOAELs from different studies. In this case (key number 1 S), rats were exposed to toxaphene via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.0005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs .

(10) Reference The complete reference citation is given in chapter 8 of the profile.

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

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.0005 ppm.

LEGEND

See Figure 2-1

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

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

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

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

(16) NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.0005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

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

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

SAMPLE

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

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

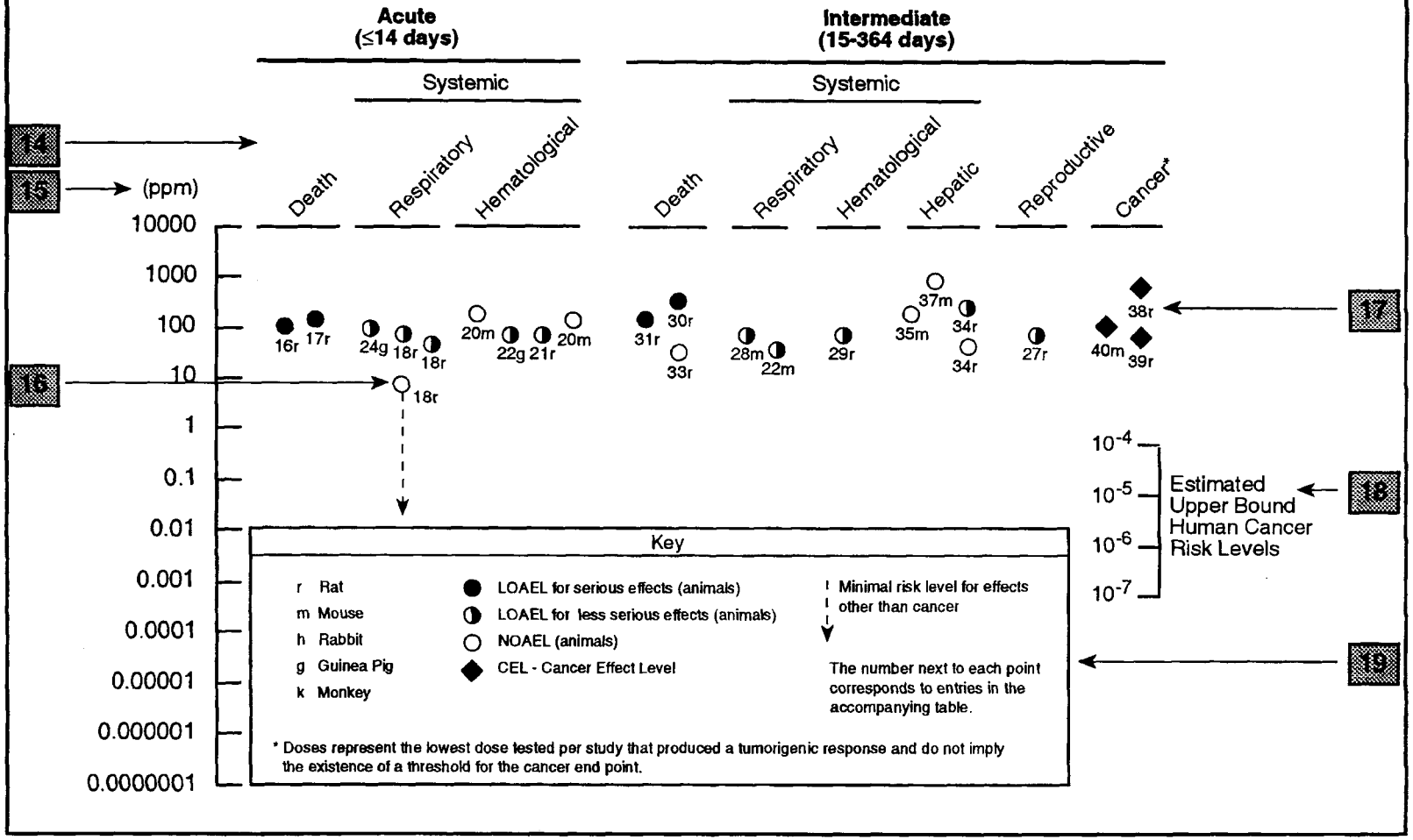
[a] The number corresponds to entries in Figure 2-1.

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

CEL = cancer effect level; d = days(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



Chapter 2 (Section 2.5)

Relevance to Public Health

The Relevance to Public Health section 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 section covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the protiled 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 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.5, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.8, "Interactions with Other Substances," and 2.9, "Populations that are Unusually Susceptible" provide important supplemental information.

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

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and

reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors usec in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

APPENDIX C

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

mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAA	nuclear activation analysis
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	Polycyclic Aromatic Hydrocarbon
PBPD	Physiologically Based Pharmacodynamic
PBPK	Physiologically Based Pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector
pg	picogram

pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppq	parts per quadrillion
ppt	parts per trillion
PSNS	Pretreatment Standards for New Sources
REL	recommended exposure level/limit
RfC	Reference Concentration
RfD	Reference Dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	Reportable Quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
sec	second
SEC	size-exclusion chromatography
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard mortality ratio
SNARL	Suggested No Adverse Response Level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	Total Organic Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
VOC	Volatile Organic Compound
yr	year
WHO	World Health Organization
wk	week
$>$	greater than
$\geq$	greater than or equal to
$=$	equal to
$<$	less than
$\leq$	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor

APPENDIX C

–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

☆U.S. GOVERNMENT PRINTING OFFICE:1999-737-478

490/490