Uploaded to VFC Website

July 2013

This Document has been provided to you courtesy of Veterans-For-Change!

Feel free to pass to any veteran who might be able to use this information!

For thousands more files like this and hundreds of links to useful information, and hundreds of "Frequently Asked Questions, please go to:

Veterans-For-Change

Veterans-For-Change is a 501(c)(3) Non-Profit Corporation
Tax ID #27-3820181

If Veteran's don't help Veteran's, who will?

We appreciate all donations to continue to provide information and services to Veterans and their families.

https://www.paypal.com/cgi-bin/webscr?cmd=_s-xclick&hosted_button_id=WGT2M5UTB9A78

Note: VFC is not liable for source information in this document, it is merely provided as a courtesy to our members.

TOXICOLOGICAL PROFILE FOR BERYLLIUM

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

September 2002

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

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

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

FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

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

Each profile includes the following:

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

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

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

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

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.

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

*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepared 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: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by *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 3.7 Children's Susceptibility
Section 6.6 Exposures of Children

Other Sections of Interest:

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

ATSDR Information Center

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

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

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

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

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

Other Agencies and Organizations

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

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

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

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. *Contact:* AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: aoec@dgs.dgsys.com • AOEC Clinic Director: http://occ-env-med.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: 847-818-1800 • FAX: 847-818-9266.

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHORS(S):

Cassandra Smith, M.S.
ATSDR, Division of Toxicology, Atlanta, GA

Lisa Ingerman, Ph.D., DABT
Syracuse Research Corporation, North Syracuse, NY

Richard Amata, Ph.D.
Syracuse Research Corporation, North Syracuse, NY

THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

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

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

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

PEER REVIEW

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

1. Dr. Derek J. Hodgson, University of Nebraska at Omaha, Omaha, NE.

2. Dr. Laurence Holland, Private Consultant, Los Alamos, NM.

3. Dr. Hanspeter Witschi, Center for Health and the Environment, University of California Davis, CA 95615.

4. Dr. Finis Cavendar, Adjunct Professor, Curriculum in Toxicology, University of North Carolina at Chapel Hill, Chapel Hill, NC.

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

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

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

CONTENTS

APPENDICES

LIST OF FIGURES

LIST OF TABLES

1. PUBLIC HEALTH STATEMENT

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

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Beryllium has been found in at least 535 of the 1,613 current or former 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 beryllium 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 are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to beryllium, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. 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 BERYLLIUM?

Beryllium is an element that occurs naturally. It is present in a variety of materials, such as rocks, coal and oil, soil, and volcanic dust. Two kinds of mineral rocks, bertrandite and beryl, are mined commercially for the recovery of beryllium. Very pure gem-quality beryl is better known as either aquamarine (blue or blue-green) or emerald (green). Beryllium is the lightest metal. A key distinction among beryllium compounds is that some are soluble in water, but many are not.

Most of the beryllium ore that is mined is converted into alloys (mixtures of metals). Most of these alloys are used in making electrical and electronic parts or as construction materials for machinery and molds for plastics. Beryllium alloys are also used in automobiles, computers, sports equipment (such as golf clubs and bicycle frames), and dental bridges. Pure beryllium metal is used in nuclear weapons and reactors, aircraft and space vehicle structures, instruments, x-ray machines, and mirrors. Beryllium oxide is also made from beryllium ores and is used to make specialty ceramics for electrical and high-technology applications. More information on the chemical and physical properties, production, and uses of beryllium is found in Chapters 4, 5, and 6.

1.2 WHAT HAPPENS TO BERYLLIUM WHEN IT ENTERS THE ENVIRONMENT?

Beryllium enters the air, water, and soil as a result of natural and human activities. Emissions from burning coal and oil increase beryllium levels in the air. In air, beryllium compounds are present mostly as fine dust particles. The dust eventually settles over land and water. Rain and snow aid in removing beryllium from air. Extremely small beryllium particles may remain in the air for about 10 days. Beryllium enters waterways from the wearing away of rocks and soil. Most beryllium products of human origin that enter waterways come from industry discharges of waste water and from beryllium dust in the air from industrial activities settling over water. Most of the beryllium in water settles in the material on the bottom with sediment. Insoluble beryllium compounds remain in ocean water for a few hundred years before settling to the bottom of the ocean. Beryllium, as a chemical component, occurs naturally in soil; however, disposal of coal ash, incinerator ash, and industrial wastes may increase the amount of beryllium in soil. A major portion of beryllium in soil does not dissolve in water and remains bound to soil, so it is not likely to move deeper into the ground and enter groundwater. In the environment, chemical reactions can change the water-soluble beryllium compounds into insoluble forms. In some cases, water-insoluble beryllium compounds can change to soluble forms. Exposure to water-soluble beryllium compounds in the environment, in general, will pose a greater threat to human health than exposure to water-insoluble forms.

The amount of beryllium that has been measured in the air in different parts of the United States by EPA ranges from not detected to 2 millionths of a gram per cubic meter (g/m^3). Very small dust particles of beryllium in the air fall out of the air onto surface water, plant surfaces, and soil either by themselves or when rain or snow falls. These beryllium particles eventually end up back in the soil or in the bottoms of lakes, rivers, and ponds, where they stay and mix with beryllium that is already there.

Beryllium in water comes from different sources. Most of it comes from dissolving beryllium out of rocks and soil that water runs over and through. Only a very small part is from the settling of beryllium dust out of the air. Some beryllium is suspended in muddy-like (cloudy) water. EPA has found that the levels of beryllium in drinking water in different parts of the United States are extremely low in most cases, and that water containing beryllium at these commonly observed levels is safe to drink. Fish do not accumulate beryllium from water into their bodies to any great extent. Some fruits and vegetables such as garden peas, kidney beans, and pears may have above average levels of beryllium (see Chapter 6). Most of the beryllium that gets into livestock is eliminated quickly in urine and feces.

Beryllium is found in soil in amounts that vary over a wide range, but the typical concentration is 3 thousandths of a gram/kilogram (g/kg) of soil. Additional beryllium can be added by industrial activities. Soluble beryllium compounds can combine with other substances in the environment to form other beryllium compounds. Beryllium compounds may stay in the soil for thousands of years without moving downward into groundwater. In addition to the beryllium found naturally in minerals, beryllium metal and compounds that are left after humans mine and process the minerals can be released back into the environment as landfill waste. More information about the fate and movement of beryllium in the environment is found in Chapter 6.

1.3 HOW MIGHT I BE EXPOSED TO BERYLLIUM?

You can be exposed to normal levels of beryllium by breathing air, eating food, or drinking water that contains beryllium. In the United States, the average concentration of beryllium in air is 0.03 nanograms (ng) (1 ng=1 billionth of a gram) in a cubic meter (ng/m^3) of air. In U.S. cities, the average air concentration is higher, and its value is 0.2 ng in a cubic meter (m^3) of air. Cities have higher levels of beryllium in the air because beryllium is released from burning coal and fuel oil. The amount of beryllium that has been measured in drinking water in different parts of the United States by EPA is generally less than 2 trillionths of a gram for every liter of water. Beryllium was found in only 5% of 1,577 drinking water samples obtained throughout the United States. Of these positive samples, the average beryllium concentration was only 190 ng in a liter (L) of water. Beryllium, as a chemical component, is found naturally in some food. The concentration of beryllium in both raw carrots and field corn grown in the United States is less than 25 micrograms (μg) (1 μg=1 millionth of a gram) in a kilogram (kg) of the fresh vegetables. Thus, in comparison with other harmful elements, such as lead and chromium, to which we are (by necessity) exposed on a daily basis, beryllium exposure is not significant.

In certain workplaces, you can be exposed to higher-than-normal levels of beryllium, mostly in the form of beryllium oxide and beryllium metal. Occupational exposure to beryllium occurs at places where the chemical is mined, processed, or converted into metal, alloys, and other chemicals. Workers engaged in machining metals containing beryllium, recycling beryllium from scrap alloys, or using beryllium products may also be exposed to higher levels of beryllium. The number of workers exposed to beryllium or beryllium compounds has been estimated to be 21,000.

As a member of the general public, you may be exposed to higher-than-normal levels of beryllium if you live near an industry that processes or uses beryllium. People who live near hazardous landfill sites that contain high concentrations of beryllium may also be exposed to higher-than-normal levels of beryllium. Beryllium, as a chemical component, occurs naturally in tobacco and may be inhaled from cigarette smoke. People who smoke may breathe higher-than-normal levels of beryllium than people who do not smoke.

Beryllium metal and metal alloys may be found in consumer products such as electronic devices (e.g., televisions, calculators, and personal computers) and special nonsparking tools. Direct contact with beryllium metal and metal alloys is not likely, since these materials are typically enclosed within a protected case that prevents exposure. No other consumer products or products used in crafts, hobbies, or cottage industries contain significant amounts of beryllium. It is therefore unlikely that beryllium present in consumer products poses any hazard. More information about beryllium exposure can be found in Chapter 6.

1.4 HOW CAN BERYLLIUM ENTER AND LEAVE MY BODY?

Beryllium can enter your body if you breathe air, eat food, or drink water containing it. Beryllium will not enter your body from skin contact with the metal unless the skin is scraped or cut and beryllium particles become imbedded in the wound. Only a small amount of beryllium may enter your body if your skin comes into contact with a beryllium salt dissolved in water. When you breathe air containing beryllium, beryllium particles can be deposited in the lungs. The beryllium that you breathe in slowly dissolves in the lungs and moves slowly into the bloodstream. Some of the beryllium deposited in the lungs can be moved to the mouth and then swallowed; the rest can remain in your lungs for a long time. If you eat food or drink water that contains beryllium, less than 1% passes from your stomach and intestines into the bloodstream. Therefore, most of the beryllium that you swallow leaves your body through the feces without entering the bloodstream. The small amount of beryllium that moves from the lungs, stomach, and intestines into the bloodstream is carried by the blood to the kidneys. Beryllium leaves the kidneys by the urine. Some beryllium can also be carried by the blood to the liver and bones where it may remain for long periods. If you swallow beryllium, beryllium leaves the body in a few days. However, if you inhale beryllium, it may take months to years before your body rids itself of beryllium. This is because it takes a long time before all the beryllium in the lungs enters the bloodstream. For more information, please read Chapter 3.

1.5 HOW CAN BERYLLIUM 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.

Beryllium is a metal that can be harmful when you breathe it. The effects depend on how much and how long you are exposed to it. When you breathe it in, beryllium can damage your lungs. When you breathe in large amounts of soluble beryllium compounds (greater than 1 mg beryllium per cubic meter of air, 1 mg/m^3), the lung damage resembles pneumonia with reddening and swelling of the lungs. This condition is called acute beryllium disease. The lung damage may heal if beryllium exposure is stopped. Human studies have shown that occupational and community ambient air standards were effective in eliminating most acute lung disease. Some people can become sensitive to beryllium. This is known as hypersensitivity or allergy. If you become sensitive (allergic) to beryllium, you may develop an immune or inflammatory reaction to small amounts of beryllium that do not cause effects in people who are not sensitive to beryllium. When this occurs, white cells accumulate around the beryllium and form a chronic inflammatory reaction called granulomas (granulomas are not tumors). This condition is called chronic beryllium disease (CBD). This disease can occur long after exposure (10–15 years) to small amounts of either soluble or insoluble forms of beryllium (greater than 0.0005 mg/m^3). If you have this disease, you may feel weak, tired, and have difficulty breathing. Some individuals that have CBD may experience anorexia, weight loss, and blueness of hands and feet. This disease could also lead to heart enlargement and heart disease in advanced cases.

Both the short-term, pneumonia-like disease and the chronic beryllium disease can be fatal. Exposure levels associated with acute or chronic beryllium disease are more 100,000 times higher than normal air levels of beryllium. Long periods of exposure to beryllium have been reported to cause cancer in laboratory animals. Some studies of workers reported an increased risk of lung cancer. The U.S. Department of Health and Human Services and the International Agency for Research on Cancer have determined that beryllium and beryllium compounds are human carcinogens. EPA has determined that beryllium is a probable human carcinogen. EPA has estimated that lifetime exposure to 0.00004 mg beryllium/m^3 can result in a one in a thousand chance of developing cancer. We do not know if breathing air, eating food, or drinking water that contains beryllium or having skin contact with beryllium has any effects on reproduction or causes birth defects in humans or animals. Swallowing beryllium has not been reported to cause effects in humans because very little beryllium can move from the stomach or intestines into the bloodstream. Ulcers have been seen in dogs ingesting soluble beryllium salts in the diet. Beryllium contact with skin that has been scraped or cut may cause rashes or ulcers. If you have developed an allergy to beryllium and have skin contact with it, you can get granulomas on the skin. These skin granulomas appear as a rash or as nodules. The skin granulomas are formed in the same way that lung granulomas are formed in sensitive people. For more information on how beryllium can affect your health, please read Chapter 3.

1.6 HOW CAN BERYLLIUM AFFECT CHILDREN?

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

It is likely that the health effects seen in children exposed to beryllium will be similar to the effects seen in adults; chronic beryllium disease was found in a child living near a beryllium factory. We do not know whether children differ from adults in their susceptibility to beryllium.

We do not know if exposure to beryllium will result in birth defects or other developmental effects in people. The studies on developmental effects in animals are not conclusive. We have no information to suggest that there are any differences between children and adults in terms of

how much beryllium will enter the body, where beryllium can be found in the body, and how fast beryllium will leave the body. It is likely that beryllium can be transferred from the mother to an infant in breast milk or that it can cross the placenta.

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

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

Higher-than-normal levels of beryllium may be in soil at hazardous waste sites. Some children eat a lot of dirt. You should prevent your children from eating dirt. Make sure they wash their hands frequently, and before eating. If you live near a hazardous waste site, discourage your children from putting their hands in their mouths or from engaging in other hand-to-mouth activities. Some children may be exposed to beryllium by contact with a family member who works in a facility using beryllium. If you work at a facility that uses beryllium, make sure you change your clothes and clean your hair and skin before leaving your job and returning home. Also, do not bring objects home such as works tools that may be contaminated with beryllium.

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

Beryllium can be measured in the urine and blood, but the amount of beryllium in the urine or blood may not reflect the amount to which you were exposed. The measurement of beryllium in urine and blood may not determine how recently you were exposed. Small amounts of human lung and skin can be removed from the body and examined to determine whether beryllium is present in these tissues. These tests can be done in a doctor's office or in a hospital. While high levels of beryllium in urine, blood, or tissues indicate that you were exposed to an excessive amount of beryllium, low levels of beryllium do not necessarily mean that you were not exposed to an excessive amount. A blood test called the beryllium lymphocyte proliferation test (BeLPT)

can determine if you have become sensitive to beryllium and may have chronic beryllium disease. For more information, please read Chapters 3 and 7.

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

The federal government develops regulations and recommendations to protect public health. Regulations *can* be enforced by law. 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 beryllium include the following:

OSHA has set a limit of 2 μg beryllium/m^3 of workroom air for an 8-hour work shift. NIOSH recommends a standard for occupational exposure of 0.5 μg beryllium/m^3 of workroom air during an 8-hour shift to protect workers from the increased cancer risk associated with beryllium exposure. EPA restricts the amount of beryllium released into the air to 0.01 μg beryllium/m^3 of air, averaged over a 30-day period. The Department of Energy (DOE) has developed a program to reduce beryllium exposure in workers at DOE facilities. EPA has set a

maximum allowable amount of 0.004 mg/L beryllium in drinking water. For more information, please read Chapter 8.

1.10 WHERE CAN I GET MORE INFORMATION?

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

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, GA 30333
Web site: http://www.atsdr.cdc.gov

* Information line and technical assistance

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

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

* To order toxicological profiles, contact

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

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO BERYLLIUM IN THE UNITED STATES

Beryllium is an extremely lightweight metal that occurs naturally in rocks, coal, soil, and volcanic dust. Commercially, bertrandite and beryl ore are mined for the recovery of beryllium. Because beryllium is one of the lightest metal and is very rigid, it has many uses in the electronics, aerospace, and defense industries. Beryllium is released into the atmosphere by windblown dust, volcanic particles, and the combustion of coal and fuel oil. Beryllium particulates in the atmosphere will settle out or be removed by precipitation. The annual average concentration of beryllium in ambient air in the United States is typically below the detection limit of 0.03 ng/m^3. Beryllium concentration in urban air is usually higher due primarily to burning of coal and fuel oil; for example, the annual average concentrations in 1982–1992 ranged from 0.02 to 0.2 ng/m^3 in Detroit, Michigan. Beryllium can be released into waterways by the weathering of soil and rocks. Beryllium entering surface water bodies and soil will be retained in the sediment and soil and will be generally immobile. The average concentration of beryllium in drinking water samples that were found to contain it was 190 ng/L. The mean concentration of beryllium in soil in the United States is 0.6 mg/kg.

Human exposure to beryllium and its compounds occurs primarily in the workplace. People who work in beryllium manufacturing, fabricating, and reclaiming industries have a greater probability of inhalation exposure than non-occupational groups. The general population can be exposed to trace amounts of beryllium through inhalation of air, consumption of food and water, and skin contact with air, water, or soil that contains beryllium. Individuals living near sources of beryllium emissions are likely to be exposed to higher levels of beryllium than the general population. Beryllium has been identified in at least 535 of the 1,613 hazardous waste sites that have been proposed for inclusion on the EPA NPL.

2.2 SUMMARY OF HEALTH EFFECTS

The general population can be exposed to beryllium via inhalation, oral, and dermal routes of exposure. The inhalation route is of greatest concern for systemic effects because beryllium and its compounds are poorly absorbed after oral and dermal exposure. The respiratory tract in humans and animals is the primary target of beryllium toxicity following inhalation exposure. Occupational exposure to high concentrations of soluble beryllium compounds can result in acute beryllium disease, while exposure to

relatively low concentrations ($0.5 μg/m^3) of soluble or insoluble beryllium compounds can result in chronic beryllium disease. Acute beryllium disease is characterized by inflammation of the respiratory tract tissues and is usually resolved within several months of exposure termination. In contrast, chronic beryllium disease is an immune response to beryllium and is only observed in individuals who are sensitized to beryllium (usually <15% of an exposed population). Other systemic effects that have been observed in individuals with severe cases of chronic beryllium disease include damage to the right heart ventricle, hepatic necrosis, kidney stones, and weight loss; these effects are probably secondary to chronic beryllium disease rather than a direct effect on the tissues.

As with inhalation exposure, dermal contact with beryllium can result in an allergic response, typically skin granulomas, in certain individuals. Dermatitis, which may be due to direct irritation rather than an immune response, has also been observed in workers exposed to high concentrations of airborne beryllium.

Unlike inhalation and dermal exposure routes, the primary effects observed after oral exposure is not an immune response to beryllium. The most sensitive effects appear to be ulcerative gastrointestinal lesions in dogs and beryllium rickets in rats exposed to beryllium carbonate; no reliable human oral exposure data were identified. The beryllium rickets are not due to a direct effect on bone; they are secondary to phosphorus deficiency. Beryllium in the gut binds to soluble phosphorus compounds to form insoluble beryllium phosphate, thus decreasing the amount of soluble phosphorus compounds available for absorption.

The available data on the potential of beryllium to induce reproductive and/or developmental effects are inconclusive. The data come from several animal studies; no reliable human data were located. No histological alterations have been observed in reproductive tissues of animals orally exposed to beryllium sulfate and no alterations in fertility were observed in dogs exposed to beryllium sulfate in the diet. Similarly, no reproductive effects were observed in rats exposed to beryllium oxide via intratracheal injection. Some developmental effects (fetal mortality, decreased fetal body weight, increased prevalence of internal abnormalities) were observed in the offspring of rats receiving a single intratracheal injection of beryllium oxide or beryllium chloride. No developmental effects were observed in the offspring of dogs orally exposed to beryllium sulfate, although the study is limited because cannibalized and stillborn animals were not examined. Human and animal data provide evidence that inhaled beryllium is a human lung carcinogen; oral data are inadequate for the assessment of carcinogenic potential.

Thus, the primary adverse health of effects of beryllium are respiratory effects and lung cancer following inhalation exposure, gastrointestinal effects following oral exposure, and skin effects following dermal exposure; these effects are discussed in greater detail below. The reader is referred to Section 3.2, Discussion of Health Effects by Route of Exposure, for additional information on other health effects.

Respiratory Effects. The toxicity of beryllium to the respiratory tract is usually manifested in one of two syndromes: acute beryllium disease and chronic beryllium disease. Acute beryllium disease is usually observed at relatively high beryllium exposure levels, has a short period of induction, and is usually resolved within a couple of months of exposure termination. It is believed to be an inflammatory response to beryllium and most regions of the respiratory tract are affected; some reported symptoms include nasopharyngitis, shortness of breath, labored breathing, and chemical pneumonitis.

Chronic beryllium disease is a systemic granulomatous disorder that predominantly affects the lungs. In general, the occurrence of this disease has been confined to workers exposed to beryllium metal and to less soluble beryllium compounds, such as beryllium oxide. However, there have been cases among residents living near beryllium manufacturing facilities and in families of workers who wore contaminated clothing at home. Chronic beryllium disease is caused by an immune reaction to the inhaled beryllium that is deposited in lung airspaces and retained for a prolonged period. In certain individuals who become sensitized to beryllium, the beryllium in the lungs acts as a hapten, binds to protein/peptides in the lungs, and elicits a proliferation of T lymphocytes, a release of inflammatory mediators, and an accumulation of inflammatory cells in the lungs. This results in the formation of noncaseating granuloma, the accumulation of mononuclear cell infiltrates, and the development of fibrosis. Susceptibility to chronic beryllium disease is believed to have a genetic component. The human leukocyte antigen (HLA) class II marker, HLA-DPB1 Glu^{69}, has been found in a large number of individuals with chronic beryllium disease.

When chronic beryllium disease was first recognized, affected individuals had a number of signs and symptoms including weight loss, dyspnea, cough, chest pain, fatigue, and cor pulmonale (hypertrophy of the right heart ventricle). Impaired lung function was detected in most of the affected individuals. The typical lung function abnormalities were decreased vital capacity and total lung capacity and/or reduction in diffusing capacity for carbon monoxide (DL_{CO}). It is likely that these cases of chronic beryllium disease were diagnosed at a late stage. Technological advances in the development of methods to detect chronic beryllium disease, in particular the beryllium lymphocyte proliferation test (BeLPT) and fiber optic bronchoscopy and transbronchial biopsy methods, now allows for the early detection of the disease.

Chronic beryllium disease can be classified into three stages: beryllium sensitization, subclinical chronic beryllium disease, and clinical chronic beryllium disease. Beryllium sensitization, usually diagnosed as consistently abnormal BeLPT results, can progress to chronic beryllium disease, but not all sensitized individuals develop chronic beryllium disease. Individuals with subclinical chronic beryllium disease are sensitized to beryllium and have histological evidence of lung granulomas, but no clinical signs. Although no clinical signs are observed, there is evidence to suggest that there may be some impairment of lung function. Slight alterations in lung function during exercise were observed in approximately 60% of individuals with subclinical chronic beryllium disease, no other consistent alterations in lung function were found. Individuals with clinical chronic beryllium disease are beryllium sensitized, and have histological evidence of lung granulomas and respiratory symptoms, changes on chest radiographs, and/or altered lung function.

A number of large-scale screening studies have examined beryllium workers and found beryllium sensitization rates of 1–15% in workers involved in the production of beryllia ceramics and nuclear weapons. More than half of the beryllium sensitized workers were diagnosed with chronic beryllium disease. Several studies attempted to establish associations between beryllium sensitization and/or chronic beryllium disease and mean, cumulative, and peak exposure levels and duration of employment. In general, no consistent associations were found. Although the data are insufficient for establishment of concentration-response relationships, the available occupation exposure studies do provide exposure levels that may result in beryllium sensitization. Beryllium sensitization and/or chronic beryllium disease have been detected at exposure levels of $0.5 μg/m^3. Respiratory disease is not likely to occur from exposure to beryllium levels in the general environment because ambient air levels of beryllium (0.03–0.2 ng beryllium/m^3) are very low.

Gastrointestinal Effects. No human data were located regarding gastrointestinal effects following exposure to beryllium. In dogs exposed to beryllium sulfate in the diet for 143–172 weeks, extensive ulcerative and inflammatory lesions were observed in the small intestine, stomach, and large intestine; the small intestine was the most severely affected. No gastrointestinal tract lesions were observed in rats exposed to similar concentrations of beryllium sulfate in the diet for 2 years. One possible explanation for the apparent species difference is the manner in which rats and dogs consumed the beryllium-containing diet. The dogs only had access to the diet for 1 hour/day, in contrast to the rats with unlimited access to the diet. Thus, immediately after eating, the dogs had a higher concentration of beryllium in the gut than the rats that ate small amounts of food throughout the day.

Dermal Effects. Two types of dermal effects have been observed in beryllium exposed workers: an inflammatory reaction and an immune reaction. Edematous papulovesicular dermatitis was observed in workers exposed to airborne beryllium sulfate, beryllium fluoride, or beryllium oxyfluoride; this is likely an inflammatory response to beryllium. Beryllium exposure may also cause a delayed, hypersensitive reaction in the skin. Biopsied skin granulomas from beryllium workers had the same mononuclear infiltrates as detected in the lungs. Sensitized guinea pigs also developed granulomatous lesions and other delayed hypersensitive reactions following dermal exposure to beryllium sulfate, beryllium fluoride, beryllium oxide, or beryllium chloride.

Cancer. A number of epidemiology studies have been conducted to assess the carcinogenic potential of beryllium. Increased incidences of lung cancer deaths were reported in retrospective cohort mortality studies of workers at beryllium extraction, processing, and fabrication facilities. Increased lung cancer mortality was also seen in entrants to the Beryllium Case Registry. No correlation between the incidence of lung cancer deaths and exposure has been established because historical exposure levels were not reported. A positive association between length of latency and lung cancer deaths was found, with the highest cancer risks among workers with a latency of $25 years. Significant increases in the occurrence of lung cancer has also been observed in rats and monkeys exposed to beryllium.

The National Toxicology Program lists beryllium and certain beryllium compounds (beryllium-aluminum alloy, beryllium chloride, beryllium fluoride, beryllium hydroxide, beryllium oxide, beryllium phosphate, beryllium sulfate, beryllium zinc silicate, and beryl ore) as human carcinogens. Based on sufficient evidence for carcinogenicity in humans and animals, the International Agency for Research on Cancer has classified beryllium and beryllium compounds in Group 1, carcinogenic to humans. In contrast, the EPA concluded that the human data only provided limited evidence and classified inhaled beryllium in Group B1, a probable human carcinogen.

No human studies investigating the carcinogenicity of ingested beryllium were located. Animal studies have not found significant associations between ingestion of beryllium in the diet and drinking water and increased incidence of neoplasms in rats, mice, or dogs. It should be noted that no toxic effects were observed in rat and mouse chronic-duration studies tested at low doses, and the duration of the dog study was too short to be predictive of late-term cancer. The EPA concluded that the human carcinogenic potential of ingested beryllium cannot be determined.

2.3 MINIMAL RISK LEVELS

Inhalation MRLs

The available human and animal data clearly identify the respiratory tract as the critical target of beryllium toxicity following inhalation exposure. In humans, symptoms of acute beryllium disease (e.g., nasopharyngitis, pneumonia) have been reported in workers exposed to high concentrations of soluble beryllium compounds (Eisenbud et al. 1948a; VanOrdstrand et al. 1945). Longer-term exposure to relatively low concentrations of beryllium can result in chronic beryllium disease (Cotes et al. 1983; Cullen et al. 1987; Eisenbud et al. 1949). More recent studies are able to detect subclinical chronic beryllium disease and beryllium sensitization (Deubner et al. 2001; Henneberger et al. 2001; Kelleher et al. 2001; Kreiss et al. 1993a, 1996, 1997; Newman et al. 2001; Stange et al. 1996b, 2001; Viet et al. 2000). There is evidence to suggest that the occurrence of chronic beryllium disease is not related to duration of exposure, and can have a long latency period. Very few studies assessing the occurrence of chronic beryllium disease also measured airborne beryllium levels. Eisenbud et al. (1949) found no cases of chronic beryllium disease in residents living at least 0.75 miles away from a beryllium manufacturing facility. The airborne beryllium concentration at this distance was estimated to range from 0.01 to 0.1 μg beryllium/m^3. Studies by Cullen et al. (1987), Kreiss et al. (1996), and Stange et al. (1996b) reported chronic beryllium disease (and/or beryllium sensitization) in workers exposed to average beryllium concentrations of 0.52, 0.55, or 1.04 μg beryllium/m^3, respectively.

Respiratory tract effects have also been observed in animals exposed to airborne beryllium. Emphysema, pneumonitis, and lung granulomas are the most commonly reported effects following acute-, intermediate-, and chronic-duration exposure (Haley et al. 1989; Hall et al. 1950; Robinson et al. 1968; Schepers et al. 1957; Sendelbach et al. 1986; Stokinger et al. 1950; Wagner et al. 1969). In general, the animal studies have not identified a reliable no-observed-adverse-effect level (NOAEL) for respiratory effects, and the lowest-observed-adverse-effect levels (LOAELs) are several orders of magnitude higher than the LOAEL identified in the Kreiss et al. (1996) occupational exposure study.

Although the critical target of beryllium toxicity has been identified, the available database does not support derivation of acute-, intermediate-, or chronic-duration inhalation MRLs. As discussed in Section 3.4.3, an animal model that mimics all aspects of chronic beryllium disease has not been identified; thus, it is inappropriate to derive inhalation MRLs from the animal data. No human acute- or intermediate-duration studies that identify a NOAEL or LOAEL for respiratory effects were located. The

Eisenbud et al. (1949) study, found no cases of chronic beryllium disease among community residents chronically exposed to 0.01–0.1 µg beryllium/m^3. This study was not selected as the basis of a chronic-duration MRL because it utilized relatively insensitive methods to detect chronic beryllium disease; in particular, it is not known if residents exposed to 0.01 µg beryllium/m^3 would test positive for beryllium sensitization or subclinical chronic beryllium disease. The LOAELs identified in the Cullen et al. (1987), Kreiss et al. (1996), and Stange et al. (1996b) studies cannot be used to derive a chronic MRL because the observed effects were classified as serious health effects.

Oral MRLs

The only available data on the acute-duration toxicity of ingested beryllium are from lethality studies in rats and mice. Thus, an acute-duration oral MRL cannot be derived. The available data from intermediate-duration studies have identified rickets (Guyatt et al. 1933; Jacobson 1933; Kay and Skill 1934) as a critical target of beryllium toxicity. The rickets do not appear to be due to a direct effect of beryllium on the bone. Rather, the rickets are due to a phosphorus deficiency, which results from the binding of beryllium to dietary phosphorus in the gut. Additionally, these effects have only been observed following exposure to beryllium carbonate. Thus, the available data are inadequate for derivation of an intermediate-duration oral MRL.

- An MRL of 0.002 mg beryllium/kg/day has been derived for chronic-duration oral exposure (>365 days) to beryllium.

A chronic-duration oral MRL of 0.002 mg beryllium/kg/day was derived for beryllium. The MRL is based on a chronic dog feeding study in which groups of five male and five female dogs were exposed to beryllium sulfate in the diet for 143–172 weeks (Morgareidge et al. 1976). Ulcerative lesions of the small intestine were observed in 9 of 10 dogs exposed to the highest dose (500 ppm; 12 and 17 mg beryllium/kg/day for the males and females, respectively); similar lesions were also observed in 1 of 10 dogs exposed to 50 ppm (1 mg beryllium/kg/day). No gastrointestinal effects were observed at the lower dose levels. Other effects observed in the 500 ppm group included erythroid hyperplasia of the bone marrow, slight anemia, bile stasis and vasculitis in the liver, and acute inflammation of the lymph nodes; these effects were considered secondary to the gastrointestinal hemorrhages and a likely systemic bacterial invasion through the damaged intestinal mucosa. The 500 ppm test dose was discontinued after 33 weeks due to high mortality and morbidity. The MRL was derived using a benchmark dose method, which involves fitting mathematical models to the dose-response data for the ulcerative lesions of the small intestine. For this analysis, the incidence data for the male and female dogs were combined and the

calculated doses for the males and females were averaged. A benchmark dose (defined as the 95% lower confidence limit of the dose corresponding to a 10% increase in the incidence of small intestine lesions compared to controls) of 0.56 mg beryllium/kg/day was estimated using a probit model. The benchmark dose was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) and a modifying factor of 3 (to account for the lack of a study that supports the gastrointestinal effects found in the Morgareidge et al. [1976] dog study and the uncertainty as to whether the benchmark dose level is the NOAEL).

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of beryllium. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not

the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (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.

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

Estimates of exposure levels posing minimal risk to humans (or MRLs) have been made for beryllium. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

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

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

Beryllium is a lightweight metal that has many uses, including some in the aerospace industry. Beryllium is present in the earth as beryllium ores, such as beryl and bertrandite. Most beryllium compounds are poorly soluble in water. The most common compound is beryllium oxide, the solubility of which decreases in water as the temperature at which it is calcined increases. Beryllium carbonate and hydroxide are also practically insoluble in water. Beryllium chloride, fluoride, nitrate, phosphate, and sulfate (tetrahydrate) are all soluble in water. Beryllium carbonate, sulfate (tetrahydrate), and hydroxide are formed during the processing of beryllium containing ores into beryllium metal. Beryllium nitrate is used as a hardening agent for mantles on gas lanterns. Beryllium phosphate has no commercial uses. As seen in the discussions below, the solubility of beryllium compounds significantly impacts in the manifestation of toxic effects.

3.2.1 Inhalation Exposure

Most of the information regarding adverse effects in humans after inhalation exposure to beryllium or its compounds is available from studies of occupational exposure. In 1952, a Beryllium Case Registry (BCR) was established to provide a central source for cases of diagnosed beryllium poisoning (acute berylliosis or chronic beryllium disease). The criteria for entry in the BCR included either documented past exposure to beryllium or the presence of beryllium in lung tissue as well as clinical evidence of beryllium disease. Dose-response relationships are difficult to establish in the case of occupational exposure because reported workroom beryllium levels have generally ranged widely from <0.002 to 1.0 mg beryllium/m^3, depending on when the measurements were made. The higher beryllium levels generally have occurred in the past; improvements in industrial hygiene over the last 30–40 years have effectively reduced workroom beryllium levels. Numerous studies provide concentration-response relationships for several end points in experimental animals. However, as discussed in Section 3.5.3, an animal model has not been identified for the most sensitive health effect, chronic beryllium disease.

3.2.1.1 Death

A number of retrospective cohort studies were conducted from data taken from the Beryllium Case Registry. The mortality rate among employees who worked at a major beryllium extraction, processing, and fabricating facility between 1942 and 1968 was higher than the national average, with respect to cardiovascular and pulmonary diseases (Wagoner et al. 1980). The incidence of death due to nonneoplastic respiratory disease was higher among employees who remained in the industry for <5 years after initial exposure and were exposed prior to 1950 when strict exposure controls were initiated.

Another retrospective cohort study of workers exposed to beryllium during 1952–1975 indicates that the overall mortality rates were significantly higher compared to the U.S. general mortality rate (Infante et al. 1980). The incidence of death due to nonneoplastic respiratory disease was significantly higher in workers exposed for $15 years and who developed acute respiratory disease. However, in workers with chronic respiratory disease, the excess number of deaths was not related to the number of years since exposure. According to case histories of 3 men and 14 women employed in the beryllium industry for an average of 17 months, 6 of the women died from pulmonary or cardiovascular disease (Hardy and Tabershaw 1946). Most of the workers reported having shortness of breath, general weakness (fatigue), and weight loss. Autopsies revealed granulomatous disease, lung fibrosis, and heart enlargement. These were the first reported cases of chronic beryllium disease.

As discussed in Section 3.2.1.2 under Respiratory Effects, exposure to beryllium can result in two types of nonneoplastic respiratory disease, acute beryllium disease and chronic beryllium disease. Both forms can be fatal. Ten fatalities occurred among 93 cases of acute beryllium pneumonitis that were documented in two beryllium refineries prior to 1950 (American College of Chest Physicians 1965). Autopsy of six of the cases revealed that the death occurred only in people with fulminating disease and resulted from massive pulmonary edema. The survival of workers diagnosed with chronic beryllium disease appears to be related to their pulmonary pathology. Patients with well-formed granulomas but with slight or absent interstitial cellular infiltration appeared to have a higher rate of survival than patients with few or absent granulomas, but with moderate to marked interstitial cellular infiltration (Freiman and Hardy 1970).

There are several studies regarding death in animals after acute inhalation exposure to beryllium compounds. Exposure to 31 mg beryllium/m^3 as beryllium oxide caused death in 2 of 20 rats (Hall et al. 1950). A 50-minute exposure to an aerosol of beryllium metal at 0.8 mg beryllium/m^3 resulted in the death of 20 of 74 rats 12–15 days after exposure (Haley et al. 1990). Upon necropsy, the rats had hemorrhagic lungs. All rats exposed to 4.3 mg beryllium/m^3 (Stokinger et al. 1950) or 2.59 mg beryllium/m^3 (Sendelbach and Witschi 1987a) as beryllium sulfate died by day 14 or 18, respectively. Three of 10 guinea pigs and 2 of 10 hamsters died when exposed to 4.3 mg beryllium/m^3 as beryllium sulfate for 14 days (Stokinger et al. 1950). All monkeys exposed to $13 mg beryllium/$m^3$ as beryllium hydrogen phosphate died after 8–10 days of exposure (Schepers 1964). Two of four monkeys exposed to 0.184 mg beryllium/m^3 as beryllium fluoride died after 7–17 days of exposure. Only one of four monkeys died after 7 days of exposure to 0.198 mg beryllium/m^3 as beryllium sulfate.

The differences observed in the lethality values for certain beryllium compounds are primarily due to their various solubilities. Beryllium oxide was less toxic than beryllium sulfate, due to its relative insolubility in the lung. Based on limited comparisons among compounds and species, rats and monkeys appear to be more sensitive than hamsters and guinea pigs.

Exposure to 0.43 mg beryllium/m^3 as beryllium sulfate for #100 days caused death in 23 of 47 rats (Stokinger et al. 1950). Death was reported in 15 of 23 rats exposed to 30 mg beryllium/m^3 as beryllium oxide for 15 days (Hall et al. 1950). When rats, hamsters, and monkeys were exposed to 0.62 mg beryllium/m^3 as beryl or 0.21 mg beryllium/m^3 as bertrandite ore for 6 months, 13, 25, and 11% died, respectively (Wagner et al. 1969). Signs of toxicity included respiratory distress, anemia, and body weight depression. One of five cats and 2 of 34 guinea pigs died when exposed to 0.43 mg beryllium/m^3 as beryllium sulfate for #100 days (Stokinger et al. 1950). Increased mortality was observed in mice, dogs, hamsters, and goats exposed to 2.0 mg beryllium/m^3 as beryllium sulfate for #51 days. The one monkey similarly exposed also died.

Chronic exposure to 0.034 mg beryllium/m^3 as beryllium sulfate for 72 weeks did not increase mortality among male rats; however, the mortality rate among exposed females was $4 times that of controls (Reeves et al. 1967). This indicates that female rats may be more sensitive than male rats to chronic inhalation exposure to beryllium.

The LC_{50} values and concentrations associated with increased mortality in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

No studies were located regarding gastrointestinal or musculoskeletal effects in humans or animals after inhalation exposure to beryllium or its compounds. The respiratory, cardiovascular, hematological, hepatic, renal, and dermal, and ocular effects observed in humans or animals after inhalation exposure to beryllium and its compounds are discussed below. The highest NOAEL values and all reliable LOAEL

Table 3-1 Levels of Significant Exposure to Beryllium - Inhalation

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m3)	LOAEL Less Serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
ACUTE EXPOSURE							
Death							
1	Monkey (Macacus)	7-17 d 6hr/d				0.184 (2/4 died)	Schepers 1964 BeF2
2	Monkey (Macacus)	8-10 d 6hr/d				13 (4/4 died)	Schepers 1964 BeHPO4
3	Monkey (Macacus)	7 d 6hr/d				0.198 (1/4 died)	Schepers 1964 BeSO4
4	Rat (Fischer- 344)	50 min				0.8 (20/74 died)	Haley et al. 1990 Be metal
5	Rat (Wistar)	10 d 5d/wk 6hr/d				31 (2/20 died)	Hall et al. 1950 BeO
6	Rat (Fischer- 344)	14 d 2hr/d				2.59 (20/20 died)	Sendelbach and Witschi 1987 BeSO4
7	Rat (NS)	14 d 5d/wk 6hr/d				4.3 (10/10 died)	Stokinger et al. 1950 BeSO4
8	Gn Pig (NS)	14 d 5d/wk 6hr/d				4.3 (3/10 died)	Stokinger et al. 1950 BeSO4
9	Hamster (NS)	14 d 5d/wk 6hr/d				4.3 (2/10 died)	Stokinger et al. 1950 BeSO4

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m3)	LOAEL Less Serious (mg/m3)		LOAEL Serious (mg/m3)		Reference Chemical Form
ACUTE EXPOSURE									
Systemic									
10	Monkey (Macacus)	8-10 d 6hr/d	Resp				13	(emphysema)	Schepers 1964 BeHPO4
			Cardio		13	(enlarged heart)			
			Hepatic		13	(hepatocyte degeneration)			
			Renal	13	97	(degeneration of the nephrons)			
			Endocr		13	(hypoplasia of the adrenal gland)			
			Bd Wt				13	(severe weight loss, 8-34%)	
11	Monkey (Macacus)	7-18 d 6hr/d	Resp				0.184	(emphysema)	Schepers 1964 BeF2
			Cardio		0.184	(enlarged heart)			
			Hepatic		0.184	(hepatocellular degeneration)			
			Renal		0.184	(degeneration of the nephrons)			
			Endocr		0.184	(adrenal hypotrophy)			
			Bd Wt				0.184	(19-23% weight loss)	

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m3)	LOAEL Less Serious (mg/m3)		LOAEL Serious (mg/m3)		Reference Chemical Form
ACUTE EXPOSURE									
12	Monkey (Macacus)	7 d 6hr/d	Resp				0.198	(emphysema)	Schepers 1964 BeSO4
			Cardio		0.198	(enlarged heart)			
			Hepatic	0.198					
			Renal		0.198	(glomerular degeneration)			
			Bd Wt				0.198	(24% average weight loss)	
13	Rat (Fischer- 344)	50 min	Resp				0.8	(acute pneumonitis progressing to chronic inflammation and necrosis)	Haley et al. 1990 Be metal
14	Rat (Wistar)	10 d 5d/wk 6hr/d	Resp	31					Hall et al. 1950 BeO
			Hemato	31					
			Musc/skel	31					
			Hepatic	31					
			Renal	31					
			Other	31					
15	Rat (Fischer- 344)	1 hr	Resp		0.447	(lung inflammation)			Hart et al. 1984 BeO

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m3)	LOAEL Less Serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
	ACUTE EXPOSURE						
16	Rat (Fischer- 344)	1 hr	Resp		7 (increased lactic dehydrogenase and alkaline phosphatase in bronchoalveolar lavage fluid)		Sendelbach and Witschi 1987 BeSO4
17	Rat (Fischer- 344)	1 hr	Resp			13 (pneumonitis)	Sendelbach et al. 1986 BeSO4
18	Rat (Fischer- 344)	1 hr	Resp			4.05 (pneumonitis)	Sendelbach et al. 1989 BeSO4
19	Mouse (BALB/c)	1 hr	Resp		7.2 (increased lactic dehydrogenase and alkaline phosphatase in bronchoalveolar lavage fluid)		Sendelbach and Witschi 1987 BeSO4
20	Mouse (BALB/c)	1 hr	Resp		13 (lung inflammation)		Sendelbach et al. 1986 BeSO4
21	Mouse (NS)	14 d 5d/wk 6hr/d	Bd Wt		4.3 (13% body weight loss)		Stokinger et al. 1950 BeSO4
22	Gn Pig (English)	10 d 5d/wk 6hr/d	Resp	31			Hall et al. 1950 BeO
			Hepatic	31			
			Renal	31			
			Bd Wt	31			

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m3)	LOAEL Less Serious (mg/m3)		LOAEL Serious (mg/m3)		Reference Chemical Form
	ACUTE EXPOSURE								
23	Dog (Beagle)	1 d	Resp				10	(granulomas in lung)	Haley et al. 1989 BeO
24	Dog (Beagle)	20 min	Resp				115	(granulomatous foci, inflammation of the lung)	Robinson et al. 1968 BeF2, BeO BeCl2
			Bd Wt		115	(transient anorexia, weight loss)			
25	Rabbit (New Zealand)	10 d 5d/wk 6hr/d	Resp	31					Hall et al. 1950 BeO
			Hemato		31	(decreased erythrocyte count)			
			Hepatic	31					
			Renal	31					
			Bd Wt	31					
	Immuno/ Lymphoret								
26	Dog (Beagle)	1 d			10	(lymph node hyperplasia, lymphocyte stimulation)			Haley et al. 1989 BeO
	INTERMEDIATE EXPOSURE								
	Death								
27	Monkey (Macacus)	30 d 6hr/d					0.198	(1/4 died)	Schepers 1964 BeHPO4
28	Monkey (NS)	51-100 d 5d/wk 6hr/d					2	(1/1 died)	Stokinger et al. 1950 BeSO4

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m3)	LOAEL Less Serious (mg/m3)	LOAEL Serious (mg/m3)		Reference Chemical Form
	INTERMEDIATE EXPOSURE							
29	Monkey (Squirrel)	6 mo 5d/wk 6hr/d				0.21	(increased mortality)	Wagner et al. 1969 BeO
30	Rat (Wistar)	15 d 5d/wk 6hr/d				30	(6/13 males, 9/10 females died)	Hall et al. 1950 BeO
31	Rat (NS)	51-100 d 5d/wk 6hr/d				0.43	(23/47 died)	Stokinger et al. 1950 BeSO4
32	Rat Charles River	6 mo 5d/wk 6hr/d				0.21	(increased mortality)	Wagner et al. 1969 BeO
33	Mouse (NS)	51 d 5d/wk 6hr/d				2	(4/38 died)	Stokinger et al. 1950 BeSO4
34	Gn Pig (NS)	51-100 d 5d/wk 6hr/d				0.43	(2/34 died)	Stokinger et al. 1950 BeSO4
35	Hamster (NS)	51-100 d 5d/wk 6hr/d				2	(5/10 died)	Stokinger et al. 1950 BeSO4
36	Hamster (Golden Syrian)	6 mo 5d/wk 6hr/d				0.21	(increased mortality)	Wagner et al. 1969 BeO
37	Hamster (Golden Syrian)	6 mo 5d/wk 6hr/d				0.62	(increased mortality)	Wagner et al. 1969 BeO

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

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m3)	LOAEL Less Serious (mg/m3)	LOAEL Serious (mg/m3)		Reference Chemical Form
	INTERMEDIATE EXPOSURE							
38	Dog (NS)	51-100 d 5d/wk 6hr/d				2	(4/5 died)	Stokinger et al. 1950 BeSO4
39	Cat (NS)	51-100 d 5d/wk 6hr/d				0.43	(1/5 died)	Stokinger et al. 1950 BeSO4
	Systemic							
40	Monkey (Rhesus)	15 d 5d/wk 6hr/d	Resp	30				Hall et al. 1950 BeO
			Bd Wt			30	(marked weight loss)	
41	Monkey (Macacus)	30 d 6hr/d	Resp			0.198	(emphysema)	Schepers 1964 BeHPO4
			Hepatic	0.198				
			Renal	0.198				
			Bd Wt			0.198	(15-39% weight loss)	
42	Monkey (NS)	51-100 d 5d/wk 6hr/d	Resp			0.04	(emphysema)	Stokinger et al. 1950 BeSO4
			Bd Wt			0.43	(31% weight loss)	

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m3)	LOAEL Less Serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
INTERMEDIATE EXPOSURE							
43	Monkey (Squirrel)	6 mo 5d/wk 6hr/d	Resp		0.21 (inflammation of lungs)		Wagner et al. 1969 BeO
			Hemato	0.21			
			Hepatic	0.21			
			Renal	0.21			
			Other	0.21			
44	Monkey (Squirrel)	6 mo 5d/wk 6hr/d	Resp		0.62 (inflammation of lungs)		Wagner et al. 1969 BeO
			Hemato	0.62			
			Hepatic	0.62			
			Renal	0.62			
			Bd Wt	0.62			
45	Rat (Wistar)	15 d 5d/wk 6hr/d	Resp			30 (respiratory distress, increased rates)	Hall et al. 1950 BeO
			Bd Wt			30 (steady weight loss)	
46	Rat (Wistar) (Sherman)	180 d 5-6d/wk 4-8hr/d	Resp			0.035 (metaplasia, granulomas)	Schepers et al. 1957 BeSO4
47	Rat (Wistar)	10 wk 6hr/d	Dermal		0.5 (inflammatory reaction on skin)		Stiefel et al. 1980 Be(NO3)2

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m3)	LOAEL Less Serious (mg/m3)		LOAEL Serious (mg/m3)		Reference Chemical Form
	INTERMEDIATE EXPOSURE								
48	Rat (NS)	51-100 d 5d/wk 6hr/d	Hemato	0.04	0.43	(macrocytic anemia; leukocytosis)			Stokinger et al. 1950 BeSO4
			Hepatic		2	(increased serum albumin and globulin)			
			Renal	0.43	2	(proteinurea)			
			Bd Wt	2					
49	Rat Charles River	6 mo 5d/wk 6hr/d	Resp				0.21	(granuloma in lung)	Wagner et al. 1969 BeO
			Hemato	0.21					
			Hepatic	0.21					
			Renal	0.21					
			Bd Wt	0.21					
50	Rat Charles River	6 mo 5d/wk 6hr/d	Resp	0.62					Wagner et al. 1969 BeO
			Hemato	0.62					
			Hepatic	0.62					
			Renal	0.62					
			Bd Wt	0.62					
51	Gn Pig (NS)	10 wk 6hr/d	Dermal		0.5	(inflammatory reaction on skin)			Stiefel et al. 1980 Be(NO3)2

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m3)	LOAEL Less Serious (mg/m3)	LOAEL Serious (mg/m3)		Reference Chemical Form
	INTERMEDIATE EXPOSURE							
52	Hamster (Golden Syrian)	6 mo 5d/wk 6hr/d	Resp	0.62				Wagner et al. 1969 BeO
			Hemato	0.62				
			Hepatic	0.62				
			Renal	0.62				
			Bd Wt	0.62				
53	Hamster (Golden Syrian)	6 mo 5d/wk 6hr/d	Resp			0.21	(granulomas of the lung)	Wagner et al. 1969 BeO
			Hemato	0.21				
			Hepatic	0.21				
			Renal	0.21				
			Bd Wt	0.21				
54	Dog (Mongrel)	17.5 d 5d/wk 6hr/d	Resp			31	(emphysema, atelectasis, inflammation)	Hall et al. 1950 BeO
			Hemato	31				
			Hepatic	31				
			Other	31				

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m3)	LOAEL Less Serious (mg/m3)		LOAEL Serious (mg/m3)		Reference Chemical Form
INTERMEDIATE EXPOSURE									
55	Dog (Mongrel)	15 d 5d/wk 6hr/d	Cardio		30	(decrease in arterial oxygen tension)			Hall et al. 1950 BeO
			Hemato		30	(leukocytosis)			
			Bd Wt				30	(7-14% body weight loss)	
56	Dog (Mongrel)	40 d 5d/wk 6hr/d	Resp				3.6	(emphysema)	Hall et al. 1950 BeO
			Cardio		3.6	(decrease in arterial oxygen tension)			
			Hemato		3.6	(macrocytic anemia)			
			Hepatic		3.6	(decreased serum protein)			
			Renal	3.6					
			Bd Wt				3.6	(anorexia and 25% weight loss)	

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m3)	LOAEL Less Serious (mg/m3)		LOAEL Serious (mg/m3)		Reference Chemical Form
	INTERMEDIATE EXPOSURE								
57	Dog (NS)	51-100 d 5d/wk 6hr/d	Resp				0.04	(emphysema)	Stokinger et al. 1950 BeSO4
			Cardio		0.04	(decreased arterial oxygen tension)			
			Hemato		0.43	(leukocytosis)			
					0.04	(macrocytic anemia)			
			Hepatic		0.04	(increased serum albumin and globulin)			
			Renal	0.04	0.43	(proteinurea)			
			Bd Wt		0.04	(body weight loss)			
58	Rabbit (New Zealand)	60 d 5d/wk 6hr/d	Resp	30					Hall et al. 1950 BeO
			Hemato		30	(macrocytic anemia)			
			Bd Wt	30					
59	Rabbit (NS)	51-100 d 5d/wk 6hr/d	Resp				0.04	(actelectasis)	Stokinger et al. 1950 BeSO4
			Hemato	0.04	0.43	(macrocytic anemia; leukocytosis)			
			Bd Wt	2					

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m3)	LOAEL Less Serious (mg/m3)		LOAEL Serious (mg/m3)		Reference Chemical Form
	INTERMEDIATE EXPOSURE								
60	Cat (Mongrel)	15 d 5d/wk 6hr/d	Resp	30					Hall et al. 1950 BeO
			Bd Wt				30	(anorexia, severe weight loss, emaciation)	
61	Cat (NS)	51-100 d 5d/wk 6hr/d	Resp				0.04	(emphysema)	Stokinger et al. 1950 BeSO4
			Bd Wt				0.04	(severe weight loss)	
62	Pig (NS)	51 5d/wk 6hr/d	Bd Wt				2	(28% weight loss)	Stokinger et al. 1950 BeSO4
	Immuno/ Lymphoret								
63	Rat (Wistar)	10 wk 6hr/d			0.5	(increased T-cell activity)			Stiefel et al. 1980 Be(NO3)2
64	Gn Pig (NS)	10 wk 6hr/d			0.5	(increased T-cell activity)			Stiefel et al. 1980 Be(NO3)2
	Cancer								
65	Rat (Wistar) (Sherman)	180 d 5-6d/wk 4-8hr/d					0.035	(CEL: lung cancer)	Schepers et al. 1957 BeSO4
	CHRONIC EXPOSURE								
	Death								
66	Rat (Sprague-Dawley)	72 wk 5d/wk 7hr/d					0.034	(increased mortality of females)	Reeves et al. 1967 BeSO4
	Systemic								
67	Human	12.6 yr average	Resp				0.0012	(breathing difficulties, scarring of the lung)	Cullen et al. 1987 mix

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m3)	LOAEL Less Serious (mg/m3)		LOAEL Serious (mg/m3)		Reference Chemical Form
CHRONIC EXPOSURE									
68	Human	(occup)	Resp				0.00052	(chronic beryllium disease)	Cullen et al. 1987 mix
69	Human	occup	Resp				0.00055	(beryllium sensitization and chronic beryllium disease)	Kreiss et al. 1996 BeO
70	Monkey (Squirrel)	12-23 mo 5d/wk 6hr/d	Resp		0.62	(inflammation of lungs)			Wagner et al. 1969 BeO
			Hemato	0.62					
			Hepatic	0.62					
			Renal	0.62					
			Bd Wt	0.62					
71	Monkey (Squirrel)	12-23 mo 5d/wk 6hr/d	Resp		0.21	(inflammation of lungs)			Wagner et al. 1969 BeO
			Hemato	0.21					
			Hepatic	0.21					
			Renal	0.21					
			Bd Wt	0.21					
72	Rat (Sprague-Dawley)	72 wk 5d/wk 7hr/d	Resp		0.034	(inflammation and proliferation in lung)			Reeves et al. 1967 BeSO4
			Bd Wt		0.034	(decrease in body weight)			

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m3)	LOAEL Less Serious (mg/m3)		LOAEL Serious (mg/m3)		Reference Chemical Form
CHRONIC EXPOSURE									
73	Rat (Sherman)	6-18 mo 5d/wk 6hr/d	Resp		0.0547	(inflammation and fibrosis of the lung)			Vorwald and Reeves 1959 BeSO4
74	Rat (Sherman)	6-18 mo 5d/wk 6hr/d	Resp		0.006	(inflammation and fibrosis of the lung)			Vorwald and Reeves 1959 BeO
75	Rat Charles River	12-17 mo 5d/wk 6hr/d	Resp				0.21	(granuloma in lung)	Wagner et al. 1969 BeO
			Hemato	0.21					
			Hepatic	0.21					
			Renal	0.21					
			Bd Wt	0.21					
76	Rat Charles River	12-17 mo 5d/wk 6hr/d	Resp		0.62	(consolidation of lung)			Wagner et al. 1969 BeO
			Hemato	0.62					
			Hepatic	0.62					
			Renal	0.62					
			Bd Wt		0.62	(decreased body weight gain)			

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m3)	LOAEL Less Serious (mg/m3)		LOAEL Serious (mg/m3)		Reference Chemical Form
	CHRONIC EXPOSURE								
77	Hamster (Golden Syrian)	12-17 mo 5d/wk 6hr/d	Resp				0.21	(granulomas in the lung)	Wagner et al. 1969 BeO
			Hemato	0.21					
			Hepatic	0.21					
			Renal	0.21					
			Bd Wt	0.21					
78	Hamster (Golden Syrian)	12-17 mo 5d/wk 6hr/d	Resp	0.62					Wagner et al. 1969 BeO
			Hemato	0.62					
			Hepatic	0.62					
			Renal	0.62					
			Bd Wt	0.62					
	Immuno/ Lymphoret								
79	Human	occup			0.00052	(increased T-cell activity)			Cullen et al. 1987 mix
	Cancer								
80	Monkey (Rhesus)	63 wk 5d/wk 6hr/d					0.035	(CEL: lung cancer)	Vorwald 1968 BeSO4
81	Rat (Sprague-Dawley)	72 wk 5d/wk 7hr/d					0.034	(CEL: lung cancer)	Reeves et al. 1967 BeSO4

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m3)	LOAEL Less Serious (mg/m3)	LOAEL Serious (mg/m3)		Reference Chemical Form
CHRONIC EXPOSURE								
82	Rat (Sherman)	6-18 mo 5d/wk 6hr/d				0.0547	(CEL: lung cancer)	Vorwald and Reeves 1959 BeSO4
83	Rat (Sherman)	6-18 mo 5d/wk 6hr/d				0.006	(CEL: lung cancer)	Vorwald and Reeves 1959 BeO
84	Rat Charles River	12-17 mo 5d/wk 6hr/d				0.62	(CEL: lung cancer)	Wagner et al. 1969 BeO

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

Bd Wt = body weight; Be = Beryllium; BeCl2 = beryllium chloride; BeF2 = beryllium fluoride; BeHPO4 = beryllium hydrogen phosphate; Be(NO3)2 = beryllium nitrate; BeO = beryllium oxide; BePO4 = beryllium phosphate; BeSO4 = beryllium sulfate; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; Gn pig = guinea pig; hemato = hematological; hr = hour(s); LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; min = minute(s); mix = beryllium oxides and ores in a refinery; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; occup = occupational; Resp = respiratory; wk = week(s)

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

Acute (≤14 days)

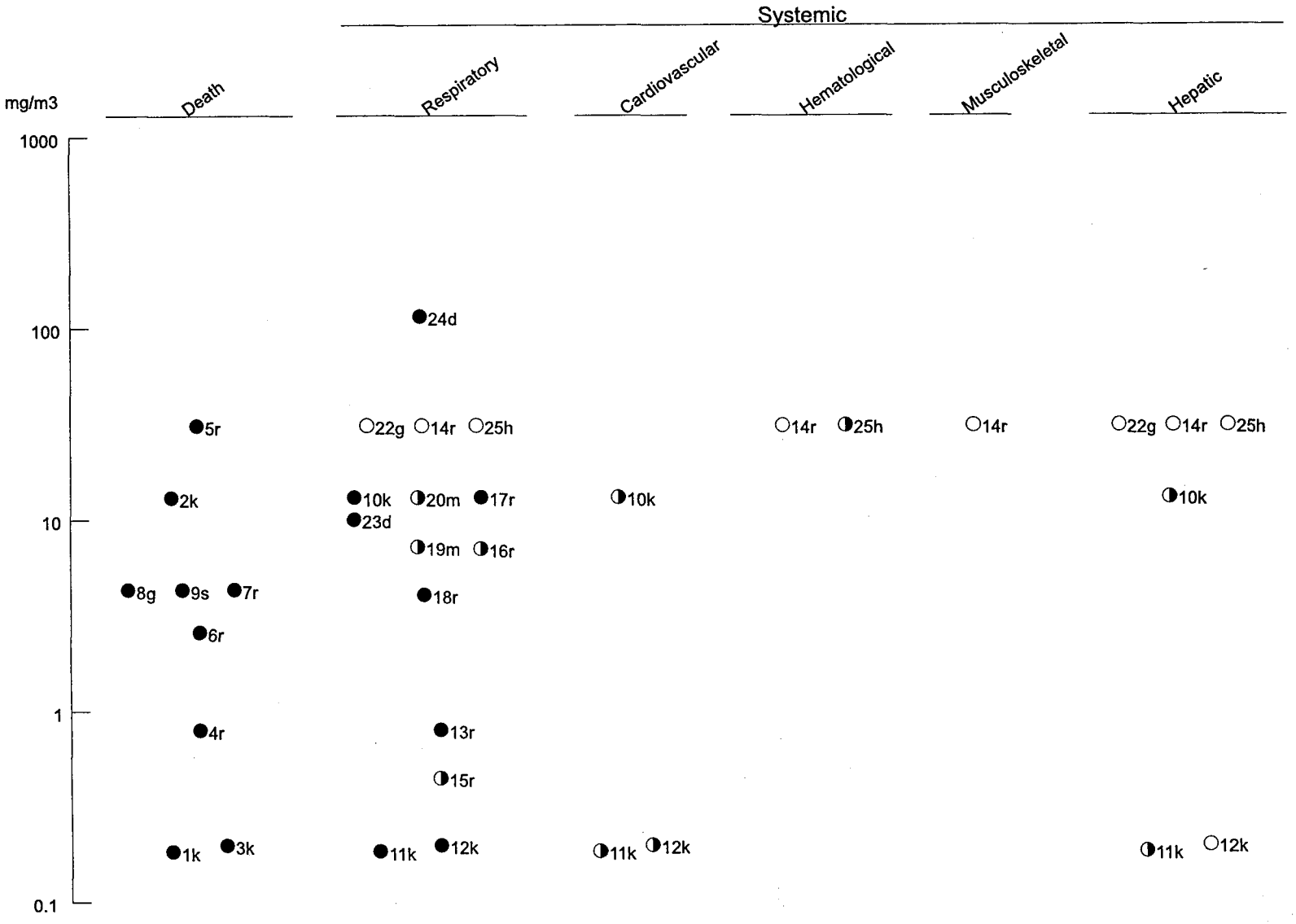


Figure 3-1. Levels of Significant Exposure to Beryllium - Inhalation (*Continued*)

Acute (≤14 days)

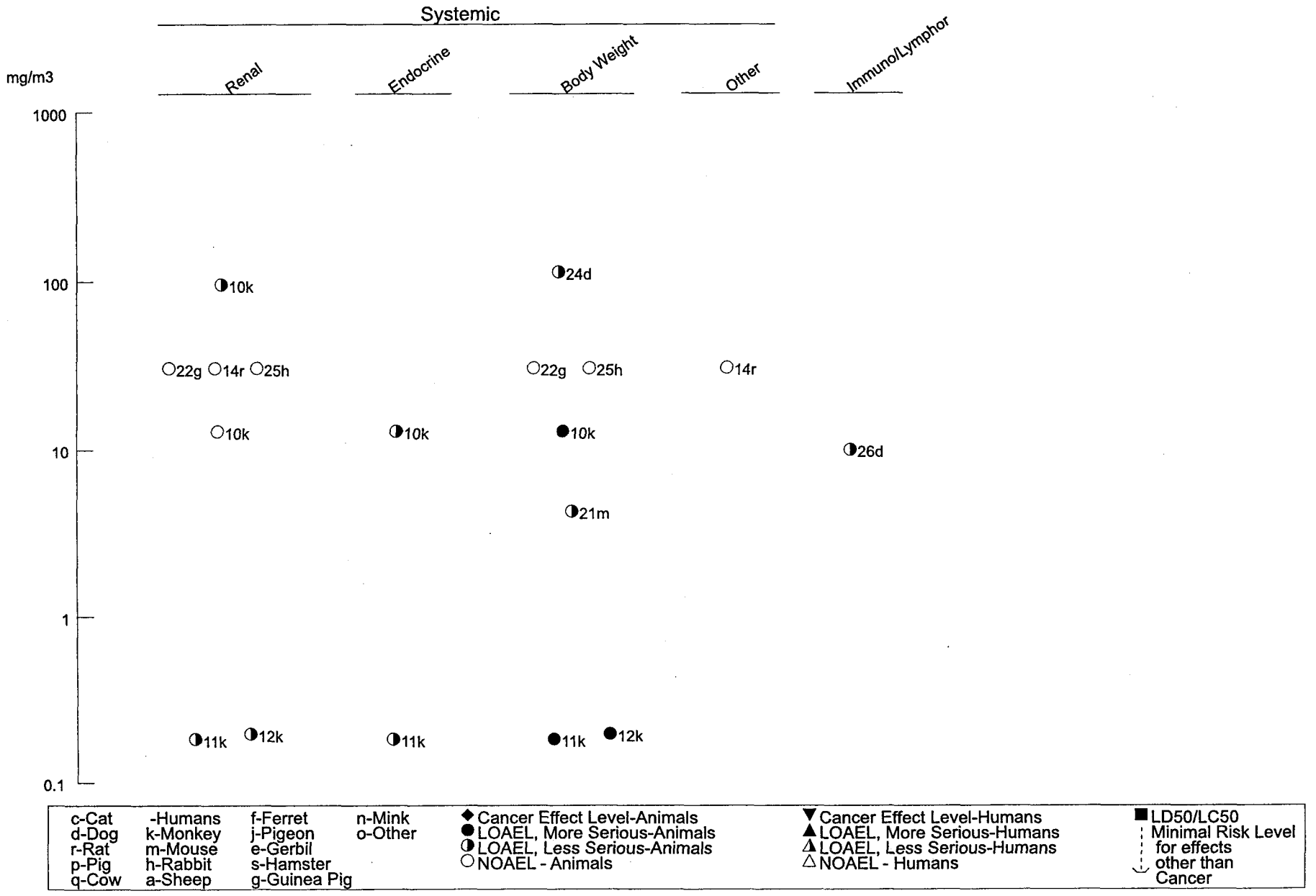


Figure 3-1. Levels of Significant Exposure to Beryllium - Inhalation (*Continued*)

Intermediate (15-364 days)

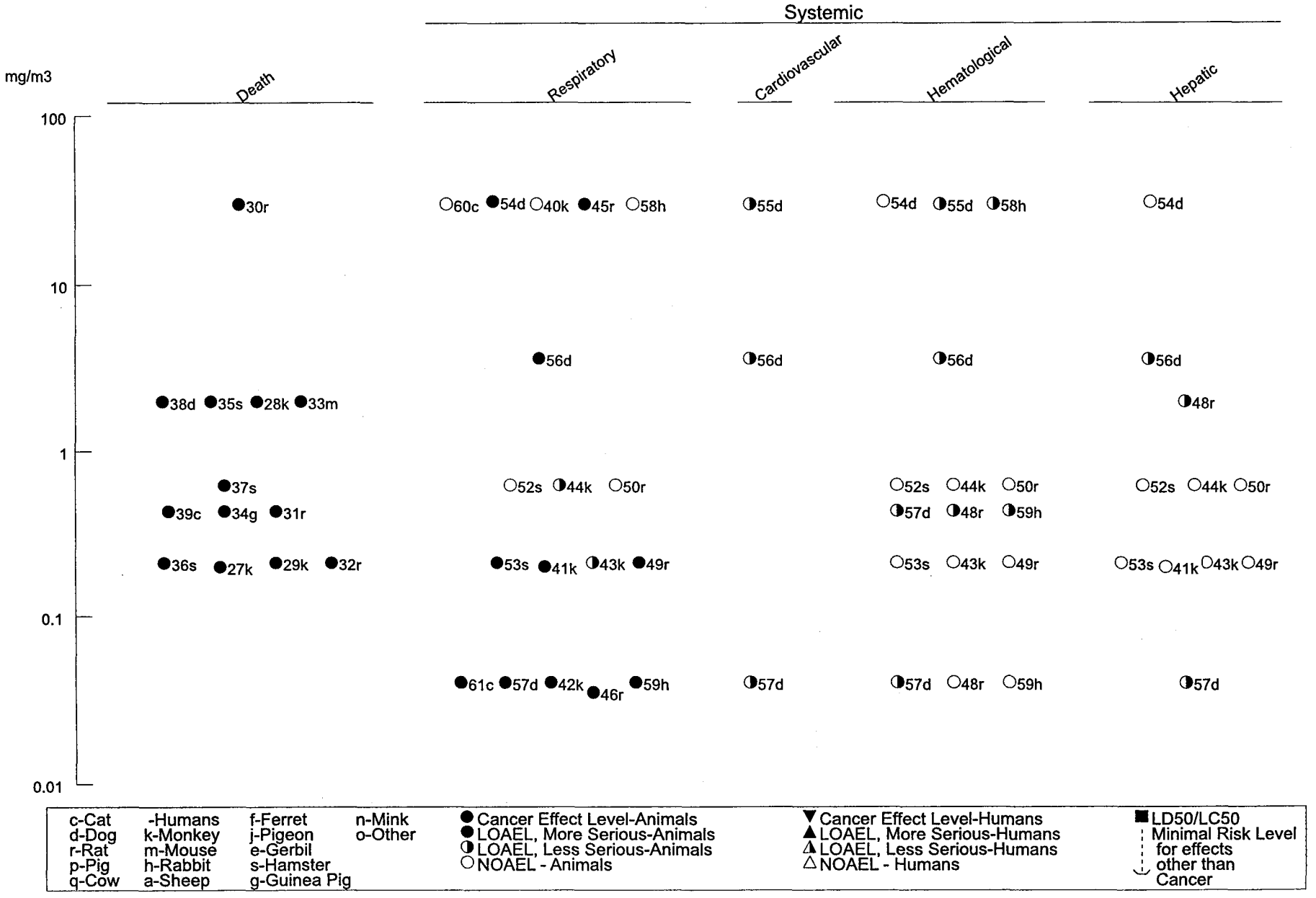


Figure 3-1. Levels of Significant Exposure to Beryllium - Inhalation (*Continued*)

Intermediate (15-364 days)

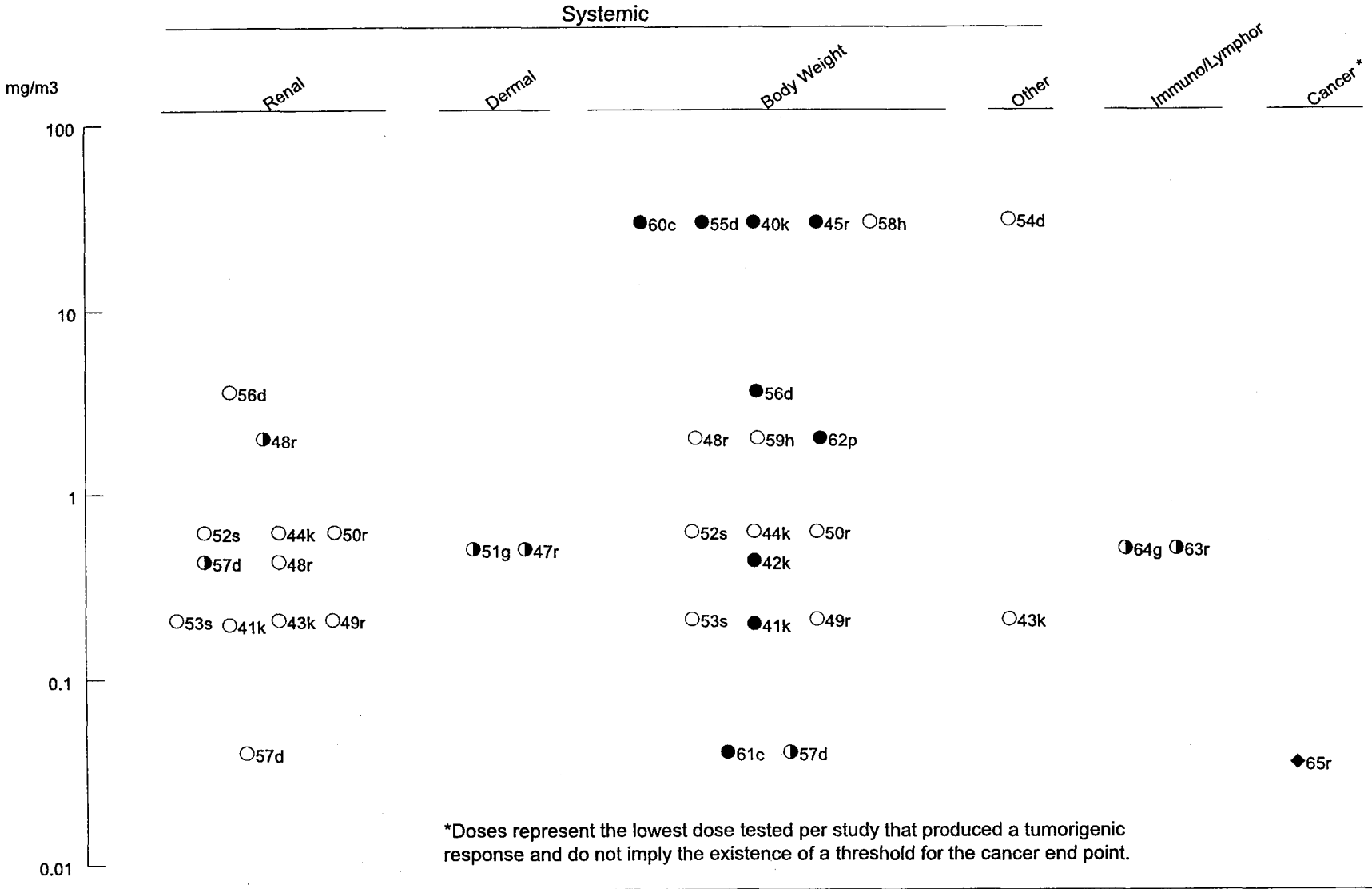
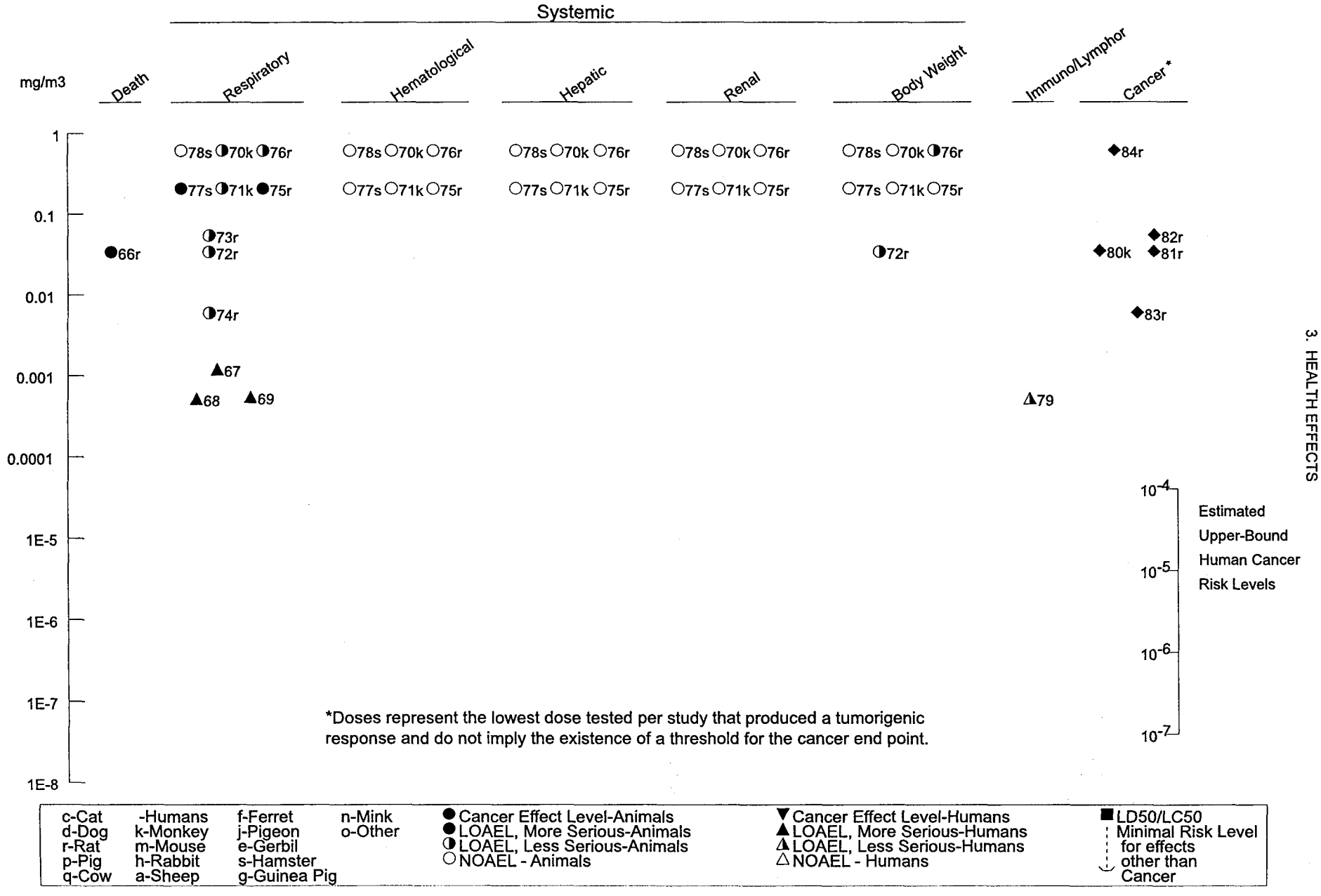


Figure 3-1. Levels of Significant Exposure to Beryllium - Inhalation (*Continued*)

Chronic (≥365 days)



values for each systemic effect in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. There is extensive evidence in humans that the respiratory tract is one of the primary targets of beryllium toxicity following inhalation exposure. In general, noncancerous respiratory effects can be divided into two categories: acute beryllium disease and chronic beryllium disease, also referred to as berylliosis or chronic berylliosis. Acute beryllium disease is a fulminating inflammatory reaction of the entire respiratory tract. The respiratory tract symptoms range from mild nasopharyngitis to a severe chemical pneumonitis, which may be fatal. Acute beryllium disease is usually associated with exposure to high concentrations of soluble beryllium compounds. VanOrdstrand et al. (1945) describe a number of cases of acute beryllium disease among workers exposed to beryllium sulfate, beryllium oxide, beryllium fluoride, and beryllium oxyfluoride. Signs and symptoms observed in the affected workers included irritation of the nasal and pharyngeal mucous membranes, sore nose and throat, weight loss, labored breathing, decreased vital capacity, anorexia, and increased fatigue. In a 1948 investigation of acute beryllium pneumonitis in three U.S. plants producing beryllium compounds from the ore and in laboratories and shops engaged in research in ceramics and metallurgy of beryllium, all cases of beryllium pneumonitis were associated with concentrations >0.1 mg beryllium/m^3, primarily as beryllium sulfate or beryllium fluoride (Eisenbud et al. 1948a). The syndrome of acute beryllium disease has been virtually eliminated in workers first exposed to beryllium after 1950 (initiation of strict exposure limits), except in instances where there is accidental exposure to high levels of beryllium (Eisenbud and Lisson 1983).

Chronic beryllium disease (CBD) is an inflammatory lung disease characterized by the formation of granulomas with varying degrees of interstitial fibrosis. Chronic beryllium disease is a beryllium-specific immune response with primary manifestations in the lung. The symptoms associated with chronic beryllium disease include chest pain, cough, and/or dyspnea with relatively mild exertion. The clinical syndrome of chronic beryllium disease was first described by Hardy and Tabershaw (1946) in fluorescent lamp workers. Seventeen chronically exposed workers developed anorexia, dyspnea, cough, easy fatigue, and weakness. An autopsy on one of the workers revealed increased lung weight, diffuse fibrosis, granuloma, abnormal epithelial lining of the bronchioles, and abnormal alveoli and vasculature. Prior to the adoption of stringent industrial hygiene measures, the incidence of chronic beryllium disease among beryllium workers was high. Historically, a number of criteria were used for the diagnosis of chronic beryllium disease: evidence of beryllium exposure, evidence of lower respiratory tract disease and clinical course consistent with chronic beryllium disease, reticulonodular infiltrates on chest x-ray, obstructive or restrictive deficits in lung function or a low diffusing capacity for carbon monoxide, and pathological

evidence of non-caseating granulomas and/or mononuclear cell interstitial infiltrates (Newman et al. 1989). Technological developments in the 1980s (e.g., fiber optic bronchoscopy and transbronchial biopsy methods, development of the beryllium lymphocyte proliferation test) now allow for the detection of subclinical cases of chronic beryllium disease and beryllium sensitization in the absence of chronic beryllium disease. Newman et al. (1989) proposed that chronic beryllium disease can be classified into three stages: (1) beryllium sensitization—consistent abnormal results for blood and/or lung BeLPT) results, (2) subclinical chronic beryllium disease—sensitized individuals with histopathological evidence but no clinical signs, and (3) clinical chronic beryllium disease—sensitized individuals with histopathological evidence with respiratory symptoms, changes on chest radiographs, or altered pulmonary physiology.

Although instituting regulatory exposure limits and improved hygiene practices has decreased the number of cases of chronic beryllium disease among beryllium workers, new cases of chronic beryllium disease are still being identified in beryllium workers. Cotes et al. (1983) examined 130 workers employed at a beryllium manufacturing facility for at least 6 months during the period of 1952–1963. Based on clinical evaluation including chest x-rays and lung function tests, there were four definite cases of chronic beryllium disease and one probable case of chronic beryllium disease. Another two workers had chest x-rays consistent with chronic beryllium disease, but did not have any other alterations. Beryllium exposure levels were estimated using facility records for total airborne concentrations over the period of 1952–1960. The mean exposure levels for different job processes were 0.029–0.72 µg beryllium/m^3 in 1952 and 0.022–0.21 µg beryllium/m^3 in 1960. Two of the confirmed cases of chronic beryllium disease worked in an area of the facility where beryllium concentrations were 0.04 and 0.18 µg beryllium/m^3 in 1952 and 1960, respectively. Because these exposure levels were based on general air samples, they may not be representative of breathing zone beryllium levels.

Five cases of chronic beryllium disease were reported among workers exposed to beryllium oxide fumes at a precious metals refinery (Cullen et al. 1987). The five workers had abnormal chest x-rays, noncaseating granulomas, pulmonary fibrosis, and abnormal results for the bronchoalveolar lavage beryllium lymphocyte proliferation test (BeLPT). A health survey of 45 workers at the same facility was also conducted (Cullen et al. 1987). Eighteen workers reported lower respiratory tract symptoms (cough, dyspnea, wheezing). Among these 18 workers, 7 also had abnormal x-rays, such as focal scarring. Time weighted-average personal air samples, measured during a 2-week period in 1983, throughout the refinery ranged from 0.22 to 43 µg beryllium/m^3, with a mean of 1.2 µg beryllium/m^3. Four of the five workers with chronic beryllium disease worked in the furnace area, where the mean concentration was 0.52 µg

beryllium/m^3. This concentration is considered a LOAEL for chronic beryllium disease. However, it is possible that the air samples collected during a 2-week period may not be reflective of current or past exposure conditions.

Reversible respiratory effects were observed in a group of beryllium extraction workers examined by Sprince et al. (1978). Health surveys (including measurement of lung function and x-rays) were conducted in 1971 and 1974. When lung function test results and arterial blood gas results were compared to the 1971 values, a slight statistically significant decrease in peak expiratory flow rate, increase in alveolar-arterial O_2 tension and decrease in alveolar-arterial CO_2 tension were observed in a group of 111 workers. When workers with radiological abnormalities suggestive of interstitial disease were re-examined in 1974, nine workers had normal radiographs and nine had radiographs suggestive of interstitial disease; it should be noted that some of these workers had previous exposure to asbestos, silica, or soft coal. Improvement in hypoxia and decreased alveolar-arterial O_2 tension were observed among 13 workers diagnosed with hypoxia in 1971; no change in lung function was observed in this group. The improvement in respiratory effects corresponded to a dramatic decrease in peak air concentrations of beryllium.

Several investigators have conducted screening studies to assess the occurrence of beryllium sensitization and subclinical chronic beryllium disease among beryllium workers. Kreiss et al. (1993a) and Stange et al. (1996b, 2001) examined workers at the Rocky Flats Technology site involved in the production of nuclear weapons, Kreiss et al. (1997) and Newman et al. (2001) examined workers at other beryllium production facilities, and Deubner et al. (2001b) examined beryllium mine workers and workers at a beryllium extraction facility. In the Kreiss et al. (1993a) study, 895 current workers were examined and beryllium sensitization, defined as consistently abnormal BeLPT results, was detected in 17 workers (1.9%). All of these workers had normal chest x-rays. Sixteen of the subjects with beryllium sensitization underwent clinical evaluation (bronchoalveolar lavage BeLPT and transbronchial lung biopsy). Chronic beryllium disease (defined as having granulomas on lung biopsy and abnormal blood or bronchoalveolar lavage [BAL] BeLPT results) was diagnosed in 13 of the subjects. Forty-two subjects had abnormal chest x-rays, 40 of which underwent clinical evaluation. An additional case of chronic beryllium disease was detected in this group (this subject had inconsistently abnormal BeLPT results). Thus, the incidence of chronic beryllium disease in this population was 15/895 (1.7%; one worker refusing clinical evaluation was included in the beryllium disease group because he had ventilatory abnormalities suggestive of restrictive disease). The beryllium sensitized individuals did not significantly differ from the whole cohort in terms of gender, age, history of atopic disease, cigarette smoking status or

pack years, prevalence of respiratory symptoms, spirometric abnormalities, or profusion of small opacities on chest x-rays.

Stange et al. (1996b) examined 4,397 current and former employees at the same facility; it is not known if any of the workers were also included in the Kreiss et al. (1993a) study. Beryllium sensitization was found in 78 of the workers (1.8%); the beryllium sensitization rate was similar in the current and former employees (1.2 versus 1.9%). Of the beryllium sensitized workers, 29 were diagnosed as having chronic beryllium disease (29/4397, 0.66%); chronic beryllium disease was defined as having histologic evidence of pulmonary granulomatous disease and a positive BAL BeLPT result. Environmental beryllium levels were measured in the main beryllium production building using fixed airhead samplers (measured for the period of 1970–1988) and personal air monitoring devices (1984–1987); the mean concentrations were 0.016 and 1.04 µg beryllium/m^3, respectively; the 1.04 µg beryllium/m^3 is considered a LOAEL because it more accurately reflected beryllium concentrations in the breathing zone. However, this value does not take into consideration beryllium levels prior to 1984 and may not be representative of historical beryllium levels.

A more recent study by this group examined 5,173 workers at the Rocky Flats facility (Stange et al. 2001). Confirmed abnormal blood BeLPT results were found in 98 workers (3.33%). Three years after the initial screening, 2,891 workers were re-examined; an additional 56 workers had abnormal blood BeLPT results. The total beryllium sensitization rate was 4.54% (154/5173). The workers with abnormal BeLPT results or with a small opacity profusion of 1/0 or greater in their chest x-ray underwent medical evaluations for chronic beryllium disease. The criteria for diagnosis of chronic beryllium disease were history of beryllium exposure, histopathologic evidence on biopsy of noncaseating granulomas or mononuclear cell infiltrates in the lung, and a positive blood or BAL BeLPT. Seventy-four cases of chronic beryllium disease were diagnosed during the initial screening period and 7 additional cases were diagnosed at the 3-year screening. Beryllium sensitization and chronic beryllium disease were found in male and female workers employed at the facility for <5 years. Increased odds ratios for beryllium sensitization were found for workers in the health physics (odds ratio=2.867; 95% confidence interval [CI]=1.12–7.36), beryllium machinist (odds ratio=3.044; 95% CI=1.95–4.77), construction trades (odds ratio=2.426; 95% CI=1.48–3.97), and general machinist (odds ratio=1.345; 95% CI=1.00–1.82) job group categories.

Viet et al. (2000) designed a case control study of workers at the Rocky Flats facility to evaluate the risks associated with various levels of historical beryllium exposure. Seventy four workers diagnosed as

beryllium sensitive and 50 workers with chronic beryllium disease were matched by age, smoking status, gender, and race to an equal number of controls. Workers were diagnosed as beryllium sensitive if two blood BeLPT results were positive and the clinical evaluation did not reveal chronic beryllium disease; the criteria used to diagnosis chronic beryllium disease were exposure to beryllium, positive blood and lung BeLPT results and noncaseating granulomas on lung biopsy. Historical beryllium exposure levels were estimated using fixed airhead samples in one building (beryllium machine shop); annual exposure levels were estimated by averaging air samples from 2 random days each month. An individual's exposure level was estimated using annual exposure levels; the individual's work history by job location, task, and time period; and assignment of relative exposure estimates to each combination of job location, task, and time period as compared with the beryllium shop machinists. For the chronic beryllium disease cases, the mean exposure level (0.070 versus 0.025 μg/m^3), cumulative exposure level (1.35 versus 0.38 μg-years/m^3), and duration of employment (19.1 versus 14.4 years) were significantly higher than for the controls. For the beryllium sensitive cases, the mean exposure level (0.036 versus 0.026 μg/m^3) was significantly higher than for controls, but there was no significant differences for cumulative exposure level (0.54 versus 0.40 μg-years/m^3) or duration of employment (13.2 versus 14.5 years). Employment start date was not significantly different for the cases versus control comparisons. Comparisons between the chronic beryllium disease cases and beryllium sensitive cases revealed significant differences in mean exposure level (0.070 versus 0.036 μg/m^3), cumulative exposure level (1.35 versus 0.54 μg-years/m^3), duration of employment (19.1 versus 13.2 years), and employment start date (1964.9 versus 1970.2). Significant relationships between chronic beryllium disease and both cumulative and mean beryllium exposure were also found using logistic regression analysis; significant relationships were not found for beryllium sensitization. This study cannot be used to establish a LOAEL for chronic beryllium disease or beryllium sensitization because method used to assess beryllium exposure (fixed airhead samples) may not be representative of beryllium levels in personal breathing zones. The study authors note that fixed airhead sampling may underestimate breathing zone levels by a factor of 0.5–9.

Beryllium sensitization and subclinical chronic beryllium disease has also been found in workers exposed to beryllium oxide at beryllia ceramics plants. Eight cases of beryllium sensitization were found among 136 current employees at the plant (Kreiss et al. 1996). Five of these workers had consistently abnormal BeLPT results and were diagnosed with chronic beryllium disease based on the observation of granulomas. Two workers had inconsistently abnormal BeLPT results and no granulomas; however, 2 years after the initial examination, one of these workers had symptoms of chronic beryllium disease (the other refused clinical follow-up). A seventh case of chronic beryllium disease was detected in a worker

who initially had normal BeLPT results but later developed a nonhealing granulomatous response to a beryllium-contaminated skin wound and an abnormal BeLPT result. Seven of the eight beryllium sensitized workers were machinists; the beryllium sensitization rate among the machinists was 14.3 versus 1.2% for all other workers. The beryllium exposure levels for the beryllium-sensitized workers ranged from 0.2 to 1.1 µg beryllium/m^3; the median concentration was 0.55 µg/m^3, this is a LOAEL for beryllium sensitization and chronic beryllium disease.

Additional cases of beryllium sensitization and chronic beryllium disease were identified in a follow-up to this study (Henneberger et al. 2001). This study examined 151 workers employed at a beryllium ceramics manufacturing facility; 77 of the workers were employed before 1992 (long-term workers, 76 of them participated in the first beryllium screening study [Kreiss et al. 1996]) and the remaining workers began employment at the facility after 1992 (short-term workers). Breathing zone and general area sample measurements taken from 1981 (when full production of beryllium ceramics began) to 1998 were used to estimate mean, cumulative, and peak exposure levels. The median and mean exposure levels were 0.39 and 14.9 µg/m^3, respectively, for long-term workers and 0.28 and 6.1 µg/m^3, respectively, for short-term workers. Using blood BeLPT, 15 cases of beryllium sensitization were diagnosed; 8 cases among long-term workers and 7 among short-term workers. Six of these workers were diagnosed as having chronic beryllium disease (defined as borderline or abnormal BAL BeLPT and/or characteristic granulomas on lung biopsy). Seven of the eight workers with chronic beryllium disease were long-term workers. Among long-term workers, no relationships between the prevalence of beryllium sensitization and time since first exposure, mean exposure level, or cumulative exposure level were found. However, a higher prevalence of beryllium sensitized workers was seen in the workers with the highest peak exposure levels. For the short-term workers, positive associations between prevalence of beryllium sensitization and mean, cumulative, and peak exposure levels were found.

A study of 627 workers at a beryllium manufacturing facility found 43 cases of beryllium sensitization (6.9%) (Kreiss et al. 1997). Chronic beryllium disease was diagnosed in 24 of the beryllium sensitized workers (incidence of 4.6%). The highest incidence of chronic beryllium disease was found in ceramic workers exposed to beryllium oxide (9.0%). The only available monitoring data for this facility is historic environmental beryllium measurements taken between 1984–1993. However, these monitoring data can not be used to establish a LOAEL for chronic beryllium disease because ceramic product manufacturing (the workers with the highest disease incidence) was terminated before 1984.

Newman et al. (2001) conducted a medical surveillance in a beryllium metal machining facility following the detection of an index case of chronic beryllium disease in 1995. All current employees were tested with the blood BeLPT between 1995 and 1997 and were retested 2 years after the initial screening. The mean age of the current workers was 39 years and the mean duration of exposure was 11.7 years. Of the 235 workers initially tested, 15 had confirmed abnormal blood BeLPT results. Eleven of these workers underwent clinical evaluation; 8 were found to have chronic beryllium disease with granulomas and/or mononuclear cell infiltrates on transbronchial lung biopsy. One worker had an abnormal BAL (bronchioalveolar lavage) BeLPT and lymphocytes in the BAL fluid, but no evidence of granulomas or infiltrates; this worker was classified as having probable chronic beryllium disease. The remaining three workers were classified as beryllium sensitized without evidence of chronic beryllium disease. During the first 2-year interval testing phase (187 workers were retested), five additional workers had consistently abnormal BeLPT results; three of these workers were diagnosed as having chronic beryllium disease and one was classified as probably having chronic beryllium disease. During the second interval testing phase, 109 workers were tested and two cases of abnormal BeLPT results were found. Both of these individuals were diagnosed as having chronic beryllium disease. Thus, the total number of beryllium-sensitized workers was 22. Of the 19 undergoing clinical evaluation, 13 workers were diagnosed with chronic beryllium disease characterized as granulomas and/or mononuclear cell infiltrates on lung biopsy, and 2 workers were diagnosed with probable chronic beryllium disease. No difference in duration of employment was found between the workers with chronic beryllium disease and the beryllium sensitized workers. The workers with chronic beryllium disease were older than the beryllium sensitized workers (41 years versus 33.5 years); three of the workers were employed for <3 months. With the exception of the index case, most of the workers with chronic beryllium disease were at the very early stages and had minimal abnormalities on pulmonary function or on exercise capacity testing.

Kelleher et al. (2001) expanded the results of the Newman et al. (2001) by examining the relationship between beryllium exposure and beryllium sensitization and chronic beryllium disease. Beryllium exposure levels for 20 of the beryllium workers with beryllium sensitization (7 workers) or chronic beryllium disease (13 workers; includes 2 workers with probable chronic beryllium disease) were compared with beryllium exposure levels for 206 workers employed at the same facility who were negative for beryllium sensitization. No significant differences in age, employment duration, or smoking status were found between the cases and controls. A significantly higher proportion of the cases worked as machinists (odds ratio=4.4; 95% CI=1.1–17.6). The median total beryllium exposure level based on personal samplers was 0.13 μg/m^3. The cases tended to have higher cumulative and median beryllium exposure levels and cumulative exposures to particle sizes of <6 or <1 μm, but the differences were not

statistically significant. The respective mean and median cumulative exposures were 6.09 and 2.93 μg/m^3-years for the cases and 2.27 and 1.24 μg/m^3-years for the controls. None of the cases had lifetime-weighted average beryllium exposure levels of <0.02 μg/m^3; 60% of the cases had lifetime-weighted averages of >0.20 μg/m^3. In the control group, 11% of the workers were exposed to <0.02 μg/m^3 and 48% were exposed to >0.20 μg/m^3.

Deubner et al. (2001b) examined 75 workers at a beryllium ore mining and milling facility in Utah. The workers involved in the mining operation were primarily exposed to beryl ore or bertrandite ore and the milling operation workers were exposed to these ores and beryllium hydroxide. Three of the workers had abnormal blood BeLPT results and one had an unconfirmed positive test. The four workers were long-term employees involved in the facility's milling operations. Two of the workers with confirmed BeLPT results underwent biopsy and BAL BeLPT; one of these workers was diagnosed with chronic beryllium disease (granulomatous lung disease on biopsy). The worker with chronic beryllium disease also worked at another beryllium facility for 10 years where he was involved in beryllium metal and beryllium oxide production. General area, breathing zone, and personal lapel samples were used to estimate historical beryllium exposure. The mean general area, breathing zone, and personal lapel samples ranges were 0.3–1.1, 1.1–8.1, and 0.05–6.9 μg/m^3, respectively. Because no cases of beryllium sensitization or chronic beryllium disease were found in workers who only worked in the mines, the study author suggested that the form of beryllium may influence the risk for developing beryllium sensitization or chronic beryllium disease.

Although chronic beryllium disease is usually associated with occupational exposure to beryllium at manufacturing facilities, it has also been reported in dental technicians (Brancaleone et al. 1998; Kotloff et al. 1993), in individuals living near beryllium manufacturing facilities, and in families of beryllium workers who wore contaminated clothing at home (Chesner 1950; Dattoli et al. 1964; Eisenbud et al. 1949; Lieben and Metzner, 1959; Lieben and Williams 1969). Eisenbud et al. (1949) examined 10,000 residents living within 1 mile of a beryllium manufacturing facility. Eleven cases of chronic beryllium disease (based on radiological evidence) were initially detected; one case was eliminated due to exposure to beryllium dust on work clothes. Three more cases were detected in a follow-up study (Sterner and Eisenbud 1951). The study authors estimated that the beryllium concentrations 0.75 miles from the facility were 0.01–0.1 μg beryllium/m^3. Because the affected residents lived within 0.75 miles of the facility, the 0.01–0.1 μg/m^3 concentration range is a NOAEL for clinical chronic beryllium disease.

Clinical chronic beryllium disease is associated with impaired lung function. Lung function testing in individuals with chronic beryllium disease has shown reduced vital capacity and total lung capacity, increased alveolar-arterial oxygen tension difference, arterial hypoxemia, and decreased carbon monoxide diffusion capacity (Andrews et al. 1969; Johnson 1983; Rossman et al. 1988). A study by Pappas and Newman (1993) investigated whether early beryllium disease was also associated with impaired lung function. In this study, lung function test results from 21 "surveillance-identified" subjects (individuals with abnormal BeLPT results who did not seek medical attention prior to the diagnosis of beryllium sensitization) were compared with the results in 15 "clinically-identified" subjects (individuals who sought medical attention because of respiratory problems or abnormal x-rays). The lung function tests consisted of spirometry, lung volumes, diffusing capacity for carbon monoxide, arterial blood gases, and maximal exercise capacity. No alterations in spirometry, lung capacity, blood gases, or diffusing capacity were found in the surveillance-identified subjects. However, subtle alterations in exercise capacity were found in 52% of the surveillance-identified subjects, the most common effect was a rise in dead space to tidal volume ratio during exercise. In contrast, 93% of the clinically-identified subjects had alteration in lung function. The alterations included mild to moderate airway obstruction, evidence of restriction, abnormal resting blood gas analysis, and impaired exercise capacity (able to perform less work than surveillance-identified subjects).

In animals, the respiratory system is also the primary target for inhalation exposure to beryllium. Rats exposed to 1–100 mg beryllium/m^3 as beryllium oxide (calcined at 1,000 EC) for 30–180 minutes had initial alveolar deposition of 1–63 µg beryllium in the lungs (Sanders et al. 1975). The exact exposure concentrations were not clearly specified. Rats developed only slight to moderate granulomatous lesions in the lungs, depending on the amount of alveolar deposition. Dust laden or degenerative macrophages and a moderate infiltration of lymphocytes were noted in the lungs of rats exposed to beryllium oxide. Hamsters, similarly exposed until an initial lung burden of 16–17 µg beryllium was achieved, developed only a few small areas of granuloma formation and degenerating macrophages. Pulmonary lavage fluid from rats exposed to 0.447 mg beryllium/m^3 as beryllium oxide (calcined at 560 EC) for 1 hour was examined at various intervals for #21 days after exposure for cell populations, acid and alkaline phosphatase enzyme activity of lysozyme and lactic dehydrogenase, and biochemical analysis of protein, lipid, phosphorus, phosphatidyl choline, and sialic acid (Hart et al. 1984). Microscopic examination of the cell populations revealed inflammation characterized by increased interstitial mononuclear cells and a thickening of the alveolar septa. Increases in the lipids and proteins and levels of acid and alkaline phosphatase, lysozyme, and lactic dehydrogenase indicated cellular damage to the type II cells or the alveolar epithelium. Similar analyses of rats exposed to $3.3 mg beryllium/$m^3$ and mice exposed to

7.2 mg beryllium/m^3 as beryllium sulfate for 1 hour and examined for #12 months indicated the occurrence of pneumonitis with thickening of the alveolar walls and inflammation of the lung (Sendelbach et al. 1986, 1989; Sendelbach and Witschi 1987b). Increased levels of acid and alkaline phosphatase, and lactic dehydrogenase in the lavage fluid of the lungs of treated rats and mice indicated damage to the cellular populations; the increase in protein indicated alveolar damage. These studies demonstrate the ability of soluble beryllium compounds to damage the lung long after exposure ceases. Dogs exposed to 10 mg beryllium/m^3 as beryllium oxide calcined at 500 or 1,000 EC developed granulomas in the lung (Haley et al. 1989). Histopathology also revealed intense alveolar septal fibrosis and epithelial hyperplasia. Beryllium oxide calcined at 500 EC was associated with higher incidences of lesions, due to its greater solubility. Dogs exposed to 115 mg beryllium/m^3 as a mixture of beryllium oxide, beryllium fluoride, and beryllium chloride for 20 minutes, had inflamed lungs and granulomatous foci (Robinson et al. 1968). Increased lung weight, inflammation, emphysema, and fibrosis of the lung were observed in monkeys exposed to 0.198 mg beryllium/m^3 as beryllium sulfate for 7–17 days (Schepers 1964). Monkeys exposed to $13 mg beryllium/$m^3$ as beryllium hydrogen phosphate for 8–10 days, and 0.184 mg beryllium/m^3 as beryllium fluoride for 7–18 days had severely inflamed and fibrotic lungs with granulomas. Histology revealed pleuritis, congestion, emphysema, consolidation, and edema of the lung. The severity of these effects was more notable with beryllium fluoride than with beryllium sulfate or beryllium hydrogen phosphate, partly due to the fluoride component which may form hydrofluoric acid in the lung as beryllium fluoride dissociates. Rats, rabbits, and guinea pigs exposed to 31 mg beryllium/m^3 as beryllium oxide for 10 days did not have any histological evidence of lung damage (Hall et al. 1950).

Animals exposed to beryllium compounds for intermediate durations had health effects similar to those caused by acute exposure. Rats and hamsters exposed to 0.21 mg beryllium/m^3 as bertrandite ore for 6 months developed granulomatous lesions composed of several large, tightly packed, dust laden macrophages and a few lymphocytes (Wagner et al. 1969). However, when the rats were exposed to 0.620 mg beryllium/m^3 as beryl ore, the lungs were largely unaffected except for a few small areas of atypical alveolar wall cell proliferation. Monkeys exposed to 0.210 or 0.620 mg beryllium/m^3 as bertrandite or beryl ore, respectively, had relatively minor changes in the lung. The changes observed were aggregates of dust-laden macrophages, lymphocytes, and plasma cells near respiratory bronchioles and small blood vessels. Vascular congestion, emphysema, and pneumonitis were observed during histological examination of the lungs of dogs exposed to 3.6 mg beryllium/m^3 as beryllium oxide for 40 days or to 31 mg beryllium/m^3 as beryllium oxide for 17.5 days (Hall et al. 1950). Epithelialization of the alveoli, focal metaplasia, and granulomas were observed in rats exposed to beryllium sulfate for

6 months (Schepers et al. 1957); however, a nonexposure-related outbreak of pneumonia limits the interpretation of these results. Exposure of rabbits, dogs, cats, and monkeys to 0.04 mg beryllium/m^3 as beryllium sulfate for 100 days caused distortion of the lung structure (Stokinger et al. 1950). The lung appeared to be severely inflamed and emphysematous, resulting in an increase in dead air space. No respiratory effects were observed in rabbits, cats, and monkeys exposed to 30 mg beryllium/m^3 as beryllium oxide for 15 days; however, rats experienced respiratory distress (Hall et al. 1950).

Chronic exposure to beryllium and its compounds causes similar health effects as those observed after shorter exposure durations. Hamsters and monkeys exposed chronically to 0.210 and 0.620 mg beryllium/m^3 as bertrandite or beryl ore, respectively, had relatively normal lung morphology, except that monkeys had inflamed lungs and hamsters exposed to the bertrandite ore had a few granulomatous lesions (Wagner et al. 1969). Rats exposed to 0.210 mg beryllium/m^3 as bertrandite ore had bronchial lymphocytic infiltrates, abscesses, consolidated lobes, and granulomatous lesions. Inflamed lungs and areas of fibrosis and granuloma were observed in rats exposed to 0.620 mg beryllium/m^3 as beryl ore. Proliferative responses of the alveolar epithelium were also observed. Although the beryllium exposure levels were fairly low in this study, the animals were exposed to 15 mg/m^3 of bertrandite ore or beryl ore, which was the TLV for inert dust. Additionally, the beryllium ores contained high levels of silica (approximately 64%). It is possible that the high dust and silica exposure levels may have contributed to the observed effects; it should be noted that silicosis was not observed. Rats exposed to levels as low as 0.006 mg beryllium/m^3 as beryllium oxide had inflamed lungs and some fibrosis (Vorwald and Reeves 1959). Chronic exposure of rats to other beryllium compounds caused health effects similar to those caused by beryllium oxide. Rats exposed to 0.034 mg beryllium/m^3 as beryllium sulfate for 72 weeks had inflamed lungs, emphysema, arteriolar wall thickening, granulomas, fibrosis, and proliferative responses within the alveoli (Reeves et al. 1967). Rats exposed to 0.0547 mg beryllium/m^3 as beryllium sulfate for 6–18 months had inflamed lungs and fibrosis (Vorwald and Reeves 1959).

Cardiovascular Effects. Data regarding the cardiovascular effects of beryllium and its compounds in humans are limited. Severe cases of chronic beryllium disease can result in cor pulmonale, which is hypertrophy of the right heart ventricle. In a case history study of 17 individuals exposed to beryllium in a plant that manufactured fluorescent lamps, autopsies revealed right atrial and ventricular hypertrophy (Hardy and Tabershaw 1946). An increase in deaths due to heart disease or ischemic heart disease was found in workers at a beryllium manufacturing facility (Ward et al. 1992). It is not likely that the cardiac effects are due to direct toxicity to the heart, but rather are a response to impaired lung function.

Heart enlargement was observed in monkeys after acute inhalation exposure to $13 mg beryllium/$m^3$ as beryllium hydrogen phosphate, 0.184 mg beryllium/m^3 as beryllium fluoride, or 0.198 mg beryllium/m^3 as beryllium sulfate (Schepers 1964). Decreased arterial oxygen tension was observed in dogs exposed to 30 mg beryllium/m^3 beryllium oxide for 15 days, 3.6 mg beryllium/m^3 as beryllium oxide for 40 days (Hall et al. 1950), or 0.04 mg beryllium/m^3 as beryllium sulfate for 100 days (Stokinger et al. 1950). The effects of beryllium compounds on the cardiovascular system probably represent compensatory increases in cardiac musculature due to pulmonary fibrosis caused by inhalation exposure. The decrease of arterial oxygen tension reflects the reduced ability of the lung to oxygenate blood.

Hematological Effects. Information regarding the hematological effects of beryllium and its compounds in humans is limited to case histories. No difference in white blood cell counts, hematocrit, or differential white blood cell percentages was observed in a machinist with chronic beryllium disease who worked with beryllium metal (Johnson 1983). A study involving 170 case histories of beryllium workers in the Cleveland area reported few differences in erythrocyte sedimentation rates, blood counts, or blood chemistry (VanOrdstrand et al. 1945).

Acute exposure of animals to beryllium and its compounds had little effect on hematological parameters; however, intermediate-duration exposures caused anemia in several species. Hematological evaluation of rats and hamsters exposed to 1–100 mg beryllium/m^3 for 30–180 minutes to achieve initial alveolar deposition of 1–63 µg beryllium revealed no statistical difference between treated animals and controls (Sanders et al. 1975). The exact exposure concentration and duration were not clearly reported. Exposure to 31 mg beryllium/m^3 as beryllium oxide did not cause effects on the hematopoietic system in rats (Hall et al. 1950). No significant differences in leukocyte counts were observed in rabbits similarly exposed to beryllium oxide for 10 days. However, erythrocyte counts decreased slightly during the course of exposure.

Rabbits exposed to 307 mg beryllium/m^3 as beryllium oxide for 60 days developed macrocytic anemia (Hall et al. 1950). The erythrocyte counts decreased over time, and there was a tendency to develop hypochromia, indicated by transient decreases in the average mean corpuscular hemoglobin concentration. Dogs exposed to 30 mg beryllium/m^3 as beryllium oxide for 15 days exhibited a moderate, progressive leukocytosis, while dogs exposed to 3.6 mg beryllium/m^3 for 40 days developed macrocytic anemia manifested as an increased mean corpuscular volume and decreased erythrocyte count. The bone marrow was almost exhausted. Differential counting of the bone marrow smears indicated a decrease in erythroblasts and an increase in normoblasts. Exposure to the more soluble compounds of beryllium

caused effects similar to those of beryllium oxide. Macrocytic anemia developed in rats and rabbits exposed to 0.43 mg beryllium/m^3 and dogs exposed to 0.04 mg beryllium/m^3 as beryllium sulfate for 100 days (Stokinger et al. 1950). Exposure to 2.0 and 0.43 mg beryllium/m^3 as beryllium sulfate in rats, rabbits, and dogs caused transient leukocytosis; exposure to 2.0 mg beryllium/m^3 caused mild thrombocytosis. With increasing exposure durations, dogs exposed to 0.04 mg beryllium/m^3 as beryllium sulfate had decreased phospholipid and cholesterol content of the red blood cells. The changes in the biochemical constituents of the red blood cells may reflect a toxic effect on erythropoietic processes in the bone marrow.

Hematological effects were not observed in rats, hamsters, or monkeys exposed to 0.21 or 0.62 mg beryllium/m^3 as bertrandite or beryl ore, respectively, for 6–23 months (Wagner et al. 1969).

Hepatic Effects. Information regarding hepatic effects in humans after inhalation exposure to beryllium and its compounds is limited. Following an accidental leakage of beryllium dust, 25 laboratory workers were exposed to an undetermined concentration of beryllium chloride over a period of 10–20 hours (Zorn et al. 1986). During a 10-month follow-up, no increase was observed in liver enzymes, serum glutamic oxaloacetic transaminase, or serum glutamic pyruvic transaminase. In another study involving case histories of 17 individuals exposed to beryllium in a plant that manufactured fluorescent lamps, autopsy revealed hepatic necrosis in one individual (Hardy and Tabershaw 1946).

Few hepatic effects have been observed in animals after inhalation exposure to beryllium and its compounds, except at lethal exposure levels. Acute exposure to $13 mg beryllium/$m^3$ as beryllium hydrogen phosphate causes hepatocellular degeneration in monkeys (Schepers 1964). Hepatocellular degeneration was also observed in monkeys exposed to 0.184 mg beryllium/m^3 as beryllium fluoride for 7–18 days. These exposure levels were lethal to monkeys. Histological examination revealed no hepatic changes in rats, rabbits, guinea pigs or hamsters following acute inhalation exposure to either beryllium oxide or beryllium sulfate (Hall et al. 1950; Sanders et al. 1975).

Intermediate-duration exposure of rats, monkeys, and hamsters to 0.210 and 0.620 mg beryllium/m^3 as bertrandite or beryl ore did not result in histological evidence of hepatic damage (Wagner et al. 1969).

Decreases in serum protein concentration and the albumin/globulin ratio in the blood indicated that some liver damage occurred in dogs exposed to 3.6 mg beryllium/m^3 as beryllium oxide (Hall et al. 1950). Rats and dogs exposed to 2.0 and 0.04 mg beryllium/m^3 as beryllium sulfate, respectively, had increased serum

albumin and globulin levels (Stokinger et al. 1950). Histological examination of rats exposed to 0.035 mg beryllium/m^3 as beryllium sulfate for 30 days revealed no hepatic damage (Schepers et al. 1957).

No adverse hepatic effects were revealed by histological examination or liver enzyme analysis of rats, hamsters, and monkeys chronically exposed to beryllium oxide as bertrandite or beryl ore (Wagner et al. 1969).

Renal Effects. Kidney stones were observed in . 10% of the cases of chronic beryllium disease collected by the Beryllium Case Registry up to 1959 (Hall et al. 1959). In addition, an excess of calcium in the blood and urine has been seen quite frequently in patients with chronic beryllium disease. These effects are only suggestive and cannot be absolutely attributed to beryllium disease (Stoeckle et al. 1969). In a cohort mortality study of workers employed at beryllium manufacturing facilities, an increased risk of death from chronic and unspecified nephritis, renal failure, and other renal sclerosis was observed (Ward et al. 1992).

Renal effects in animals after inhalation exposure to beryllium and its compounds are minor, except at lethal concentrations. No adverse renal effects were detected by urinalysis, kidney weight measurement, or histological examination in rats, rabbits, hamsters, and guinea pigs exposed to beryllium oxide for acute durations (Hall et al. 1950; Sanders et al. 1975). Guinea pigs, mice, hamsters, and rats exposed to 4.3 mg beryllium/m^3 as beryllium sulfate had protein in the urine; however, there was no protein in the urine of similarly exposed rabbits (Stokinger et al. 1950). No other measures of renal integrity were conducted in this study. Histological examination revealed glomerular degeneration in the kidneys of monkeys exposed to 0.198 mg beryllium/m^3 as beryllium sulfate, 0.184 mg beryllium/m^3 as beryllium fluoride, or $13 mg beryllium/$m^3$ as beryllium hydrogen phosphate (Schepers 1964). These concentrations were lethal to the monkeys. No histological evidence of renal damage was observed in rats exposed to 0.035 mg beryllium/m^3 as beryllium sulfate.

Intermediate-duration exposure (6 months) of rats, hamsters, and monkeys to 0.210 or 0.620 mg beryllium/m^3 as bertrandite or beryl ore, respectively, did not result in evidence of renal effects during histological examination or enzyme analysis (Wagner et al. 1969). No renal effects were observed in dogs exposed to 31 mg beryllium/m^3 as beryllium oxide for #40 days. Urinary protein increased in dogs exposed to 0.43 mg beryllium/m^3 and rats exposed to 2.0 mg beryllium/m^3 as beryllium sulfate for 51–100 days (Stokinger et al. 1950).

No renal effects were identified by histological examination or enzyme analysis in rats, hamsters, and monkeys exposed for 12–17 months to 0.21 or 0.62 mg beryllium/m^3 as bertrandite or beryl ore (Wagner et al. 1969).

Endocrine Effects. Evidence of the effects of beryllium and its compounds on the endocrine system has been observed in humans and animals. One out of 17 workers exposed to beryllium in a fluorescent lamp manufacturing plant died from chronic beryllium disease (Hardy and Tabershaw 1946). Histological examination of the adrenal glands revealed marked hyperemia and vacuolization.

Effects on the adrenal gland have also been observed in animals exposed to beryllium compounds. Histological examination of monkeys exposed to 13 mg beryllium/m^3 as beryllium hydrogen phosphate or 0.184 mg beryllium/m^3 as beryllium fluoride revealed marked hypoplasia and hypotrophy of the adrenal gland (Schepers 1964). However, the adrenal glands of monkeys exposed to 0.196 mg beryllium/m^3 as beryllium sulfate were normal. Rats and hamsters exposed to 1–100 mg beryllium/m^3 as beryllium oxide for 30–180 minutes had increased adrenal weight (Sanders et al. 1975). The exact exposure concentrations were not specified.

Dermal Effects. Skin biopsies revealed granulomas containing beryllium in twins occupationally exposed to beryllium (McConnochie et al. 1988). Positive patch tests with soluble beryllium compounds were obtained in all 32 patients tested with known chronic beryllium disease, indicating that the patch test is useful in the diagnosis of chronic beryllium disease (Curtis 1959). However, the patch test using soluble beryllium compounds itself may be sensitizing and may exacerbate the condition in patients with chronic beryllium disease (Cotes et al. 1983; Epstein 1983; Stoeckle et al. 1969; Tepper 1972), contraindicating the use of patch testing in humans.

Rats and guinea pigs exposed to 0.5 mg beryllium/m^3 as beryllium nitrate for 10 weeks had a typical delayed allergic reaction 24–48 hours after beryllium salts were applied to the skin (Stiefel et al. 1980).

Ocular Effects. There is limited information on the ocular toxicity of beryllium. According to a case history, twins occupationally exposed to beryllium had reduced tear secretions (McConnochie et al. 1988).

Body Weight Effects. Effects on body weight have been observed in humans after inhalation exposure to beryllium or its compounds. Weight loss was common among workers with acute beryllium disease (VanOrdstrand et al. 1945). Weight loss was also reported in workers at a fluorescent lamp manufacturing plant with chronic beryllium disease (Hardy and Tabershaw 1946).

Weight loss, severe at times, has been observed in monkeys, rats, mice, dogs, and cats after acute-, intermediate-, and chronic-duration inhalation exposure to a variety of beryllium compounds. Due to impaired food consumption and "metabolic changes" (no additional information was provided), monkeys exposed for acute durations to $13 mg beryllium/$m^3$ as beryllium hydrogen phosphate for 8–10 days, 0.184 mg beryllium/m^3 as beryllium fluoride for 7–18 days, or 0.198 mg beryllium/m^3 as beryllium sulfate for 7 days lost 8–34, 19–23, or 24%, respectively, of their original body weight (Schepers 1964). Mice exposed to 4.3 mg beryllium/m^3 as beryllium sulfate for 14 days had a 13% decrease in body weight (Stokinger et al. 1950). Dogs exposed to 115 mg beryllium/m^3 as beryllium fluoride, beryllium oxide, and beryllium chloride for 20 minutes had transient weight loss the first 7 days after exposure (Robinson et al. 1968). No effect on body weight was observed in rabbits exposed to 31 mg beryllium/m^3 as beryllium oxide for 10 days (Hall et al. 1950).

Most of the available information on the effect of beryllium on body weight following intermediate-duration exposure comes from three studies that tested a variety of animal species. In monkeys, weight loss was seen following exposure to 0.198 mg beryllium/m^3 as beryllium phosphate for 30 days (Schepers 1964), 30 mg beryllium/m^3 as beryllium oxide for 15 days (Hall et al. 1950), or 0.43 mg beryllium/m^3 as beryllium sulfate for 51–100 days (Stokinger et al. 1950); but not in monkeys exposed to 0.620 mg beryllium/m^3 as beryllium oxide for 6 months (Wagner et al. 1969). The magnitude of weight loss ranged from 15 to 39%. A 3–9% weight loss was observed in rats exposed to 30 mg beryllium/m^3 as beryllium oxide for 15 days (Hall et al. 1950); however, a series of studies by Wagner et al. (1969) did not find any alterations in body weight gain in rats exposed to 0.210 or 0.620 mg beryllium/m^3 as beryllium oxide. This study also did not find body weight alterations in hamsters exposed to the same concentrations of beryllium oxide. Weight loss was also observed in dogs exposed to 3.6 or 30 mg beryllium/m^3 as beryllium oxide for 40 or 15 days, respectively (Hall et al. 1950) or 0.4 mg beryllium/m^3 as beryllium sulfate for 51–100 days (Stokinger et al. 1950). Severe weight loss was also observed in cats exposed to 0.04 mg beryllium/m^3 as beryllium sulfate for 51–100 days (Stokinger et al. 1950) or 30 mg beryllium/m^3 as beryllium oxide for 15 days (Hall et al. 1950). No effect was observed in rabbits exposed to 0.04 mg beryllium/m^3 as beryllium oxide for 30 days or 2.0 mg beryllium/m^3 as beryllium sulfate for 51–100 days (Stokinger et al. 1950).

Exposure to 0.034 mg beryllium/m^3 as beryllium sulfate for 72 weeks caused more severe body weight loss among female rats than among males (Reeves et al. 1967). Rats exposed to 0.62 mg beryllium/m^3 as beryl ore for 17 months also had significantly reduced body weights, compared to controls (Wagner et al. 1969).

3.2.1.3 Immunological and Lymphoreticular Effects

While acute beryllium disease is a chemical pneumonitis, chronic beryllium disease appears to be an immunological disease. The evidence that chronic beryllium disease is an immunological disease is supported by the following. Beryllium can induce classic cell-mediated immune responses in humans and animals (Barna et al. 1981, 1984; Curtis 1951, 1959; Epstein et al. 1982; Haley et al. 1989; Marx and Burrell 1973; Saltini et al. 1989, 1990; Stiefel et al. 1980). Beryllium sensitized cells accumulate at sites of chronic beryllium disease, resulting in granulomas in the lungs (Rossman et al. 1988; Saltini et al. 1989, 1990). Beryllium has been identified within the granulomas of patients with chronic beryllium disease (Williams and Kelland 1986). Virtually all patients with chronic beryllium disease have a cell-mediated immune response to beryllium (Rossman et al. 1988; Saltini et al. 1989), and therapy that controls the immune response (i.e., corticosteroids) can ameliorate the disease (Aronchick et al. 1987).

Nonspecific immunologic findings in chronic beryllium disease include an increase in serum gamma-globulin levels (Resnick et al. 1970). The existence of specific antibodies to beryllium have been reported (Clarke 1991), and further research to confirm and identify the antibodies is continuing.

While the results of peripheral blood lymphocyte proliferative responses to beryllium have been variable in patients with chronic beryllium disease (Kreiss et al. 1989; Newman et al. 1989; Saltini et al. 1989; Stokes and Rossman 1991; Williams and Williams 1983), the results of lung lymphocyte proliferative responses to beryllium have been consistently positive (Rossman et al. 1988; Saltini et al. 1989).

Lung lavage studies in patients with chronic beryllium disease have revealed that there is an accumulation of CD4+T cells in the lungs (Rossman et al. 1988) and that these cells are memory T cells (Saltini et al. 1989). Antibodies to Class II antigens but not Class I antigens will block the beryllium-specific proliferative response. In addition, antibodies to the IL-2 receptor will also block the beryllium proliferative response.

Immunological effects have also been observed in animals after inhalation exposure to beryllium. Dogs exposed to 10 mg beryllium/m^3 as beryllium oxide had a greater immune response to beryllium oxide calcined at 500 EC than at 1,000 EC, due to the greater solubility of the 500 EC calcined beryllium oxide (Haley et al. 1989). The dogs exposed to beryllium oxide calcined at 500 EC had higher cell counts in the bronchoalveolar lavage fluid as a result of an increased lymphocyte population. There was also a greater response of pulmonary lymphocytes *in vitro* to beryllium salts. The tracheobronchial lymph nodes had moderate cortical and paracortical lymphoid hyperplasia resulting from B and T cell activation. The lymph nodes examined 365 days after treatment were characterized by lymphoid depletion, marked congestion, and medullary fibrosis. Histological examination of monkeys exposed for 8–10 days to $13 mg beryllium/$m^3$ or for 30 days to 0.198 mg beryllium/m^3 as beryllium hydrogen phosphate revealed hypoplasia of the lymph nodes (Schepers 1964). The hypoplasia may be a result of the nutritional status of the animal since most of the monkeys lost body weight and were anorexic. Histological examination of monkeys exposed for 7–18 days to either 0.198 or 0.184 mg beryllium/m^3 as beryllium sulfate or beryllium fluoride, respectively, revealed marked hyperplasia of the lymph nodes, typical of immune activation. On the other hand, exposure of rats to 0.035 mg beryllium/m^3 as beryllium sulfate for <7 or 30 days did not cause histopathological changes in the suprarenal, pulmonary, or hepatic lymph nodes (Schepers et al. 1957); the high incidence on non-exposure-related pneumonia limits the interpretation of this study.

Similar immunological effects have been observed in animals exposed to beryllium for intermediate durations. Rats and guinea pigs exposed to 0.5 mg beryllium/m^3 as beryllium nitrate for 10 weeks had inflammations typical of delayed hypersensitivity, as assessed by skin tests and lymphocyte proliferation tests (Stiefel et al. 1980). Lymphocytes exposed *in vitro* to beryllium salts had increased proliferation rates greater than those of the controls. Gross and histological examination of the thymus and spleen of rats, hamsters, and monkeys exposed to 0.21 or 0.62 mg beryllium/m^3 as bertrandite or beryl ore, respectively, for 6–23 months revealed no pathological alterations (Wagner et al. 1969).

The highest NOAEL values and all reliable LOAEL values for immunological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans or animals after inhalation exposure to beryllium or its compounds.

3.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals after inhalation exposure to beryllium or its compounds. Male and female rats were intratracheally injected with 0.6 mg beryllium/kg as radioactive beryllium oxide and allowed to mate over a 15-month period (Clary et al. 1975). There were no consistent effects on reproductive performance as determined by the average number of pregnancies per female, live pups per litter, dead pups per litter, live pups per female, lactation index, or average weight of live pups per female.

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to beryllium or its compounds. A study conducted by Selivanova and Savinova (1986) examined the developmental toxicity of 50 mg beryllium/kg as beryllium chloride and beryllium oxide administered via intratracheal injection on gestational days 3, 5, 8, or 20. An increase in fetal mortality was observed in rats dosed on gestational day 3 with beryllium oxide and in rats dosed on gestational day 5 with either beryllium compound. Exposure to beryllium oxide or beryllium chloride on gestational day 3 resulted in decreased fetal body weights and an increased percentage of pups with internal abnormalities. The latter effect was also observed in the pups of rats exposed to beryllium chloride or beryllium oxide on gestational day 5 and beryllium oxide on gestational day 8. There were no differences in the number of live births per dam or in fetal length.

3.2.1.7 Cancer

A number of retrospective cohort mortality studies examining workers at beryllium processing facilities in Pennsylvania and Ohio have been conducted by Mancuso and Associate (Mancuso 1970, 1979, 1980; Mancuso and El-Attar 1969) and the National Institute of Occupational Safety and Health (NIOSH) (Bayliss et al. 1971; Sanderson et al. 2001a; Wagoner et al. 1980; Ward et al. 1992); many of these studies examined one or two facilities and others looked at seven facilities. One of the earliest cancer mortality studies of these workers was conducted by Mancuso and El-Attar (1969). This study examined a cohort of 3,685 Caucasian male workers employed at two beryllium facilities in Ohio and Pennsylvania from 1937 to 1948; the cohort was followed through 1966. Social Security Administration data, Beryllium Registry data, and death certificates were used to identify employees, deaths, and causes of death. A group of workers in the rubber industry were used as a control group (no additional information on this cohort was provided). The study authors note that a "slightly higher" rate of deaths from malignant neoplasms of the lung, trachea, and bronchus were observed in the beryllium workers; no statistical analyses of the data were conducted. Interpretation of these data is limited by the inclusion of nonexposed workers (no data were available on which departments the workers were employed in), lack of information on exposure characterization, incomplete reporting of deaths or cause of death, large employee turnover rate (78% of the workers were employed for <2 years), and lack of statistical analysis. An additional limitation of the study is the selection of rubber workers as the comparison group, as increased incidence of lung cancer has been found in other studies of rubber workers (Mancuso 1979).

In the second phase of the cohort mortality study (Mancuso 1970), duration of employment and age as of 1940 were considered and the observation period was extended to 1967. The small number of deaths in each duration category, as well as the limitations discussed above in the Mancuso and El-Attar (1969) study, precludes drawing conclusions from this study. A third study by this group (Mancuso 1979) restricted the cohort to workers employed during the period of 1942–1948, extended the observation period to 1974 for the Ohio cohort and 1975 for the Pennsylvania cohort, and compared mortality in the beryllium workers to mortality for the U.S. white male population (using vital statistics data for the period ending in 1967). An increase in the number of lung cancer deaths was observed in workers with a latency period of 15 years or higher (22 observed versus 9.86 expected in the Ohio cohort and 36 observed versus 22.02 expected in the Pennsylvania cohort); the study author notes that the differences are statistically significant. EPA (1987) and MacMahon (1994) have criticized this study. In particular, EPA (1987) notes that using U.S. white male lung cancer death rates for the period ending in 1967 to estimate expected cases for 1968–1975 resulted in a 10–11% underestimation of expected lung cancer deaths

because nationwide lung cancer rates were increasing. EPA (1987) and MacMahon (1994) comment that Mancuso (1979) did not account for the potential confounding effect of cigarette smoking on lung cancer mortality.

To determine whether the increased lung cancer deaths that have been observed in the previous papers by Mancuso and Associate (Mancuso 1970, 1979; Mancuso and El-Attar 1969) were due to beryllium exposure, or the excess risk could be attributed to personal characteristics of workers having unstable employment patterns, Mancuso (1980) conducted a fourth study of the Ohio and Pennsylvania cohorts followed through 1976. Employees in the viscose rayon industry served as a comparison group. A significant increase in lung cancer deaths was observed in the beryllium workers when compared to the entire cohort of rayon workers (standardized mortality ratio [SMR]=140) or a subcohort of workers who did not transfer between departments during their employment in the viscose rayon industry (SMR=158). When the cohorts were divided into employment durations, significant increases in lung cancer deaths were observed in the workers employed for <12 months (SMRs=138 and 164 for total rayon cohort and those not transferring departments, respectively) and workers employed for >49 months (SMRs=222 and 172, respectively), but not in workers employed for 13–48 months. As with the other Mancuso studies, the design of this study has been criticized. One limitation of this study is the lack of adjustment for the potential confounding effect of smoking. EPA (1987) questioned whether there was an adjustment for potential age differences between the beryllium cohort and noted that NIOSH re-analyzed the data from this study and found “serious problems with Mancuso’s analysis”.

NIOSH studies have examined workers at the same facilities as Mancuso, as well as several other beryllium processing facilities. The study by Bayliss et al. (1971) examined workers at a number of beryllium processing facilities in Ohio and Pennsylvania. The original cohort consisted of over 10,000 male and female workers who had employment of at least a few days or longer in the beryllium industry. Removal of approximately 2,000 workers with inadequate records and all female workers (approximately 1,100 workers) resulted in a study cohort of approximately 7,000 workers. The number of deaths among the beryllium workers was lower than expected (SMR=92.2), which was attributed to a healthy worker effect. An increased number of deaths due to lung cancer was observed in the beryllium workers (SMR=105.7), but the increase was not statistically significant. Limitations of this study include lack of analysis for potential effect of latency, elimination of over 2,000 workers due to incomplete records, and the combining of populations from several different plants into one cohort (EPA 1987; MacMahon 1994).

A subsequent study sponsored by NIOSH and the Occupational Safety and Health Administration (OSHA) (Wagoner et al. 1980) examined beryllium workers at one facility in Reading, Pennsylvania. The study cohort of 3,055 white males employed between 1942 and 1967 were followed through 1975, and mortality rates were compared to the U.S. white male population (using NIOSH vital statistics data for the period ending in 1967). A significant increase in lung cancer deaths (47 observed versus 34.29 expected) was observed in the beryllium workers. When deaths from lung cancer were segregated by latency period, significant increases in lung cancer deaths were found in workers with a latency period of at least 25 years (20 observed versus 10.79 expected); significant increases in lung cancer deaths were also observed in workers employed for <5 years and a latency period of at least 25 years (17 observed versus 9.07 expected). To assess the influence of lowering beryllium exposure concentrations, lung cancer deaths were segregated by date of initial employment. A significant increase in lung cancer deaths was observed in workers initially hired before 1950 (when strict beryllium controls were instituted) and a 25-year or higher latency period (20 observed versus 10.76 expected). An increase in lung cancer deaths was also observed in workers initially employed after 1950, across latency periods, but the difference was not statistically significant (7 observed versus 4.60 expected). The study authors note that using national mortality rates probably resulted in a 19% underestimation of cancer risk because Berks County, Pennsylvania (where 87% of the workers resided) has a lower age-adjusted lung cancer rate than the U.S. general population (31.8 per 100,000 versus 38.0 per 100,000). However, EPA (1987) notes that most of the beryllium workers residing in Berks County lived in the city of Reading, Pennsylvania with a lung cancer mortality rate 12% higher than the national rate. Thus, using the national rates may have resulted in an underestimation of expected deaths. Wagoner et al. (1980) attempted to account for the contribution of cigarette smoking to lung cancer deaths by comparing smoking histories of the beryllium cohort (obtained during a 1968 medical survey) with U.S. white male smoking history (obtained by the 1964–1965 Health Interview Survey conducted by the Public Health Service). Using these data, the study authors estimated that the smoking habits of the beryllium workers would result in a 14% higher risk of lung cancer than the comparison population. The study authors note that the frequency of cigarette smoking and the distribution of lung cancer cell type distribution support the conclusion that it is unlikely that "cigarette smoking per se could account for the increased risk of lung cancer among beryllium-exposed workers in this study." EPA (1987), MacMahon (1994), and Bayliss (1980) have discussed a number of severe limitations of this study: (1) using male mortality data for the period of 1941–1967 resulted in a 10–11% underestimation of expected lung cancer deaths, (2) the influence of cigarette smoking was probably underestimated by the study authors, EPA estimated that differences in cigarette smoking patterns would result in a 4.6–18.8% underestimation of expected deaths, and (3) the inclusion of one individual who died of lung cancer but did not work at the beryllium facility because he

failed the pre-employment physical. After adjusting for use of outdated mortality data and cigarette smoking, EPA (1987) estimated that the rightful omission of this worker would result in a nonstatistically significant association between beryllium exposure and lung cancer mortality (46 observed versus 41.90 expected deaths for all workers and 20 observed and 14.67 expected deaths for workers with a $2 year latency period).

In a more recent study, Ward et al. (1992) examined mortality data for a cohort of 9,225 male workers employed at seven beryllium processing facilities in Ohio and Pennsylvania for at least 2 days in the period of 1940–1969; the workers were followed through 1988. Mortality rates in the beryllium cohort were compared to the U.S. white male population. Mortality from all causes was slightly elevated among the beryllium workers (SMR=1.05; 95% CI=1.01–1.08). The elevated mortality rate was largely due to increases in respiratory tract cancer, nonmalignant respiratory disease, and deaths from ischemic heart disease. The SMRs for trachea, bronchii, and lung cancer, nonmalignant respiratory disease, and ischemic heart disease were 1.26 (95% CI=1.12–1.42), 1.21 (95% CI=1.06–1.38), and 1.08 (95% CI=1.01–1.14), respectively. Analysis of mortality data for each individual plant revealed that significant increases in lung cancer deaths were only found in two facilities: Lorain, Ohio (SMR=1.69) and Reading, Pennsylvania (SMR=1.24). To assess the effect of duration of exposure and latency on lung cancer mortality, the total cohort and the Lorain and Reading cohorts were divided into several latency and duration of employment category. For the total cohort, duration of employment was not associated with increased lung cancer deaths, but increased latency was associated with increased lung cancer deaths. In the total cohort, statistically significant increases in lung cancer deaths were observed in the >30 year latency category (SMR=1.46), workers employed for <1 year with a >30 year latency (SMR=1.52), and in the 25–30 year latency period for workers employed for <1 year. Among workers at the Lorain and Reading facilities, significant increases in cancer mortality were also observed in workers employed for <1 year with a 30-year latency (SMRs=1.68 and 1.42, respectively). The decade of hire also influenced lung cancer deaths; this was independent of potential latency. The highest cancer mortality rates were observed among workers hired before 1950. Three of the seven beryllium-processing facilities were open in the 1940s; elevated cancer risks were observed at two of the facilities: Lorain (SMR=1.69; 95% CI=1.28–2.19) and Reading (SMR=1.26; 95% CI=1.02–1.56). The cancer risk was not significantly elevated in the plants operating during the 1950s or 1960s (the Lorain plant closed in 1948). The study authors also examined the influence of geographic variation in lung cancer mortality by comparing cancer mortality in the cohort with county lung cancer data. This comparison did not change the overall conclusions of the study. As with the Wagoner et al. (1980) study, Ward et al. (1992) used smoking habit data available from a 1968 Public Health Survey (included approximately 16% of cohort and four

facilities [including the Reading, Pennsylvania facility]) to account for this confounding variable. A smoking adjustment factor of 1.1323 was estimated using the available data on the beryllium cohort and smoking habit data for the U.S. population (obtained from the National Center for Health Statistics, 1965 and Office of Health, Research, Statistics, and Technology, 1970). The smoking-adjusted SMRs for the entire cohort, the Reading cohort, and the Lorain cohort are 1.12, 1.09, and 1.49, respectively.

As a follow-up to this study, Sanderson et al. (2001a) conducted a case control study using workers from the Reading, Pennsylvania facility. The study consisted of 142 lung cancer cases and 5 age-race matched controls for each lung cancer case. Three quantitative exposure metrics were used to estimate beryllium exposure levels: cumulative beryllium exposure, average beryllium exposure level, and maximum exposure level. Cumulative beryllium exposure was calculated by summing the products of the number of days a worker held a particular job times the estimated annual average beryllium exposure for the job on those specific days. Average beryllium exposure was calculated by dividing the cumulative exposure level by the number of days the worker was employed. The maximum exposure level was the highest time-weighted average (TWA) exposure of any job the worker held, regardless of duration. As described in a companion paper (Sanderson et al. 2001b), historical measurements were estimated using actual industrial hygiene measurements and extrapolations from existing measurements over time and across jobs. No industrial hygiene measurements were available before 1947. Data from 1947 to 1960 were used to estimate exposure during the period of 1935 to 1960 based on the assumption that exposure levels remained constant during this time period. When job-specific exposure levels were not available, measurements from other areas of the facility that were expected to have similar types of exposures were used as surrogates. No measurements were available for general laborers, maintenance workers, or salaried personnel (e.g., managers, engineers, office workers). Exposure levels for the general laborers and maintenance workers were estimated by averaging exposure estimates for a variety of jobs. For the salaried personnel, the exposure levels were estimated using measured data for janitors. The overall lung cancer mortality rate for the Reading plant through 1992 was 1.22 (95% CI=1.03–1.43), which is slightly lower than the mortality rate of this cohort through 1988 (see discussion of the Ward et al. 1992 study). Most of the cases and controls (approximately 60%) were hired during the 1940s when beryllium levels were uncontrolled. The average duration of employment was 3.7 years for the cases and 5.5 years for the controls; however, approximately 67 and 50% of the cases and controls, respectively, were employed for <1 year. The difference in employment duration was statistically significant. As compared to controls, a higher percentage of cases worked as general labor or maintenance departments where some of the highest beryllium exposures occurred; the difference was statistically significant when tenure was lagged 10 or 20 years to discount exposures that may not have contributed to causing cancer because they

occurred after cancer induction. Cumulative, average, and maximum exposure levels were 4,606 μg/m^3 days, 22.8 μg/m^3, and 32.4 μg/m^3, respectively, for the cases and 6,328 μg/m^3 days, 19.3 μg/m^3, and 27.1 μg/m^3 for the controls; the differences between the two groups was not statistically significant. However, when the exposure was lagged 10 or 20 years, the exposure levels were significantly higher among the cases. Cumulative beryllium exposure levels were 4,057 and 2,036 μg/m^3 days for the cases and controls, respectively, when lagged 10 years and 844 and 305 μg/m^3 days, respectively, when lagged 20 years. Average exposure levels for the cases and controls were 22.6 and 12.3 μg/m^3, respectively, when lagged 10 years and 10.2 and 5.3 μg/m^3 respectively, when lagged 20 years. The maximum exposure levels were 30.8 and 16.1 μg/m^3 for the cases and controls, respectively, when lagged 10 years and 13..1 and 6.5 μg/m^3 when lagged 20 years. Significantly elevated odds ratios were observed in three highest quartiles (when compared to the first quartile) of average exposure and maximum exposure when exposure was lagged for 10 or 20 years, but not when unadjusted exposure levels were used. The odds ratios were significantly elevated in the three highest quartiles of maximum exposure when exposure was lagged 20 years and in the highest quartile of unadjusted maximum exposure. Similarly, significantly elevated odds ratios were found when the average and maximum exposure levels were divided into three categories (#2, >2-20, and >20 μg/m^3) when the exposure was lagged 10 or 20 years. In general, no significant relationship between duration of employment and cancer risk were found. Sanderson et al. (2001a) also attempted to address two potential confounding variables: cigarette smoking and exposure to other chemicals. The workers were potentially exposed to a number of other chemicals including nitric acid aerosols, aluminum, cadmium, copper, fluorides, nickel, and welding fumes. Significant odds ratios were found for copper and fluorides when exposure was lagged 10 or 20 years. Interpretation of this finding is difficult because there were no workers exposed to fluorides or copper only and exposure to fluorides and copper was highly associated with exposure to several beryllium compounds. Smoking history was only available for a small number of cases and controls. Thus, the study authors used an indirect method for assess the possible association between smoking status and cancer risk. The authors noted that in order for smoking to be a confounding variable, there would have to be an association between smoking status and beryllium exposure level; such an association was not found.

In addition to these retrospective mortality studies of beryllium workers, there are two epidemiology studies of Beryllium Case Registry enrollees (Infante et al. 1980; Steenland and Ward 1992). In the Infante et al. (1980) study, a cohort of 421 white male workers entered into the Beryllium Case Registry (BCR) between July 1952 and December 1975; the cohort consisted of workers in the beryllium extraction and smelting, metal production, and fluorescent tube production industries and individuals not exposed occupationally but living near a beryllium facility. Mortality rates were compared to the U.S.

white male population for the period lung cancer (which includes trachea and bronchii cancers) was observed (7 observed compared to 2.81 expected), but the difference was not statistically significant. When the lung cancer rate was determined from workers with previously diagnosed respiratory problems, the number of observed deaths was 6 versus 1.91 expected ($p<0.05$). As with the Mancuso (1979) and the Wagoner et al. (1980) studies, using lung cancer mortality data for the period ending in 1967 probably resulted in a 10–11% underestimation of the number of expected deaths. The contribution of cigarette smoking to the observed increase in lung cancer deaths was not adjusted for because no smoking data were available for the cohort; the study authors note that it is unlikely that individuals with acute beryllium illness had smoking habits of sufficient magnitude to account for the excessive lung cancer risk in this group.

A follow-up of the study by Infante et al. (1980) included female workers in the analysis and extended the follow-up period by 13 years to 1988 (Steenland and Ward 1992). The cohort consisted of 689 patients, 66% of which were men. Of the entire cohort, 34% had been diagnosed with acute beryllium disease and 64% with chronic beryllium disease (2% of the subjects had unknown disease type). The mortality rates due to specific causes were compared with that of the U.S. population after stratification by age, race, sex, and calendar time. Increases in mortality were observed among the beryllium workers; the primary cause of death was pneumoconiosis and other respiratory diseases (SMR=34.23; 95% CI=29.1–40.0), followed by deaths from beryllium poisonings (SMR=34.93; 95% CI=19.1–61.4), all cancers (1.51; 95% CI=1.17–1.91), and lung cancer (SMR=2.00; 95% CI=1.33–2.89). There were 70 deaths from all types of cancer, 28 of which were due to lung cancer. Of these, 22 lung cancer deaths occurred in men (SMR=1.76, 95% CI=1.02–2.67), and 6 occurred in women (SMR=4.04, 95% CI=1.47–8.81). No trend was found for duration of exposure or for time since initial exposure. The lung cancer excess was more pronounced among those with acute beryllium disease (SMR=2.32; 95% CI=1.35–3.72) than those with chronic beryllium disease (SMR=1.57; 95% CI=0.75–2.89). Data on smoking status were available for 141 men and 82 women, and data on amount smoked were available for 51 men and 16 women. Analysis showed that the cohort smoked less than the U.S. population, and there were more former smokers and fewer current smokers in the cohort than in the U.S. population. Thus, the study authors concluded that the lung cancer excess was probably not due to smoking; the study authors also ruled out selection bias, concluding that excess exposure to beryllium was the causative factor. It is also possible that the beryllium disease process (particularly the acute disease) contributes to the development of lung cancer.

In general, the early (prior to 1987) studies that associated beryllium exposure with lung cancer have been inadequately controlled for confounding factors such as smoking, improperly calculated expected deaths

from lung cancer, included employees in the beryllium industry who were not actually exposed to beryllium (e.g., salesmen, clerks), or used inappropriate controls. The more recent studies by Ward et al. (1992), Steenland and Ward (1992), and Sanderson et al. (2001a) have addressed many of these issues and provide strong data on the carcinogenic potential of beryllium in humans. NTP (1999, 2002) and IARC (2001) have concluded that beryllium is a human carcinogen; EPA (IRIS 2002) classified it as a probably human carcinogen (group B1). IARC (2001) noted that several aspects of the Ward et al. (1992) and Steenland and Ward (1992) studies support the conclusion that beryllium is a human carcinogen. In particular IARC noted (a) the consistency of lung cancer excess in most of the locations, (b) greater excess cancer risk in workers hired prior to 1950 when beryllium levels were much higher than in subsequent decades, and (c) the highest risk of lung cancer in individuals with acute beryllium disease and at the facility with the greatest proportion of acute beryllium disease. However, IARC (2001) also noted a number of limitations with the existing cancer database. The limitations include poor exposure characterization, relatively low excess cancer risk, and the lack of discussion of exposure to other lung carcinogens. Additionally, several reviewers have criticized the conclusions of the Steenland and Ward (1992) and Ward et al. (1992) studies. In general, the criticism focuses on the relatively low excess of cancer risk and the inadequate adjustment for smoking habits (Eisenbud 1993, 1997; Kolanz 2001; Kotin 1994; MacMahon 1994; Trichopoulos 2000). Using the data from the Ward et al. (1992) study, Levy et al. (n.d.) recalculated the SMRs for lung cancer using city mortality rates rather than county or U.S. rates and a different indirect method for adjusting for smoking and did not find significant increases in the incidence of lung cancer among beryllium workers. A meta-analysis of the data did find a significant increase in lung cancer risk, although the SMRs were lower than those calculated by Ward et al. (1992).

Some beryllium compounds are carcinogenic in animals exposed via inhalation. A single nose-only exposure to 410–980 mg/m^3 beryllium metal aerosol for 8–48 minutes resulted in a 64% incidence of lung tumors in rats; lung tumors were first observed 14 months after exposure (Nickell-Brady et al. 1994). Rats exposed to 0.035 mg beryllium/m^3 as beryllium sulfate for 180 days had increased lung cancer rates, compared to controls (Schepers et al. 1957).

Cancer incidence was not increased in hamsters exposed to 0.21 or 0.62 mg beryllium/m^3 as bertrandite or beryl ore for chronic durations (Wagner et al. 1969). In addition, rats similarly exposed to bertrandite ore did not have a greater incidence of lung cancer than that observed in the controls. However, 18 of 19 rats exposed to 0.62 mg beryllium/m^3 as beryl ore developed tumors that were classified as bronchial alveolar cell tumors, adenomas, adenocarcinomas, or epidermoid tumors. Primary pulmonary cancer of the bronchiole was observed at 9 months in rats exposed to 0.006 or 0.0547 mg beryllium/m^3 as beryllium

oxide (Vorwald and Reeves 1959). The rats were examined for signs of cancer at 6, 9, 12, and 18 months. Lung tumors, which appeared to be adenocarcinomas with a predominantly alveolar pattern, were observed after 13 months of exposure in 100% of rats exposed to 0.034 mg beryllium/m^3 as beryllium sulfate (Reeves et al. 1967). Monkeys exposed to 0.035 mg beryllium/m^3 as beryllium sulfate had tumors in the hilus and peripheral portions of the lung, and scattered throughout the pulmonary tissue, as determined by histological examination (Vorwald 1968). Moreover, there were extensive metastases to the mediastinal lymph nodes and to other areas of the body. It should be noted that many of the studies conducted in animals have been criticized because of poor documentation, being conducted at single dose levels, or failure to include controls (EPA 1987). However, collectively, the animal data indicate that beryllium is carcinogenic in animals.

The CELs in each species are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2 Oral Exposure

3.2.2.1 Death

No studies were located regarding death in humans after oral exposure to beryllium or its compounds.

Oral LD_{50} values in animals vary according to the compound. LD_{50} values for beryllium sulfate were 120 mg beryllium/kg in rats (Lanchow University 1978) and 140 mg beryllium/kg in mice (Ashby et al. 1990). The LD_{50} values for beryllium chloride in rats were 200 mg beryllium/kg (Kimmerle 1966). The LD_{50} values for beryllium fluoride were 18–20 mg beryllium/kg in mice (Kimmerle 1966; Lanchow 1978). The LD_{50} value for beryllium oxyfluoride was 18.3 mg beryllium/kg in rats. The additional toxicity of the fluoride ion accounted for the lower LD_{50} value observed for beryllium fluoride and beryllium oxyfluoride. The difference in the LD_{50} values for the other beryllium compounds is due to differences in solubility and the potential to form insoluble beryllium phosphate in the gastrointestinal tract.

Increased mortality was observed in dogs exposed to 12 mg beryllium/kg/day as beryllium sulfate in the diet; the likely cause of death was severe ulcerative lesions in the gastrointestinal tract (Morgareidge et al. 1976). In chronic studies, no effect on survival was observed in rats and dogs exposed to #31 or 1 mg beryllium/kg/day, respectively, as beryllium sulfate in the diet (Morgareidge et al. 1975, 1976) or in rats and mice exposed to 0.6–0.7 or 1 mg beryllium/kg/day, respectively, as beryllium sulfate in drinking water (Schroeder and Mitchener 1975a, 1975b).

The LD_{50} values in rats and mice and doses associated with increased mortality in dogs are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, or dermal, and ocular effects in humans after oral exposure to beryllium or its compounds. The systemic effects observed in animals after oral exposure to beryllium compounds are discussed below.

Table 3-2 Levels of Significant Exposure to Beryllium - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Mouse (CBA)	1 d (GW)				140 (LD50)	Ashby et al. 1990 BeSO4
	INTERMEDIATE EXPOSURE						
2	Dog (Beagle)	33 wk (F)				12 (increased mortality)	Morgareidge et al. 1976 BeSO4
	Systemic						
3	Rat (Sprague-Dawley)	91d (W)	Bd Wt	0.7			Freundt and Ibrahim 1990 BeSO4
4	Rat (NS)	24-28 d (F)	Musc/skel			35 (rickets)	Guyatt et al. 1933 BeCO3
5	Rat (Wistar)	13-42 d (F)	Musc/skel			345 (rickets)	Jacobson 1933 BeCO3+Be(OH)2
			Bd Wt	345			
6	Rat (NS)	21-22 d (F)	Musc/skel			70 (severe rickets)	Kay and Skill 1934 BeCO3
			Metab		70 (decreased blood phosphate levels)		
7	Rat (Wistar)	4 wk (F)	Bd Wt		480 (18% decrease in body weight gain)		Matsumoto et al. 1991 BeCO3
			Metab		480 (decreased serum phosphate and alkaline phosphatase)		

Table 3-2 Levels of Significant Exposure to Beryllium - 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						
8	Rat (Wistar)	2 yr (F)	Resp	31			Morgareidge et al. 1975 BeSO4
			Cardio	31			
			Gastro	31			
			Hemato	31			
			Musc/skel	31			
			Hepatic	31			
			Renal	31			
			Endocr	31			
			Ocular	31			
			Bd Wt	31			
9	Rat (Long- Evans)	3.2 yr (W)	Resp	0.7			Schroeder and Mitchener 1975a BeSO4
			Cardio	0.7			
			Hepatic	0.7			
			Renal	0.7			
			Bd Wt	0.7			
			Metab	0.7			

Table 3-2 Levels of Significant Exposure to Beryllium - 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							
10	Mouse (Swiss)	898 d (W)	Resp	1			Schroeder and Mitchener 1975b BeSO4
			Cardio	1			
			Hemato	1			
			Hepatic	1			
			Renal	1			
			Bd Wt	1			
11	Dog (Beagle)	143-172 wk (F)	Resp	12 M			Morgareidge et al. 1976 BeSO4
			Cardio	12 M			
			Gastro	1[b]		12 M (ulcerative and inflammatory lesions in the gastro intestinal tract of 9/10 dogs)	
			Hemato	1	12 M (erythroid hypoplasia of bone marrow)		
			Musc/skel	12 M			
			Hepatic	12 M			
			Renal	12 M			
			Endocr	12 M			
			Dermal	12 M			
			Ocular	12 M			
			Bd Wt	1		12 M (weight loss and anorexia)	
Reproductive							
12	Dog (Beagle)	143-172 wk (F)		1			Morgareidge et al. 1976 BeSO4

Table 3-2 Levels of Significant Exposure to Beryllium - 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						
	Developmental						
13	Dog (Beagle)	143-172 wk (F)		1			Morgareidge et al. 1976 BeSO4

aThe number corresponds to entries in Figure 3-2.

b Used to derive a chronic-duration oral minimal risk level (MRL) of 0.002 mg Be/kg/day. The MRL was calculated using a benchmark dose method; the probit model was fit to the combined male and female incidence of ulcerative lesions in the small intestine and average doses for male and female dogs to estimate a BMDL (defined as the 95% lower confidence limit on the dose corresponding to a 10% increase in the incidence of small intestine lesions compared with controls) of 0.56 mg/Be/day. The BMDL was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for intrahuman variability) and a modifying factor of 3 (to account for the lack of a study which supports the gastrointestinal effects found in the Morgareidge et al. [1976] dog study and the uncertainty as to wether the benchmark dose in the NOAEL).

Bd Wt = body weight; Be = Beryllium; BeCl2 = beryllium chloride; BeCO3.Be(OH)2 = beryllium carbonate; BeF2 = beryllium fluoride; BeO = beryllium oxide; BeSO4 = beryllium sulfate; Cardio = cardiovascular; d = day(s); Endocr = endocrine; (F) = feed; (G) = gavage; Gastro = gastrointestinal; (GW) = gavage in water; hemato = hematological; hr = hour(s); LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; (NS) = not specified; Resp = respiratory; (W) = drinking water; wk = week(s); yr = year(s)

Figure 3-2. Levels of Significant Exposure to Beryllium - Oral

Acute (≤14 days)

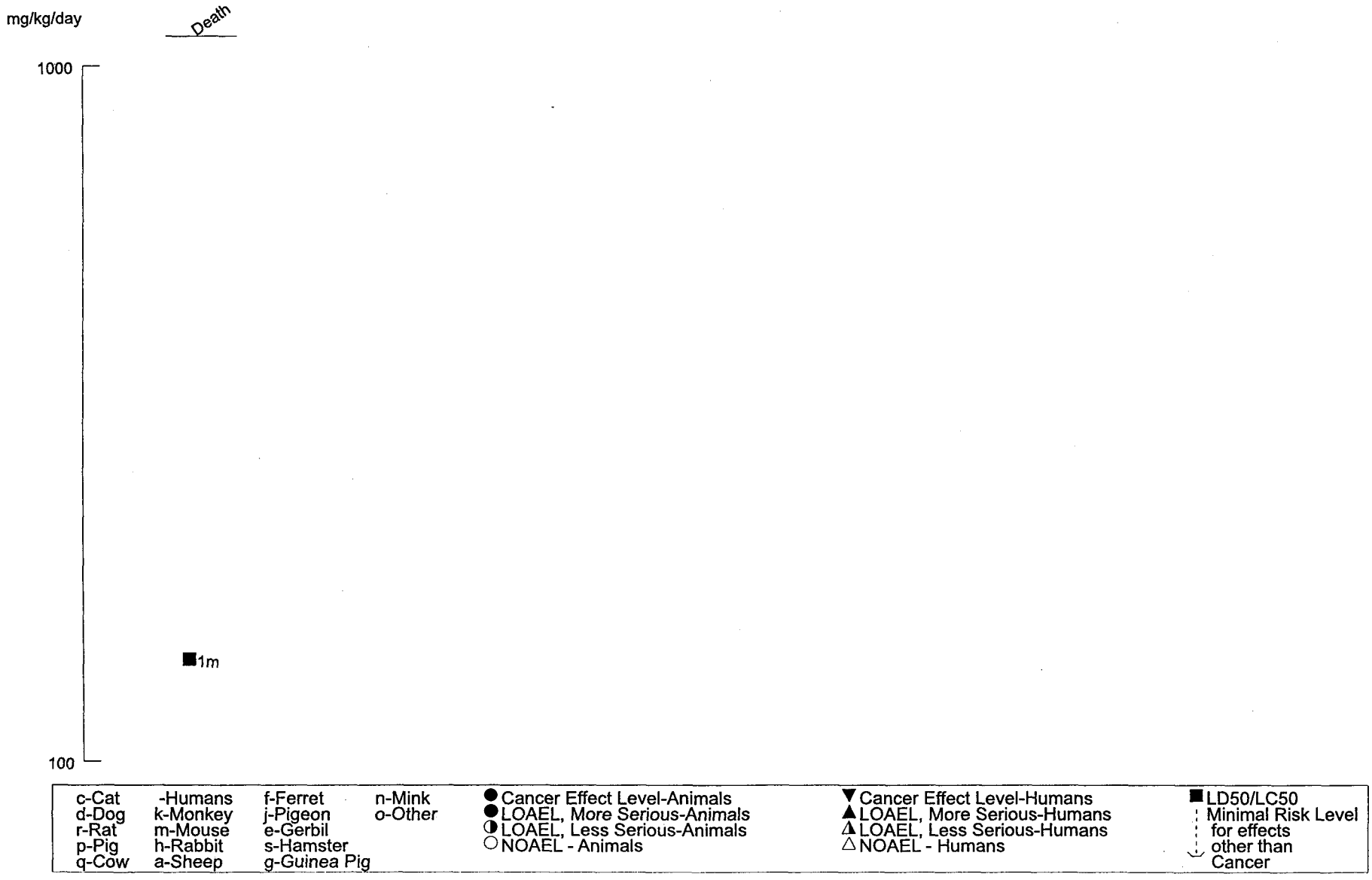


Figure 3-2. Levels of Significant Exposure to Beryllium - Oral (*Continued*)

Intermediate (15-364 days)

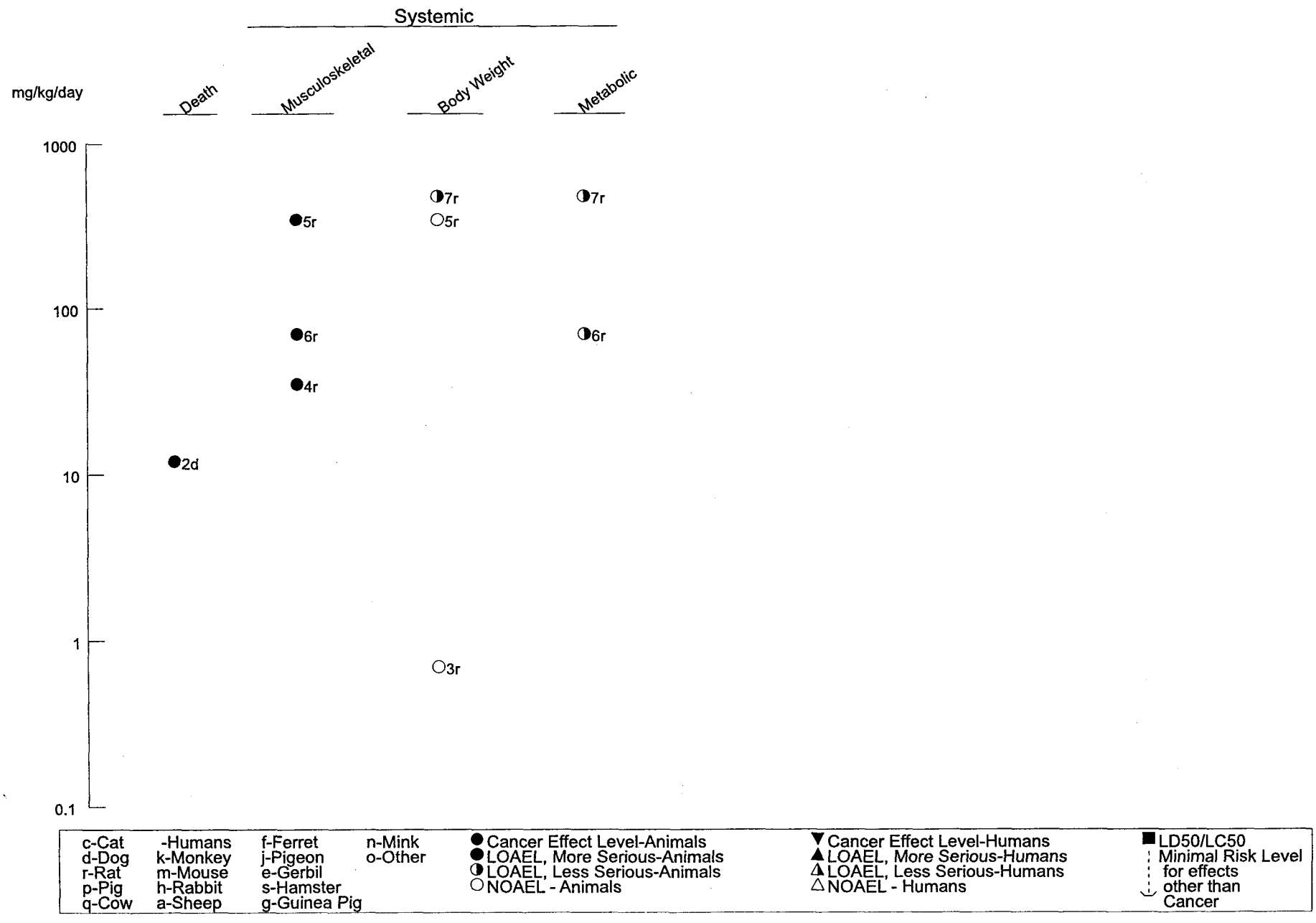
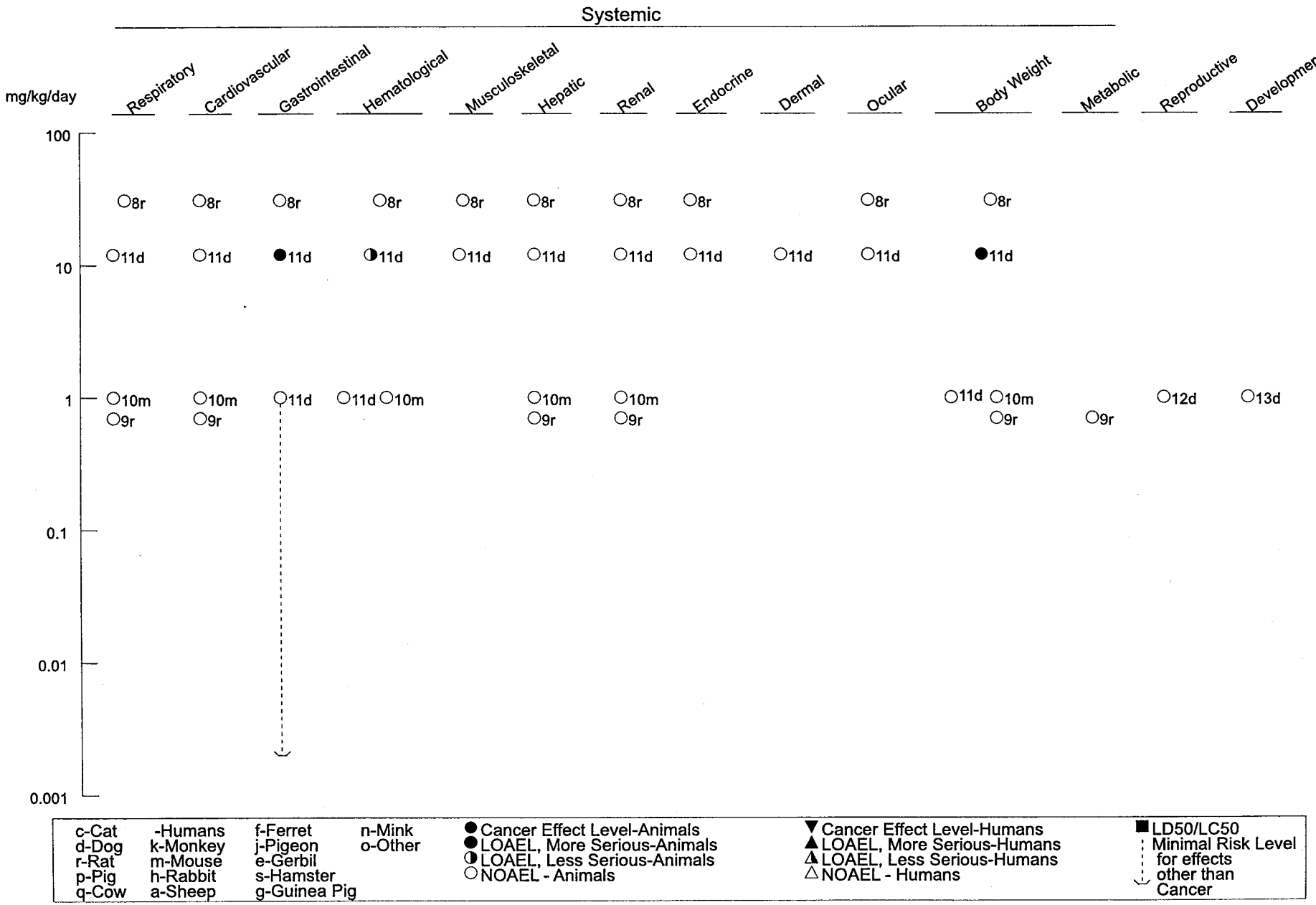


Figure 3-2. Levels of Significant Exposure to Beryllium - Oral (*Continued*)

Chronic (≥365 days)



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

Respiratory Effects. The respiratory system does not appear to be a target of oral exposure to beryllium or its compounds. Thickening of the alveolar epithelium with areas of necrosis was observed in rats maintained on diets containing beryllium nitrate that provided 2 mg beryllium/kg every 3 days for 40 days (Goel et al. 1980). However, since the beryllium nitrate was mixed with food pellets, it is possible that the lung effects resulted from aspiration of the beryllium nitrate particulates into the lungs during feeding.

No microscopic lung abnormalities were observed in dogs exposed to 12 mg beryllium/kg/day as beryllium sulfate in the diet for 143-172 weeks, respectively (Morgareidge et al. 1976) or in rats exposed to #31 mg beryllium/kg/day as beryllium sulfate in the diet for 2 years (Morgareidge et al. 1975). Furthermore, chronic exposure to 0.7 or 1 mg beryllium/kg/day as beryllium sulfate in the drinking water did not cause lung effects in rats and mice (Schroeder and Mitchener 1975a, 1975b).

Cardiovascular Effects. Data regarding cardiovascular effects in animals after oral exposure to beryllium or its compounds are limited. Dietary exposure to beryllium sulfate did not result in microscopic abnormalities in the heart or aorta of dogs exposed to 12 mg beryllium/kg/day for 143-172 weeks (Morgareidge et al. 1976) or rats exposed to #31 mg beryllium/kg/day for 2 years (Morgareidge et al. 1975). Histological examination revealed that chronic exposure to 0.7 or 1 mg beryllium/kg/day as beryllium sulfate in the drinking water did not cause cardiac effects in rats or mice (Schroeder and Mitchener 1975a, 1975b). The results from these studies suggest that oral exposure to beryllium is not likely to cause cardiac effects. However, other indices of cardiovascular effects, such as blood pressure determinations, were not examined.

Gastrointestinal Effects. In a chronic exposure study, extensive ulcerative and inflammatory lesions were observed in the small intestine, stomach, and large intestine of dogs exposed to 12 mg beryllium/kg/day as beryllium sulfate in the diet; similar, but less severe, lesions were observed in 1 of 10 dogs exposed to 1 mg beryllium/kg/day (Morgareidge et al. 1976). No lesions were observed in dogs exposed to 0.1 mg beryllium/kg/day. The dose-response data from this study were used to derive a chronic-duration MRL of 0.002 mg beryllium/kg/day. The only other study that examined gastrointestinal tract tissues was a chronic rat study conducted by the same group. No microscopic abnormalities of the

stomach, small intestine, or large intestine were observed in rats exposed to #31 mg beryllium/kg/day as beryllium sulfate in the diet for 2 years (Morgareidge et al. 1975).

Hematological Effects. Two studies examined hematological end points in animals after oral exposure to beryllium sulfate. Erythroid hypoplasia of the bone marrow and slight decreases in erythrocyte, hemoglobin, and hematocrit levels were observed in dogs exposed to 12 mg beryllium/kg/day; no effects were observed at 1 mg beryllium/kg/day (Morgareidge et al. 1976). It is likely that these effects were secondary to the severe gastrointestinal hemorrhages also observed in these animals rather than a direct effect on the hematological system. No evidence of microscopic abnormalities of the bone marrow or spleen was observed in rats exposed to #31 mg beryllium/kg/day for 2 years (Morgareidge et al. 1975).

Musculoskeletal Effects. Early studies indicate that rats fed large amounts of beryllium carbonate in the diet developed rickets. Rickets were observed in rats fed diets supplemented with 35–840 mg beryllium/kg/day as beryllium carbonate (Guyatt et al. 1933; Jacobson 1933; Kay and Skill 1934). The severity in the fragility of the bones increased with increasing concentrations of beryllium. These "beryllium rickets" are likely due to impaired gastrointestinal phosphate absorption rather than a direct effect of beryllium on bone. Following ingestion of beryllium carbonate, the beryllium in the gut binds to soluble phosphorus compounds and forms an insoluble beryllium phosphate; the rickets are a result of the decreased phosphorus levels. Although there are a number of methodological deficiencies in these studies, such as small numbers of animals per group and lack of statistical analysis, collectively, the studies suggest a relationship between beryllium carbonate ingestion and the occurrence of rickets. No bone effects were observed in dogs chronically exposed to 12 mg beryllium/kg/day as beryllium sulfate in the diet (Morgareidge et al. 1976). Chronic exposure to #31 or #12 mg beryllium/kg/day as beryllium sulfate did not cause morphological abnormalities in the muscle tissue of rats (Morgareidge et al. 1975) or dogs (Morgareidge et al. 1976), respectively.

Hepatic Effects. Oral exposure to beryllium compounds causes few effects, if any, on the liver of animals. Biochemical analysis of the lipid and protein contents of liver homogenates from rats exposed to 0.2 mg beryllium/kg/day as beryllium sulfate did not reveal any hepatic damage (Reeves 1965), however, histological examination was not performed.

Dogs fed 12 mg beryllium/kg/day as beryllium sulfate for 143-172 weeks (Morgareidge et al. 1976) and rats fed #31 mg beryllium/kg/day as beryllium sulfate for 2 years (Morgareidge et al. 1975) did not

develop morphological abnormalities of the liver or changes in liver weight. Rats given 0.7 mg beryllium/kg/day as beryllium sulfate in drinking water for 3.2 years had transient increases in serum cholesterol (Schroeder and Mitchener 1975a). Histological examination of the livers of the exposed rats did not provide evidence of morphological alterations. In mice exposed to beryllium sulfate via a similar regimen, no changes in serum cholesterol or morphological abnormalities were observed (Schroeder and Mitchener 1975b).

Renal Effects. Oral exposure to beryllium compounds causes few renal effects, if any, in animals. Histological examination of rats fed #31 mg beryllium/kg/day as beryllium sulfate for 2 years established no evidence of morphological damage to kidney tissue; however, kidney weight increased slightly (Morgareidge et al. 1975). No significant alterations in kidney weight or histological examinations were observed in dogs exposed to 12 mg beryllium/kg/day as beryllium sulfate in the diet for 143- 172 weeks (Morgareidge et al. 1976). Morphological alterations of the kidney were not observed in either sex of rats or mice exposed to 0.6–1 mg beryllium/kg/day as beryllium sulfate, respectively (Schroeder and Mitchener 1975a, 1975b). Female rats, however, developed a transient glucosuria (Schroeder and Mitchener 1975a).

Endocrine Effects. There is limited information on potential endocrine effects following oral exposure to beryllium. No adverse effects were observed in the adrenal, thyroid, pituitary, or pancreas of dogs exposed to 12 mg beryllium/kg/day as beryllium sulfate in the diet for 143-172 weeks (Morgareidge et al. 1976) or in rats exposed to #31 mg beryllium/kg/day as beryllium sulfate in the diet for 2 years (Morgareidge et al. 1975).

Dermal Effects. Information regarding dermal effects in animals after oral exposure to beryllium or compounds is limited. Histological examination of the skin of rats exposed to #31 mg beryllium/kg/day as beryllium sulfate in the diet for 2 years (Morgareidge et al. 1975) or in dogs exposed to 12 mg beryllium/kg/day as beryllium sulfate in the diet for 143-172 weeks (Morgareidge et al. 1976) did not indicate morphological changes.

Ocular Effects. Two studies examined the eyes of animals repeatedly exposed to beryllium sulfate in the diet. No ocular effects were observed in rats exposed to #31 mg beryllium/kg/day for 2 years (Morgareidge et al. 1975) or dogs exposed to 12 mg beryllium/kg/day for 143-172 weeks (Morgareidge et al. 1976).

Body Weight Effects. In general, exposure to beryllium sulfate in the diet or drinking water does not adversely affect body weight gain. Intermediate-duration exposure to high doses of beryllium carbonate in the diet (480 mg beryllium/kg/day) resulted in an 18% decrease in body weight gain in rats (Matsumoto et al. 1991). At lower doses (0.7 mg beryllium/kg/day), no body weight effects were observed (Freundt and Ibrahim 1990). Anorexia and weight loss was observed in dogs exposed to 12 mg beryllium/kg/day as beryllium sulfate in the diet; no effects on body weight gain were observed in dogs exposed to #1 mg beryllium/kg/day (Morgareidge et al. 1976). The weight loss observed at the highest dose was probably secondary to the ulcerative gastrointestinal lesions present in these animals. No alterations in weight gain were observed in rats (Morgareidge et al. 1975) chronically exposed via the diet to 31 mg beryllium/kg/day, or in rats (Schroeder and Mitchener 1975a) and mice (Schroeder and Mitchener 1975b) exposed via drinking water to 0.7 or 1 mg beryllium/kg/day, respectively.

Metabolic Effects. There are very limited data on metabolic effects in animals following oral exposure to beryllium or its compounds. Decreases in serum phosphate levels and alkaline phosphatase activity were observed in rats exposed to $70 mg beryllium/kg/day as beryllium carbonate in the diet (Kay and Skill 1934; Matsumoto et al. 1991). As discussed under Musculoskeletal Effects, it is likely that these effects are due to beryllium binding to soluble phosphorus compounds causing a decrease in phosphorus absorption.

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after oral exposure to beryllium or its compounds.

No histopathological lesions were observed in the spleen, lymph nodes, or thymus of rats chronically exposed to #31 mg beryllium/kg/day as beryllium sulfate in the diet (Morgareidge et al. 1975) or in dogs exposed to 12 mg beryllium/kg/day as beryllium sulfate in the diet for 143-172 weeks (Morgareidge et al. 1976). More sensitive tests of the immune function were not conducted.

3.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to beryllium or its compounds.

No changes in brain weight and no histopathological lesions were observed in the brain, nerve, or spinal cord of rats chronically exposed to #31 mg beryllium/kg/day as beryllium sulfate in the diet (Morgareidge et al. 1975) or in dogs exposed to 12 mg beryllium/kg/day as beryllium sulfate in the diet for 143-172 weeks (Morgareidge et al. 1976). This information is insufficient to conclude that beryllium does not cause neurological effects because more sensitive neurological or neurobehavioral tests were not performed.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to beryllium or its compounds.

There is limited information available on beryllium effect on reproduction. In a chronic duration dog study conducted by Morgareidge et al. (1976), male and female dogs were housed together at the time of the second heat, were allowed to mate and wean their pups; the study authors reported that there were no significant alterations in the number of pregnancies, number of pups, or number of live pups observed at doses of #1 mg beryllium/kg/day as beryllium sulfate in the diet. The result of this study should be interpreted with caution because very few study details were provided. Rats maintained for 2 years on diets containing beryllium sulfate had a significantly decreased average testes-to-body weight ratio at concentrations of 0.3 and 2.8 mg beryllium/kg/day, but not at #31 mg beryllium/kg/day (Morgareidge et al. 1975). Histological examination of the testes, prostate, seminal vesicles, and epididymis did not reveal any abnormalities. No decrease in ovary weight was observed in female rats similarly exposed. Furthermore, histological examination of the ovaries, uterus, and oviducts did not reveal any abnormalities (Morgareidge et al. 1975). The absence of further evidence of adverse effects of reproductive organs and of a positive dose relationship makes the toxicological significance of the decreased testes-to-body weight ratio unclear.

3.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to beryllium or its compounds.

There is limited information on beryllium's potential to induce developmental effects in animals following oral exposure. As discussed under Reproductive Effects, the Morgareidge et al. (1976) chronic dog study co-housed males and females, allowed them to mate, and wean their pups. Pups in the first litter were examined for gross and skeletal malformations. No significant alterations in the occurrence of gross or skeletal malformations, number of live pups, pup body weights, or pup survival were observed at 1 mg beryllium/kg/day; however, stillborn or cannibalized pups dying within the first few postnatal days were not examined.

3.2.2.7 Cancer

No studies were located regarding cancer in humans after oral exposure to beryllium or its compounds.

Beryllium has not been found to cause cancer in animals after oral exposure. This could be due to the poor absorption of beryllium compounds from the gastrointestinal tract. Nonsignificant increases in the number of lung reticulum cell carcinomas were observed in male rats exposed to 0.3 or 2.8 mg beryllium/kg/day as beryllium sulfate in the diet for 2 years; the incidences were 10/50, 17/50, 16/50, and 5/50 in males and 5/50, 7/50, 7/50, and 5/50 in females in the 0, 0.3, 2.8, and 31 mg beryllium/kg/day groups, respectively (Morgareidge et al. 1975). No differences in the number of reticulum cell carcinoma bearing rats were observed in the beryllium-exposed rats (18/50, 16/50, and 13/50 for males and 11/50, 7/50, and 8/50 for females in the 0.3, 2.8, and 31 mg beryllium/kg/day groups, respectively) compared to controls (12/50 and 8/50 for males and females, respectively). The incidence of tumors in rats or mice exposed chronically to 1 mg beryllium/kg/day as beryllium sulfate in the drinking water was not significantly altered, although the incidence of total tumors in treated male rats (9/33) was slightly increased, compared to controls (4/26) (Schroeder and Mitchener 1975a, 1975b). The incidence of neoplasms was not significantly increased in dogs exposed to 12 or 1 mg beryllium/kg/day as beryllium sulfate in the diet for 33 or 172 weeks, respectively (Morgareidge et al. 1976).

3.2.3 Dermal Exposure

3.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to beryllium or its compounds.

3.2.3.2 Systemic Effects

No studies were located regarding cardiovascular, gastrointestinal, musculoskeletal, hepatic, renal, endocrine, ocular, or body weight effects in humans or animals after dermal exposure to beryllium or its compounds.

Most of the available information on the systemic toxicity of beryllium following dermal exposure comes from a series of studies conducted by Marx and Burrell (1973). In these studies, guinea pigs were sensitized via 12 biweekly intradermal injections of beryllium sulfate and/or received a single intradermal injection of beryllium oxide or a single intradermal injection of beryllium oxide, beryllium sulfate, and beryllium fluoride. Another group of guinea pigs received two intraperitoneal injections of beryllium sulfate. The study authors note "a number of guinea pigs which were being sacrificed were examined for evidence of any systemic involvement of the disease state." No additional information was provided as to which group(s) of animals were examined; however, an assumption can be made that it was animals receiving intradermal doses. The observed effects are described below, but are not presented in the LSE table or figure.

Respiratory Effects. No studies were located regarding respiratory effects in humans after dermal exposure to beryllium or its compounds.

Several respiratory effects were described in the Marx and Burrell (1973) study; the observed effects included mild to moderate interstitial fibrosis of the alveolar wall, mild to moderate emphysema with dilatation of the respiratory bronchioles, hypertrophy of smooth muscle, and mucosal hypertrophy of the terminal bronchioles.

Hematological Effects. No studies were located regarding hematological effects in humans after dermal exposure to beryllium or its compounds.

Splenic effects were observed in the guinea pigs examined by Marx and Burrell (1973). The observed effects in the spleen included follicular hyperplasia and focal hematopoietic tissue hyperplasia and large deposits of hemosiderin in the medullary area.

Dermal Effects. Dermatological abnormalities due to beryllium exposure were reported in the case histories of 42 workers exposed to beryllium sulfate, beryllium fluoride, or beryllium oxyfluoride (VanOrdstrand et al. 1945). The dermatological manifestations were characterized as edematous, papulovesicular dermatitis. Ulceration occurred only after the skin was accidentally abraded. These ulcers began as small indurated papules surrounded by an area of erythema which later underwent necrosis. Conjunctivitis occurred only as a splash burn or in association with contact dermatitis of the face. Granuloma formation was reported in the case histories of 26 beryllium workers with skin lesions resulting from cuts and abrasions sustained at work (Williams et al. 1987). Skin biopsies of six workers showed that the granulomatous lesions of the skin contained beryllium. Eight other workers had skin lesions only. Twelve of the workers had nonspecific inflammation of the skin without granuloma (Williams et al. 1987). An allergic contact dermatitis can occur and is most frequently caused by beryllium fluoride (Curtis 1951) (see Section 3.2.3.3).

Delayed hypersensitivity reactions, as described under Immunological and Lymphoreticular Effects, were observed in beryllium-sensitized guinea pigs dermally exposed to beryllium sulfate, beryllium fluoride, beryllium oxide, or beryllium chloride (Belman 1969; Marx and Burrell 1973).

3.2.3.3 Immunological and Lymphoreticular Effects

Thirteen patients with dermatitis as a result of occupational dermal contact with beryllium fluoride, ground metallic beryllium, or water drippings from overhead pipes coated with dust of various compounds were evaluated with patch tests using different beryllium compounds to determine whether the dermatitis was due to an immune response (Curtis 1951). Positive patch tests were obtained in 5 of 13 patients challenged with 0.019 mg beryllium/mL as beryllium fluoride. The incidence and severity of positive reactions increased with increasing concentrations of test substance. The relative ability of the compounds to elicit reactions was as follows: beryllium fluoride > beryllium sulfate=beryllium chloride > beryllium nitrate.

Sensitization of guinea pigs with 12 biweekly intradermal injections of 0.0019 or 0.0005 mg beryllium as either beryllium fluoride or beryllium sulfate increased the amount of macrophage inhibition factor and lymphotoxin when the lymphocytes were cultured with beryllium salts (Marx and Burrell 1973). The sensitivity of the lymphocytes to beryllium salts, as noted by the increase in lymphokine levels, could be passively transferred from a sensitized donor to a naive recipient. Delayed hypersensitivity reactions also developed in guinea pigs tested with beryllium fluoride or beryllium chloride after dermal or intracutaneous sensitization with beryllium fluoride (Belman 1969) and in guinea pigs tested with beryllium sulfate or metallic beryllium after intradermal sensitization with beryllium sulfate (Zissu et al. 1996). The LOAEL values for immunological effects in each species and duration category are recorded in Table 3-3.

No studies were located regarding the following health effects in humans or animals after dermal exposure to beryllium or its compounds:

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

3.2.4 Other Routes of Exposure

Animal models of chronic beryllium disease have increased our understanding about the potential pathogenesis of chronic beryllium disease in humans. Hartley guinea pigs that were injected intratracheally with 16 mg beryllium/kg as beryllium oxide calcined at 560 EC developed slight edema and had focal interstitial lymphomononuclear infiltration at 1 week after injection (Barna et al. 1981). Granulomatous lesions were found at 2 weeks after injection and became progressively more severe at 4–6 weeks, with the level of severity persisting up to the end of the observation period (6 months). *In vitro* blood lymphocyte transformation tests in response to beryllium sulfate challenge were consistently positive with cells from beryllium oxide injected guinea pigs and consistently negative in cells from controls. Treatment of the guinea pigs with immunosuppressive agents (prednisone, L-asparaginase,

Table 3-3 Levels of Significant Exposure to Beryllium - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL		Reference Chemical Form
				Less Serious	Serious	
ACUTE EXPOSURE						
Immuno/ Lymphoret						
Human	48 hr			0.19 mg/ml	(allergic dermatitis)	Curtis 1951 BeSO4
Human	48 hr			0.19 mg/ml	(allergic dermatitis)	Curtis 1951 BeCl2
Human	48 hr			0.019 mg/ml	(allergic dermatitis)	Curtis 1951 BeF2
Human	48 hr			0.19 mg/ml	(allergic dermatitis)	Curtis 1951 Be(NO3)2
Gn Pig (albino)	1 x			0.1 M	(delayed type hypersensitive reaction)	Belman 1969 BeCl2
Gn Pig (albino)	1 x			0.02 M	(delayed type hypersensitive reaction)	Belman 1969 BeF2
Gn Pig (Hartley)	1 d			0.25 ug	(delayed hypersensitive reaction, splenic hyperplasia. lung inflammation)	Marx and Burrell 1973 BeSO4
Gn Pig (Dunkin Hartley)	24 hr			3 Percent (%)	(delayed type hypersensitivity)	Zissu et al. 1996 beryllium sulfate

Table 3-3 Levels of Significant Exposure to Beryllium - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL		Reference Chemical Form
				Less Serious	Serious	
INTERMEDIATE EXPOSURE						
Immuno/ Lymphoret						
Gn Pig (Hartley)	24 wk 1x/2wk			0.0005 ug	(increased macrophage inhibition factor and T-cell activity)	Marx and Burrell 1973 BeSO4

BeCl2 = beryllium chloride; BeF2 = beryllium fluoride; Be(NO3)3 = beryllium nitrate; BeSO4 = beryllium sulfate; Gn pig = guinea pig; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; wk = week(s); x = times

cytoxan) decreased the severity of beryllium oxide-induced lung disease. Pretreatment with beryllium sulfate prior to beryllium instillation delayed the development and reduced the severity of lung granuloma and also suppressed the delayed skin reactions to beryllium sulfate injected intradermally in guinea pigs intratracheally exposed to beryllium oxide. These experiments demonstrate that the development of granulomas in response to beryllium involves cell-mediated immune mechanisms. Similar studies with strain 2 and strain 13 guinea pigs demonstrated that strain 2 guinea pigs consistently developed chronic beryllium disease, while strain 13 guinea pigs did not, indicating that the immune mechanisms are genetically controlled in guinea pigs, and may explain the low prevalence of chronic beryllium disease in humans (Barna et al. 1981, 1984). In an attempt to develop a murine model for chronic beryllium disease, A/J (H-2^a haplotype) mice received intratracheal injections of beryllium sulfate or beryllium oxide calcined at 550 or 1,100 EC (Huang et al. 1992). In mice that received beryllium oxide, no histological differences or differences in bronchoalveolar lavage cells were found from the control mice until 8 months after instillation. At 8 months, there were moderate infiltrates and diverse microgranulomatous lesions, but these were apparently resolved at 10 months. The mice that received beryllium sulfate intratracheally were preimmunized with beryllium sulfate subcutaneously. Nonspecific inflammatory cells plus perivascular areas of lymphocytic infiltrates were seen at 2 weeks after beryllium sulfate instillation; numerous active areas containing macrophages, microgranulomas, and fibrosis were seen at 4 weeks; more severe granulomas and fibrosis were seen at 8 weeks, but at 20 weeks the lungs were generally normal. Results of tests on cells obtained by bronchoalveolar lavage showed increases in lymphocytes that corresponded with the time course of pathological changes. At 2 weeks, . 30% of the lymphocytes expressed the γ/σ T lymphocyte receptor. Most of the lymphocytes at 4 weeks were Thy1+, LdT4+ (CD4+), and expressed the α/β T lymphocyte receptor. Significant *in vitro* proliferation of bronchoalveolar lavage lymphocytes from preimmunized mice in response to beryllium sulfate was observed. During the acute phase (2 weeks), macrophage activation antigens were expressed, while at later times beyond the acute inflammatory phase, monocyte-macrophage antigens were expressed. Similar effects could not be induced in BALB/c (H-2_d haplotype) or C57BL/6 (H-2_b haplotype) mice, suggesting that genetic differences at the H-2 major histocompatibility complex gene complex may account for the differential responses to beryllium sulfate. Another cellular mechanism by which beryllium is thought to induce toxicity is by interaction with the cell lysosome (Witschi and Aldridge 1968). It has been postulated that beryllium destroys the integrity of the lysosomal membrane and releases lysosomal enzymes, which are injurious to the cell (Reeves and Preuss 1985).

3.3 GENOTOXICITY

Genotoxic Effects. No studies were located regarding genotoxicity in humans after inhalation, oral, or dermal exposure to beryllium or its compounds. CBA mice were exposed by gavage to 117 and 71 mg/kg as beryllium sulfate corresponding to 80 and 50% of the LD_{50} values, respectively (Ashby et al. 1990). The number of micronucleated polychromatic erythrocytes was not exceptional 24, 48, and 72 hours after dosing. *In vitro* studies are summarized in Table 3-4. The results of genotoxicity assays of soluble beryllium compounds are inconsistent; however, the carcinogenicity of beryllium is supported by the positive mutagenic potential reported in some of these studies. The inconsistencies may have been due to the physical/chemical properties of beryllium; in particular the binding of beryllium to phosphate, hydroxide, or proteins in the culture media. Beryllium nitrate was not mutagenic in the *Salmonella typhimurium* reverse mutation assay (Ames test) (Arlauskas et al. 1985). Beryllium sulfate was mutagenic in the forward mutation assay in *Bacillus subtilis* (Kanematsu et al. 1980) but was not mutagenic in the Ames test, regardless of the presence of microsomal fractions (Ashby et al. 1990; Rosenkranz and Poirier 1979; Simmon 1979b). Beryllium chloride was mutagenic in the reverse mutation assay in *Photobacterium fischeri* (Ulitzur and Barak 1988). Beryllium chloride was not mutagenic in the forward mutation assay with *Escherichia coli* (Zakour and Glickman 1984). Beryllium sulfate did not cause gene mutations in *Saccharomyces cerevisiae* (Simmon 1979b). Gene mutations were induced in whole mammalian cell cultures by the addition of either beryllium sulfate or beryllium chloride (Hsie et al. 1979; Miyaki et al. 1979). According to one study, beryllium sulfate induced chromosomal aberrations in mammalian cells (Larramendy et al. 1981); however, other studies indicate that beryllium sulfate did not induce chromosomal aberrations in cultured mammalian cells (Ashby et al. 1990; Brooks et al. 1989). Beryllium sulfate did not affect deoxyribonucleic acid (DNA)-repair in mammalian cells (Williams et al. 1989). Differences in the positive and negative results depend on the assay conditions, the concentrations of the beryllium compounds *in vitro*, and the differences among bacterial strains. Thus, soluble beryllium compounds appear to be weakly genotoxic.

Table 3-4. Genotoxicity of Beryllium and Its Compounds *In Vitro*

Species (test system)	End point	With activation	Without activation	Reference	Compound
Prokaryotic organisms:					
Salmonella typhimurium	Gene mutation	—	—	Arlaukas et al. 1985; Ashby et al. 1990; Rosenkranz and Poirer 1979; Simmon et al. 1979; Simmon 1979a	Beryllium sulfate
S. typhimurium	Gene mutation	No data	—	Arlauskas et al. 1985	Beryllium nitrate
Bacillus subtilis	Gene mutation	No data	+	Kanematsu et al. 1980	Beryllium sulfate
Escherichia coli	Gene mutation	No data	—	Zakour and Glickman 1984	Beryllium chloride
Photobacterium fischeri	Gene mutation	No data	+	Ulitzur and Barak 1988	Beryllium chloride
Eukaryotic organisms:					
Fungi:					
Saccharomyces cerevisiae	Gene mutation	No data	—	Simmon 1979b	Beryllium sulfate
Mammalian cells:					
Chinese hamster ovary K1-BH4 cell	Gene mutation	No data	+	Hsie et al. 1979	Beryllium sulfate
Chinese hamster ovary cell	Chromosomal aberration	No data	—	Brooks et al. 1989	Beryllium sulfate
Chinese hamster CHL cells	Chromosomal aberration	—	—	Ashby et al. 1990	Beryllium sulfate
Chinese hamster V79 cells	Gene mutation	No data	+	Miyaki et al. 1981	Beryllium chloride
Human lymphocytes	Chromosomal aberration	No data	+	Larramendy et al. 1981	Beryllium sulfate
Rat hepatocytes	DNA-repair	No data	—	Williams et al. 1989	Beryllium sulfate
Syrian hamster cells	Chromosomal aberration	No data	+	Larramendy et al. 1981	Beryllium sulfate

— = negative result; + = positive result; CHL = Chinese hamster lungs; DNA = deoxyribonucleic acid

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Beryllium compounds are absorbed primarily through the lungs, but sufficient information to determine the rate and extent of absorption was not located. Due to an accidental leakage of beryllium dust in a laboratory, 25 people were exposed to an undetermined concentration for 10–20 hours (Zorn et al. 1986). The day after exposure, serum beryllium levels were 3.5±0.47 ppb beryllium, compared to 1.0 ppb in unexposed controls. Six days later, the serum level decreased to 2.4±0.3 ppb beryllium, and 2–8 weeks after exposure the serum levels returned to normal. The biological half-time of beryllium was calculated to be 2–8 weeks. In eight men accidently exposed to .8 ng beryllium/m^3 as beryllium chloride for 4–6 hours/day for 10 days, the beryllium levels in urine and blood increased 4-fold above the levels of .1 ng beryllium/g of either blood or urine in unexposed individuals (Stiefel et al. 1980).

Rats exposed to 0.034 mg beryllium/m^3 as an aerosol of beryllium sulfate 7 hours/day, 5 days/week for 72 weeks achieved steady state concentrations in the lungs in .36 weeks of exposure (Reeves and Vorwald 1967). The beryllium concentration in tracheobronchial lymph nodes peaked between 36 and 52 weeks, and decreased thereafter. In guinea pigs and rats exposed to 2–40 mg beryllium/m^3 as beryllium nitrate for 16 hours, steady-state concentrations in the blood were reached after 8–12 hours of exposure (Stiefel et al. 1980).

3.4.1.2 Oral Exposure

No studies were located regarding absorption in humans after oral exposure to beryllium or its compounds.

Beryllium and its compounds are poorly absorbed from the gastrointestinal tract in animals. Urinary excretion data from rats treated by gavage with radioactive beryllium chloride indicate that the cumulative excretion of beryllium in the urine and feces was 0.11 and 104.7% of the total dose, respectively (Furchner et al. 1973). In mice, dogs, and monkeys similarly exposed, the urinary output was 0.24, 0.38, and 3.71% of the total dose, respectively, while most of the radiolabel was excreted in the feces. Therefore, although intestinal absorption of beryllium varies somewhat among species, beryllium was

poorly absorbed in these animals. Mice exposed to radioactive beryllium retained beryllium in the gastrointestinal tract (LeFevre and Joel 1986). The amount found in the tissues other than intestinal was <0.1%.

Urinary excretion accounted for #0.5% of the total dose of beryllium sulfate administered to rats as 0.019 and 0.190 mg beryllium/kg/day in drinking water for 24 weeks (Reeves 1965). The percent absorption, determined as the percentage of the dose that could be recovered from the total body load and excreta, was #0.9% in the 0.019 mg beryllium/kg/day group and #0.2% in the 0.190 mg beryllium/kg/day group. Rats exposed to #31 mg beryllium/kg/day as beryllium sulfate in drinking water for 2 years excreted very little beryllium via the urine (Morgareidge et al. 1975). Oral absorption of beryllium and its compounds may be reduced by the formation of beryllium phosphate precipitates in the alkaline environment of the intestine (Reeves 1965).

3.4.1.3 Dermal Exposure

It is unlikely that beryllium is absorbed through intact skin. Skin ulceration in workers exposed to beryllium occurred only after the skin was accidentally cut or abraded (Williams et al. 1987).

Only small amounts of beryllium were absorbed through the tail skin of rats after exposure to an aqueous solution of beryllium chloride (Petzow and Zorn 1974). Beryllium has been demonstrated to bind to alkaline phosphatase and nucleic acids in guinea pig epidermis *in vitro* (Belman 1969). This binding could account for the inefficient transfer of beryllium from the epidemis to the blood.

3.4.2 Distribution

Average concentrations of beryllium were measured in human organs as follows: 0.21 ppm in lungs; 0.08 ppm in brain; 0.07 ppm in both the kidney and spleen; 0.04 ppm in each of liver, muscle, and vertebrae; 0.03 ppm in heart; and 0.02 in bone (Meehan and Smythe 1967). Further information regarding the nature of exposure (e.g., environmental or occupational) or the source of the organ samples (e.g., autopsy or biopsy) was not provided. A study by Krachler et al. (1999a) provides evidence that beryllium is transferred across the placenta and excreted via breast milk. The levels of beryllium in umblical cord serum and in colostrum were higher than in maternal serum.

3.4.2.1 Inhalation Exposure

In eight men exposed to . 8 ng beryllium/m^3, 4–6 hours/day for 10 days due to an accidental leak of beryllium chloride, 60–70% of the beryllium found in the blood was bound to two classes of serum proteins, prealbumins and γ-globulins (Stiefel et al. 1980).

Beryllium is widely distributed to the organs of animals, as a result of pulmonary absorption. Immediately after rats were exposed to radioactive beryllium (beryllium sulfate and beryllium chloride) for 3 hours, the percentage of total body radioactivity in tissues was 60% in lungs, 0.9% in the liver, 1.5% in the kidney, 0.1% in the spleen, 0.4% in the heart, 1.4% in the brain, 9.5% in the muscle, 13.5% in the skeleton, 5.0% in the blood, and 10% in the excreta (Zorn et al. 1977). After 408 hours, the liver, spleen, heart, brain, and muscle had concentrations <0.0005%; concentrations in the kidneys, skeleton, blood, and excreta were 0.0005, 6.8, 0.05, and 92.0%, respectively. The beryllium concentrations in the bone increased until 96 hours after exposure and then decreased. Dogs exposed to beryllium oxide calcined at 500EC had higher beryllium concentrations in the extrapulmonary tissue, principally the liver and skeleton, than dogs exposed to beryllium oxide calcined at 1,000 EC, due to the greater solubility of the 500 EC calcined product (Finch et al. 1990). The translocation of beryllium to the tracheobronchial lymph nodes increased and by day 64 accounted for a higher concentration than found in the lung. Beryllium was also detected in the liver, skeleton, and blood.

Distribution studies in rats and guinea pigs exposed to 2–40 mg beryllium/m^3 as beryllium nitrate for 16 hours report that 60–70% of the beryllium in the blood was bound to prealbumins and γ-globulins (Stiefel et al. 1980). Rats and hamsters exposed to beryllium oxide did not have detectable beryllium concentrations in the liver, skeleton, or urine 7 days after exposure (Rhoads and Sanders 1985; Sanders et al. 1975). At 63 days after exposure, 1.7% of the initial alveolar deposit was present in the pulmonary lymph nodes in rats. Exposure to 0.04 mg beryllium/m^3 as beryllium sulfate for 90–100 days resulted in the following concentrations (in μg beryllium/g fresh tissue) of beryllium in rabbits: 1.6 in the lungs, 0.02 in the femur, 0.01 in the spleen, 0.004 in the liver, and 0.003 in the kidney (Stokinger et al. 1950). Dogs similarly exposed had the highest concentrations in the pulmonary lymph node (0.7), followed by lung (0.6), femur (0.03), spleen (0.01), liver (0.01), and kidney (0.003). In monkeys, the pulmonary lymph nodes (1.3) also had the highest concentrations followed by lung (1.2), spleen (0.5), femur (0.1), and kidney (0.01). In cats, the concentrations of beryllium from greatest to least were lung (0.08), femur (0.03), liver (0.02), spleen (0.01), and kidney (0.01). In rats, hamsters, and monkeys exposed to 0.21 or 0.62 mg beryllium/m^3 as bertrandite or beryl ore, concentrations were highest in the lung followed by

bone or liver, and kidney (Wagner et al. 1969). The greater degree of distribution of beryllium sulfate, compared with beryllium oxide or the ores, reflects its greater solubility and absorption rate.

3.4.2.2 Oral Exposure

No studies were located regarding distribution in humans after oral exposure of beryllium or its compounds.

Beryllium is poorly absorbed from the gastrointestinal tract in animals; however, that which is absorbed is distributed to the organs and tissues. Beryllium was found in the liver, large intestine, small intestine, kidneys, lungs, stomach, and spleen in hamsters given beryllium sulfate, beryllium oxide, or beryllium metal in the diet for 3–12 months (Watanabe et al. 1985). In mice given a radioactive dose of beryllium chloride by gavage, the accumulation of radioactivity was greatest in the liver followed by the kidney, mesenteric lymph nodes, lungs, blood, and carcass, 3 hours after exposure (LeFevre and Joel 1986). The pattern of beryllium distribution to tissues and organs in rats given beryllium sulfate indicated that as the exposure duration increases, accumulation levels also increase (Reeves 1965). In tissue, beryllium concentrations were highest in the gastrointestinal tract (with contents), followed by bone, blood, and liver. Other studies indicate that in animals, high levels of beryllium accumulate in bone tissue as a result of oral exposure to the chemical or its compounds. In rats treated by gavage with radioactive beryllium chloride, the greatest accumulation (other than that in the gastrointestinal tract) was detected in the bone, followed by viscera, pelt, and muscle (Furchner et al. 1973). Beryllium accumulation in the bones of rats exposed for 2 years to dietary concentrations of the chemical was proportional to the administered dose (Morgareidge et al. 1975).

3.4.2.3 Dermal Exposure

No studies were located regarding distribution in humans or animals after dermal exposure to beryllium or its compounds. The lack of data is expected because beryllium is poorly absorbed after dermal exposure (see Section 3.4.1.3).

3.4.2.4 Other Routes of Exposure

In rats receiving a single intravenous injection of radiolabelled beryllium sulfate, circulating beryllium was found almost exclusively in the plasma (Vacher and Stoner 1968). Two fractions of plasma

beryllium were identified. The smaller fraction was presumably bound to plasma organic acids. In the larger fraction, the beryllium sulfate was converted to beryllium phosphate, which formed aggregates associated with plasma globulins, presumably α-globulin. The size of the aggregates appeared to increase with increasing beryllium sulfate doses.

3.4.3 Metabolism

Beryllium and its compounds are not biotransformed, but soluble beryllium salts are partially converted to less soluble forms in the lung (Reeves and Vorwald 1967).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

In eight men accidentally exposed to .8 ng beryllium/m^3 as beryllium chloride 4–6 hours/day for 10 days, urinary levels were four times higher than the average levels of .1.0 ng beryllium/g in unexposed individuals (Stiefel et al. 1980). Accidental exposure of 25 individuals to beryllium dust for 10–20 hours increased serum levels to 3.5 ppb beryllium 1 day after exposure, compared to .1 ppb for unexposed individuals (Zorn et al. 1986). Serum levels returned to normal 2–8 weeks after exposure. The biological half-life was estimated to range from 2 to 8 weeks.

Beryllium oxide deposited in the lungs of rats was cleared in a biphasic manner (Rhoads and Sanders 1985). In the first phase, 30% of the total lung burden was cleared; the half-life was 2.5 days. In the second phase, the remaining 70% of the beryllium in the lung was cleared with a half-life of 833 days. The whole body clearance yielded a single-phase exponential curve with a half-life of 356 days. Rats exposed to beryllium oxide were able to clear 12 and 21% (female and male, respectively) of the alveolar lung burden within 63 days of exposure (Sanders et al. 1975). Hamsters, however, cleared 38 and 45% (female and male, respectively) of the beryllium in the alveoli. The study indicates that male rats are better able to clear beryllium particles from the lungs than female rats are. The biological half-life for beryllium oxide in the rat lung was estimated to be .6 months. Approximately 95% of the beryllium was excreted through the feces. Rats and guinea pigs exposed to 2–40 mg beryllium/m^3 as beryllium nitrate for 16 hours had increased concentrations of urinary beryllium (300 ng beryllium/g), compared to normal concentrations (2.1 ng beryllium/g) (Stiefel et al. 1980). Rats exposed to radioactive beryllium compounds excreted 92% of the dose in 408 hours (Zorn et al. 1977). In dogs exposed only via nose to

10 mg beryllium/m^3 as beryllium oxide calcined at 500 or 1,000 EC (the solubility of beryllium oxide decreases as the temperature at which it is calcined increases) for sufficient durations to result in low (. 5 µg beryllium/kg) initial lung burdens and high (36–64 µg beryllium/kg) initial lung burdens, there were no differences in whole-body retention with regard to initial lung burdens (Finch et al. 1990). Whole-body clearance after exposure to beryllium oxide calcined at 500 EC was described by a two-component, negative exponential function. The short-term component accounted for 59% of the initial lung burden and had a half-life of 54 days. The long-term component accounted for 41% of the initial lung burden and had a half-life of >1,000 days. The long-term component may have represented beryllium that dissolved from beryllium oxide particles and bound to extrapulmonary compartments, such as, bone and liver. Whole-body clearance after exposure to beryllium oxide calcined at 1,000 EC was described by a single-component negative exponential function with a half-life of 310 days. Clearance from the lung was more rapid and greater amounts were translocated to the liver, blood, and skeleton in the dogs exposed to beryllium calcined at the lower temperature than in dogs exposed to beryllium calcined at the higher temperature. However, lung clearance of both was described by a single-component negative exponential function. Clearance half-lives were 64 days for 500 EC calcined beryllium oxide and 240 days for 1,000 EC calcined beryllium oxide. Fecal excretion predominated at early times after exposure to either beryllium oxide aerosols, and at all times for 1,000 EC calcined beryllium oxide. Dogs exposed to beryllium oxide calcined at 500 EC excreted a significantly ($p<0.05$) greater total percentage of the initial lung burden of beryllium than dogs exposed to beryllium calcined at the higher temperature by 180 days. Thus, beryllium oxide calcined at 500 EC was cleared more rapidly than beryllium oxide calcined at 1,000 EC. This is consistent with the fact that more soluble beryllium compounds are cleared faster than relatively insoluble beryllium compounds because the solubility of beryllium oxide decreases as the temperature at which it is calcined increases. Although clearance of beryllium oxide calcined at the lower temperature was relatively fast during the first few days after exposure due to mucociliary clearance, later clearance may result from slow translocation of tracheobronchial lymph nodes, macrophage clearance from the pulmonary to the tracheal regions, and pulmonary solubilization of beryllium followed by mobilization through blood to liver and bone or excretion in urine. Beryllium decreased the clearance rate of radioactive plutonium oxide from the lungs of rats 60 and 90 days after exposure to beryllium oxide (Sanders et al. 1975). Inhalation exposure to beryllium may decrease the overall rate of lung clearance by damaging alveolar macrophages.

3.4.4.2 Oral Exposure

No studies were located regarding excretion in humans after oral exposure to beryllium or its compounds.

Animals exposed to oral doses of beryllium or its compounds excrete the greatest percentage of the dose via the feces, which indicates that beryllium is poorly absorbed by the gastrointestinal tract. Analysis of the excreta of rats exposed to 0.019 and 0.190 mg beryllium/kg/day as beryllium sulfate in the drinking water indicated that $99% of the dose was excreted in the feces and <0.5% was excreted in the urine (Reeves 1965). The excretion pattern of beryllium in the feces reached steady-state after 9 weeks (Reeves 1965). Similarly, excretion of beryllium occurred mainly via the feces of rats exposed to 0.3, 2.8, and 31 mg beryllium/kg/day as beryllium sulfate in the diet for 2 years (Morgareidge et al. 1975). The feces contained 10.7 ppm and the urine 29.7 ppb of the 0.3 mg beryllium/kg/day dose, and a similar pattern was observed with the other doses. Rats, monkeys, mice, and dogs orally exposed to radioactive beryllium chloride excreted 98% of the dose via the feces (Furchner et al. 1973).

3.4.4.3 Dermal Exposure

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

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

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

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al.

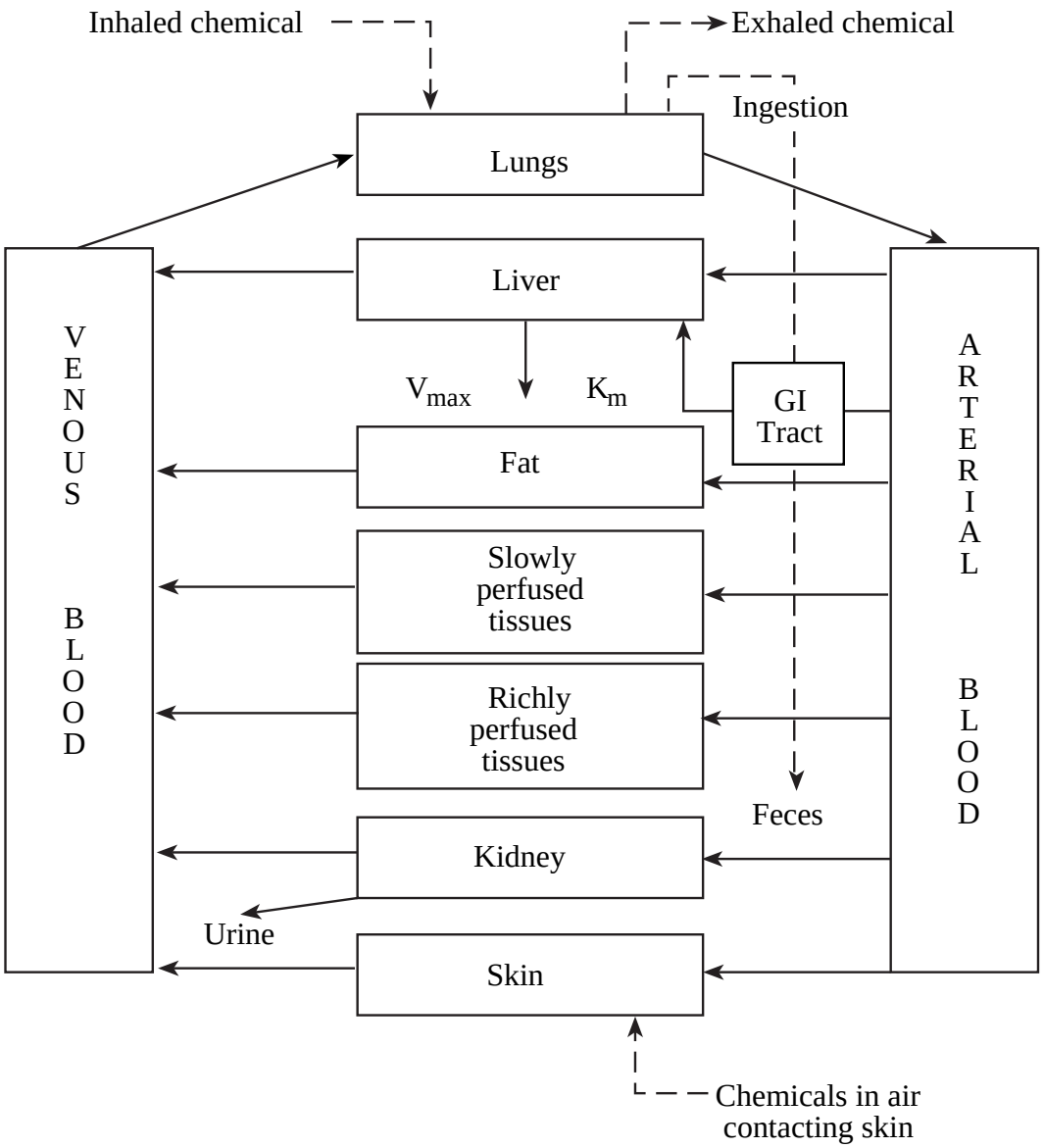
1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

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

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

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

Figure 3-3. 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 or by exhalation.

No PBPK modeling studies were located for beryllium.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

The absorption of inhaled beryllium depends on a number of factors, including physical and chemical properties of the particles (e.g., size, solubility) and the activity of alveolar macrophages. Following deposition, beryllium is slowly cleared from the lung; clearance half-lives range from days to years in animals. Beryllium clearance from the lungs is biphasic, the initial phase is rapid and involves clearance via the mucociliary escalator. Approximately 30% of the total lung burden was cleared during the first phase with a half-life of 2.5 days (Rhoads and Sanders 1985). The second phase is slower, involving translocation to the tracheobronchial lymph nodes, alveolar macrophage clearance, and solubilization. The half-life for this phase was 833 days (Rhoads and Sanders 1985). Beryllium is poorly absorbed through the gastrointestinal tract; <1% of the dose is absorbed (Furchner et al. 1973; Reeves 1965). It is also poorly absorbed through intact skin (Petzow and Zorn 1974; Williams et al. 1987).

Absorbed beryllium is distributed throughout the body via blood, with the highest concentrations in the liver and skeleton (Finch et al. 1990; Furchner et al. 1973; Morgareidge et al. 1975; Stokinger et al. 1950). Beryllium has been detected in breast milk (Krachler et al. 1999a), but the relationship between beryllium exposure and breast milk levels has not been established.

The primary routes of elimination of absorbed beryllium is urine and feces. In rats and dogs, whole body clearance of inhaled beryllium follows a single-phase exponential curve with a half-life of 300–400 days (Finch et al. 1990; Rhoads and Sanders 1985).

3.5.2 Mechanisms of Toxicity

The respiratory tract is the primary target of beryllium toxicity following inhalation exposure. In humans, chronic beryllium disease and lung cancer are the principal effects observed. In animals, the respiratory tract effects include emphysema, pneumonitis, and lung cancer. Chronic beryllium disease begins as a sensitizing cell-mediated response to beryllium antigen that progresses to noncaseating granulomatous lung disease. Although the mechanism has not been fully elucidated, a number of recent studies using bronchoalveolar lavage (BAL) fluid from individuals with chronic beryllium disease provide information

on some of the components of the toxic sequence. Beryllium, acting as a hapten, interacts with antigen presenting cells in the lungs (i.e., alveolar macrophages) resulting in a beryllium-peptide becoming physically associated with a major histocompatability (MHC) class II molecule (Newman 1996b; Saltini et al. 1989). The MHC class II-beryllium-peptide complex is recognized by the T lymphocyte receptor, with the help of $CD4^+$ molecules. This interaction triggers $CD4^+$ T lymphocyte activation and proliferation. There is evidence to suggest that there is a selective expansion of certain $CD4^+$ lymphocyte subsets. In a study by Fontenot et al. (1998), a number of individuals with chronic beryllium disease had an increase in the percentage of T cell receptor (TCR) variable β3 regions (Vβ3). Further work by this group showed that in four of five individuals with chronic beryllium disease, expansions within the Vβ3 region resulted in homologous or identical CDR3 amino acid sequences (Fontenot et al. 1999). The expansion of the CDR3 motif appeared to be unique to chronic beryllium disease.

The antigen-specific inflammatory response to beryllium is a cell-mediated process orchestrated by cytokines. The results of several studies support the role of cytokines in chronic beryllium disease. Using alveolar macrophages present in BAL fluid from individuals with chronic beryllium disease, Bost et al. (1994) found elevated mRNA levels for tumor necrosis factor α (TNF-α) and interleukin (IL)-6 cytokines, as compared to levels in normal subjects. Additionally, TNF-α levels in the BAL fluid were higher. Another study found that the addition of beryllium to a culture of BAL cells from chronic beryllium disease patients, resulted in increases in the TNF-α, IL-6, IL-2, and interferon-gamma (IFN-γ) (Tinkle et al. 1996). Although for many inflammatory diseases IL-10 inhibits antigen-induced T lymphocyte proliferation, it does not play a role in chronic beryllium disease (Tinkle et al. 1996a). In chronic beryllium disease, as in other delayed-type hypersensitivity diseases, IL-2 plays an important role in the T lymphocyte proliferation and the regulation of IFN-γ (Tinkle et al. 1997). BAL cells from control subjects did not show any measurable spontaneous or beryllium sulfate-stimulated release of IL-2, α-sIL-2R (α subunit of the soluble IL-2 receptor), IL-4, or IFN-γ. Beryllium sulfate stimulation of BAL cells from chronic beryllium disease subjects resulted in the production of IL-2, α-sIL-2R, and IFN-γ, but not IL-4. In the absence of beryllium sulfate stimulation, the response was the same as in controls. Although IL-2 has a dose-dependent role in T lymphocyte proliferation, T lymphocyte proliferation is only partially dependent on it. Beryllium sulfate stimulated T lymphocyte proliferation remained elevated in the presence of anti-IL-2 antibodies. INF-γ levels were also decreased in the presence of anti-IL-2 antibodies suggesting that it is also partially dependent on IL-2.

There appears to be a genetic factor associated with susceptibility to chronic beryllium disease. The MHC class II molecules play a critical role in the T lymphocyte proliferation and the development of

chronic beryllium disease; thus, MHC class II genes (human leukocyte antigen, HLA-DR, DQ, DP) probably play a role in susceptibility to the disease. Analysis of the MHC class II genes shows a biased usage of the HLA-DPB1 gene alleles in individuals with chronic beryllium disease (Richeldi et al. 1993, 1997; Wang et al. 1999). Genetic susceptibility to chronic beryllium disease is discussed in greater detail in Section 3.10.

3.5.3 Animal-to-Human Extrapolations

As reviewed in EPA (1998) and Finch et al. (1996), a number of animal models of human chronic beryllium disease have been developed, but none of the models to date mimic all aspects of the human disease. Numerous studies in dogs, monkeys, and rats have reported granulomatous inflammation in the lungs. However, the lung lesions do not histopathologically resemble chronic beryllium disease in humans, the effects are transient, or are not consistently associated with beryllium-specific immune responses. Recent studies in mice (Huang et al. 1992; Nikula et al. 1997) suggest that mice may be an appropriate model. In the model developed by Huang et al. (1992), mice were preimmunized with beryllium sulfate and then administered a single intratracheal dose of beryllium sulfate. A number of aspects of this model mimicked chronic beryllium disease, influx of $CD4^+$ T lymphocytes in to the lungs, sensitization of T lymphocytes to beryllium, interstitial inflammation, and granuloma formation. However, these effects were observed at 8 months and were resolved by 10 months. The study by Nikula et al. (1997), in which mice received a 90-minute nose-only exposure to beryllium metal, also found many similarities between effects observed in mice and human chronic beryllium disease. The study authors concluded that this mouse model can be used to study the influence of dose, exposure pattern, and physicochemical form of beryllium on the development of chronic beryllium disease. A comparison of the histologic characteristics of beryllium-induced disease in humans and mice is presented in Table 3-5.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate

Table 3-5. Histologic Characteristics of Beryllium-induced Disease in Mice and Humans[a]

Histologic findings	Mice	Humans
Interstitial cellular infiltration of macrophages, lymphocytes, and variable numbers of plasma cells	Mild to moderate	Moderate to marked
Granulomas	Present; poorly formed	Variable; absent to poorly formed to well formed
Giant cells	Numbers variable; may be scattered or associated with granulomas	Numbers variable; may be scattered or associated with granulomas
Cholesterol clefts	Numerous and often seen within giant cells	Numerous and often seen within giant cells
Interstitial fibrosis	Present in 75% of cases; minimal to mild	Present in large percentage of cases; minimal to mild in 50% and moderate to marked in 50%
Calcific inclusions	Absent	Present in approximately 55% of cases
Hyalinzed nodules	Absent	Present in lung or hilar lymph nodes of 40% of cases
Interstitial compact aggregates of lymphocytes	Present	Not described
Beryllium	Metal evident in H&E sections	Increased tissue levels found by spectrographic and chemical analysis

[a]Taken from Nikula et al. (1997)

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

There are no data to assess whether exposure to beryllium will adversely affect the endocrine system.

3.7 CHILDREN'S SUSCEPTIBILITY

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

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

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

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their

alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Data on the toxicity of beryllium in children is limited to a case report of a child diagnosed with chronic beryllium disease (Eisenbud et al. 1948b). The child lived near a beryllium manufacturing facility. The only available studies on young animals are the beryllium carbonate dietary studies that found beryllium rickets in young rats (Guyatt et al. 1933; Jacobson 1933; Kay and Skill 1934). The observed skeletal effects are not due to a direct effect of beryllium on the bone, but rather an interaction between beryllium carbonate and dietary phosphorus. The potential of beryllium to induce developmental effects has not been adequately investigated. A chronic study did not find developmental effects (gross and skeletal malformations, fetal survival, and fetal body weights were examined) in dogs exposed to beryllium sulfate in the diet (Morgareidge et al. 1976). However, intratracheal and intravenous exposure studies have found increases in fetal/neonatal mortality, internal abnormalities, and behavioral abnormalities in rat and mouse offsprings (Bencko et al. 1979; Mathur et al. 1987; Selivanova and Savinova 1986; Tsujii and Hoshishima 1979). More details about these studies can be found in Chapter 2 and Section 3.2.2.6.

No human or animal data were located that examined possible age-related differences in the toxicokinetics of beryllium. There are no data on the toxicokinetic properties of beryllium in children or immature animals. The results of a study by Krachler et al. (1999a) suggests that beryllium is transferred across the placenta and via maternal milk. Beryllium levels in the umbilical cord sera and in colostrum were higher than maternal sera levels.

Subsequent sections of this chapter (Sections 3.8, 3.10, and 3.11) discuss the available information on biomarkers, interactions, and methods for reducing toxic effects. The available information is from adults and mature animals; no child-specific information was identified. It is likely that this information will also be applicable to children.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic

substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to beryllium are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by beryllium are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10 “Populations That Are Unusually Susceptible”.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Beryllium

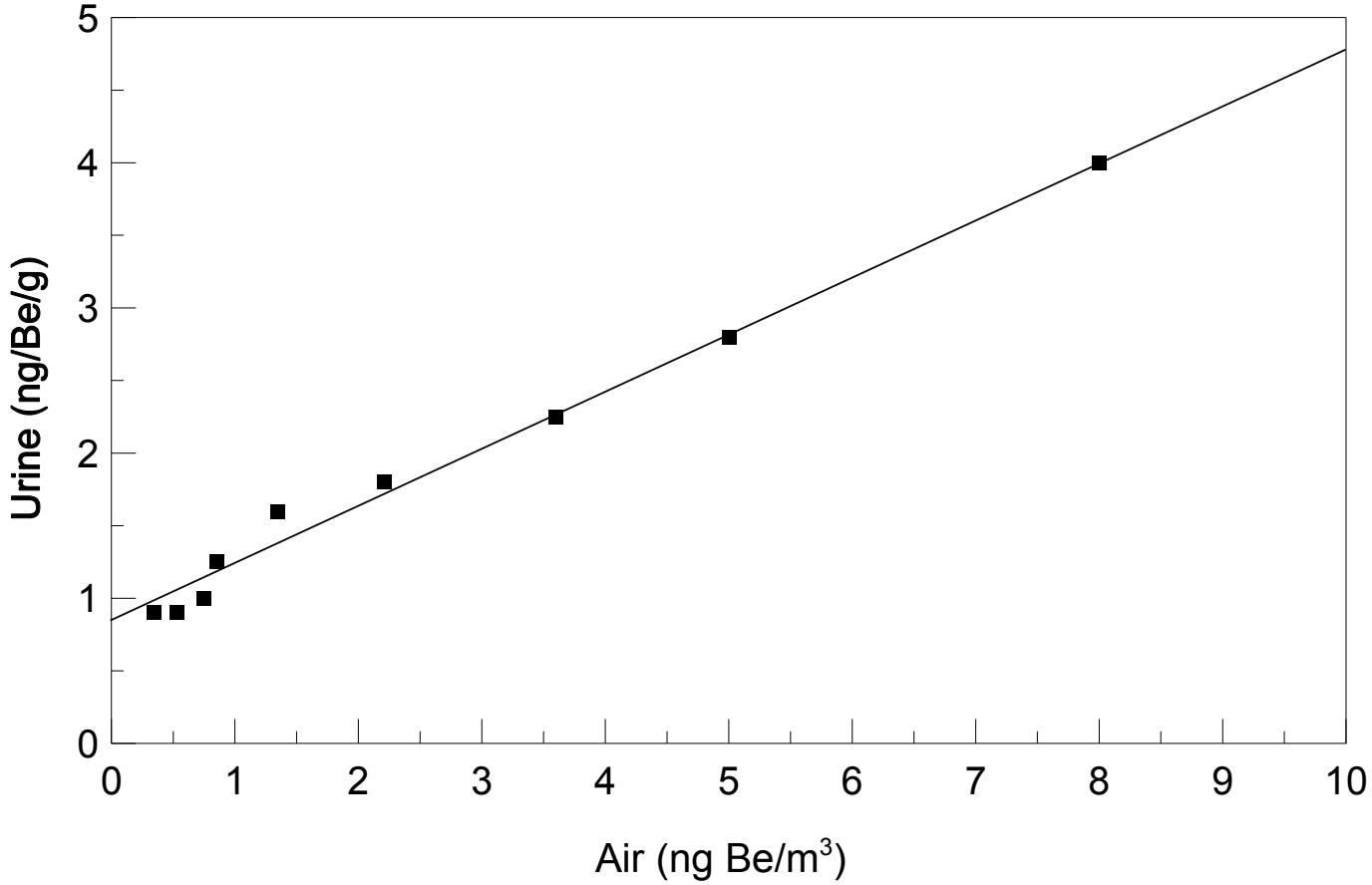
There are several tests for measuring beryllium in biological fluids and tissues (Frame and Ford 1974; Foreman et al. 1970; Hurlburt 1978; IARC 1980; Martinsen and Thomassen 1986; Paschal and Bailey 1986; Shan et al. 1989). These include measurement of beryllium levels in the blood and urine. Information regarding normal background levels of beryllium and tissue levels associated with exposure

levels are limited or unreliable. Normal background levels of 1 ng beryllium/g (1 ppb) for blood (Stiefel et al. 1980; Zorn et al. 1986), 0.28–1 µg/L for urine (Paschal et al. 1998; Stiefel et al. 1980), and of 0.02 µg beryllium/g (0.02 ppm) for lung tissue (Kanarak et al. 1973) have been reported. Average beryllium levels in human tissues have been measured as follows: 0.21 ppm in lungs; 0.08 ppm in brain; 0.07 ppm in both kidney and spleen; 0.04 in each of liver, muscle, and vertebrae; 0.03 ppm in heart; and 0.02 in bone (Meehan and Smythe 1967). However, it was not clear whether these organ samples were obtained at biopsy or autopsy or whether the subjects had been exposed occupationally or environmentally in the compilation by Meehan and Smythe (1967).

Background urinary levels of beryllium were determined to be . 1.0 µg beryllium /L using flameless atomic absorption spectroscopy (Stiefel et al. 1980). Beryllium levels in urine were analyzed in eight laboratory workers and compared to the levels of beryllium in the laboratory atmosphere for 30 days after an accidental leakage of beryllium chloride. Figure 3-4 represents urinary levels versus atmospheric levels. The urinary levels appear to be directly proportional to atmospheric levels at #8 ng/m^3. Based on serum levels of beryllium in workers accidentally exposed, the biological half-life was estimated to be 2–8 weeks (Zorn et al. 1986). These are the only available data that associate airborne beryllium levels with urinary levels in humans. A sampling of 500 urine samples collected during the NHANES III study, suggested that background levels of beryllium in the urine may be lower; the mean urinary level was 0.28 µg beryllium/L (Paschal et al. 1998). Nonetheless, urinary excretion of beryllium is irregular and not useful for diagnostic purposes (Reeves 1986).

Biopsy tissue has been analyzed to determine beryllium concentrations in the body. Lung tissue of two employees of a beryllium extraction and processing plant, where beryllium concentrations exceeded the recommended standards of 2 µg beryllium/m^3 for an 8-hour day and 25 µg beryllium/m^3 for a 30-minute

Figure 3-4. Relationship Between Urine Level of Beryllium and Air Concentration*



*Source: Stiefel et al. 1980

maximum level, contained 0.18 and 0.65 µg beryllium/g dry weight compared to the normal level of 0.02 µg beryllium/g (Kanarek et al. 1973). The subject with the higher beryllium level did not have lung lesions; however, the subject with the lower beryllium level had granulomas. Thus, beryllium levels in lung biopsies indicate exposure to beryllium but may not confirm the presence of chronic beryllium disease. The presence of beryllium in lung tissue also will not indicate how recently the exposure occurred because the clearance of beryllium from the lungs depends upon the solubility of the beryllium compound (see Section 3.3.4.1). Biomarkers of oral or dermal exposure to beryllium were not located, probably because very little beryllium is absorbed after exposure by these routes (see Section 3.4.1).

3.8.2 Biomarkers Used to Characterize Effects Caused by Beryllium

The lung is the most sensitive target organ of beryllium exposure. As a consequence of long term exposure to beryllium, lung function decreases. This decrease has been measured by spirometry, such as forced expiratory volume in 1 second, maximum breathing capacity, maximum mid-expiratory flow, and vital capacity (Andrews et al. 1969; Kriebel et al. 1988a, 1988b). Blood gases such as carbon dioxide tension, oxygen tension, alveolar oxygen tension, alveolar carbon dioxide tension, and carbon monoxide diffusion capacity have also been analyzed.

Radiographic examinations revealed opacities in the lung following chronic exposure to beryllium (Kanarek et al. 1973). X-rays have been used to determine three stages of chronic beryllium poisoning: a fine diffuse granularity in the lungs, followed by a diffuse reticular pattern, followed by the appearance of distinct nodules. However, x-ray results cannot distinguish between chronic beryllium disease and sarcoidosis. A patch test using soluble beryllium salts was evaluated in 32 patients with known chronic beryllium disease (Curtis 1959). The patch test was positive in all 32 patients and negative in 16 of 18 patients with lung diseases other than chronic beryllium disease, indicating that the patch test may be useful in the diagnosis of chronic beryllium disease. However, the patch test using soluble beryllium compounds itself may be sensitizing and may exacerbate the condition in patients with chronic beryllium disease (Cotes et al. 1983; Epstein 1983; Stoeckle et al. 1969; Tepper 1972). Therefore, this method is not recommended as a diagnostic tool. Analysis of secretions and cells of the lower respiratory tract obtained by bronchoalveolar lavage is useful for detecting granulomatous lung disease; however, it alone cannot distinguish chronic beryllium disease from sarcoidosis (James and Williams 1985). The presence of beryllium in the bronchoalveolar fluid, however, would aid the diagnosis.

Because chronic beryllium disease is caused by an immune reaction to beryllium, several tests have been developed to assess beryllium hypersensitivity. The most commonly used test is the beryllium lymphocyte proliferation test (BeLPT). This test, originally referred to as the lymphocyte blast transformation test (LTT or LBTT), measures cell proliferation via thymidine incorporation in cultured cells in the presence or absence of beryllium salts. Both peripheral blood cells and bronchioalveolar lavage cells can be used in the BeLPT. In early studies, abnormal blood BeLPT results were found in 100% of the subjects with chronic beryllium disease (Williams and Williams 1982, 1983), normal results in all individuals who were suspected of having chronic beryllium disease (Williams and Williams 1983), and abnormal results in approximately 2% of the healthy beryllium workers (Williams and Williams 1983). Despite these results, the blood BeLPT test was not widely used because it was very difficult to perform and not very reproducible. Refinement of the test methodology resulted in a more reproducible test that could be used as a screening tool (Newman 1996a). A number of large-scale screening studies have utilized this test for identifying beryllium sensitized workers (Kreiss et al. 1993a, 1996, 1997; Newman et al. 2001; Stange et al. 2001). In these studies, the majority (53–86%) of the workers with consistently abnormal blood BeLPT results were also diagnosed as having chronic beryllium disease. Using the blood BeLPT to screen workers for beryllium sensitization and chronic beryllium disease is not foolproof; Kreiss et al. (1993a, 1996) found a small percentage of workers with chronic beryllium disease and normal or inconsistent blood BeLPT results. Deubner et al. (2001a) assessed the predictive value of the blood BeLPT as a screening tool for chronic beryllium disease among 129 beryllium workers. The incidences of chronic beryllium disease among workers with a single unconfirmed abnormal blood BeLPT result, workers with confirmed abnormal blood BeLPT results, and workers with first-time double abnormal blood BeLPT results were 7/19 (37%), 34/75 (45%), and 17/35 (49%), respectively. One limitation of the blood BeLPT is high inter- and intra-laboratory variability. Using split blood samples, Stange et al. (1996b) found an 85–96% agreement rate among three laboratories; however, the agreement rate was only 21–33% for positive blood BeLPT results. Similarly, Deubner et al. (2001a) found poor to moderate agreement in blood BeLPT results among three laboratories.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Mortality rates were lower if rats exposed to 2.59 mg beryllium/m^3 as beryllium sulfate were injected daily with ferric ammonium citrate beginning 4 days prior to beryllium exposure (Sendelbach and Witschi 1987a). The protective action of ferric ammonium citrate may be related to the ability of beryllium to form a complex with citrate (Reeves 1986). In addition, the protective action of iron on beryllium toxicity may be related to the ability of iron to increase ferritin synthesis, making more ferritin

available to bind with beryllium (Lindenschmidt et al. 1986). Ferritin chelates with beryllium to protect against the inhibition of phosphoglucomutase (Joshi et al. 1984).

Ingested soluble beryllium compounds may interact with phosphate to form insoluble beryllium phosphate particles that are sequestered in Kupffer cells of the liver (Tepper 1972). Diffusion of beryllium from the deposited particulates may cause damage to these cells and necrosis of the liver.

Intravenous injection of rats or mice with the ammonium salt of aurine tricarboxylic acid increased the survival of both species that were injected intravenously with lethal doses of beryllium sulfate (White et al. 1951). The protective effect was observed when the aurine tricarboxylic acid was administered from 1 hour before to 8 hours after injection of beryllium sulfate. The protective effect was attributed to the ability of aurine tricarboxylic acid to complex with the beryllium ion, thereby reducing the amount of beryllium ion available to induce tissue injury.

Co-exposure of Chinese hamster ovary cells to beryllium sulfate and x-rays resulted in an increased rate of chromatid-type exchanges compared to the rates resulting from exposure to beryllium sulfate or x-rays alone (Brooks et al. 1989). The increase was multiplicative rather than additive. Experiments on cell cycle kinetics suggested that the multiplicative interaction occurs only in cells in the S and G_2 stages.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

There are strong data to suggest that there is genetic susceptibility factor that may predispose certain individuals to development of chronic beryllium disease. A human leukocyte antigen (HLA) class II marker has been strongly associated with chronic beryllium disease. Studies conducted by Fontenot et al. (2000) and Lombardi et al. (2001) suggest that the HLA-DP allele, in particular alleles with HLA-DP containing Glu at DP69, are involved in the presentation of beryllium to CD^{4+} T cells, which are involved in the pathogenesis of chronic beryllium disease. Richeldi et al. (1993) found a higher frequency of

allelic variants of the HLA-DP gene coding for a glutamate in position 69 of HLA-DPB1 chain (HLA-DPB1 Glu^{69}) among individuals with chronic beryllium disease than in beryllium-exposed individuals without the disease. The HLA-DPB1 Glu^{69} DNA marker was found in 5 of 6 beryllium workers with chronic beryllium disease, 0 of 2 beryllium-sensitized individuals without disease and 36 of 119 (30%) unsensitized beryllium-exposed individuals (Richeldi et al. 1997).

Further analysis by Wang et al. (1999) found the Glu^{69} marker on the HLA-DBP1 gene was not very predictive of chronic beryllium disease (predictive value of 0.36). However, the presence of the relatively rare HLA-DP allele, HLA-non*0201 DPB1 Glu^{69}, had a predictive value of 0.57. Wang et al. (1999) also found a higher percentage of homozygous Glu^{69} carriers in the chronic beryllium disease group as compared to controls. The study authors estimated that carriers of the Glu^{69}/Glu^{69} markers or non-*0201Glu^{69} allele accounted for 85% of the chronic beryllium disease cases and only 16% of unaffected beryllium-exposed individuals. Additional studies by this group found that most beryllium sensitized individuals without chronic beryllium disease also carried rare HLA-non*0201 Glu^{69} DPB1 alleles (Wang et al. 2001).

Stubbs et al. (1996) also found allelic differences in the DR isotype of class II HLAs. The HLA-DRB1 alleles associated with beryllium sensitization were *0103, *09, *1302, *0403, and *0302. It is likely that chronic beryllium disease is a multigenetic disease with a number of genetic factors contributing to the development of an immune response to beryllium.

A case control study by Maier et al. (1999) was designed to assess whether polymorphisms in the angiotensin converting enzyme (ACE) were associated with chronic beryllium disease and chronic beryllium disease severity. No statistically significant associations between ACE genotype and chronic beryllium disease were found in the comparisons of individuals with chronic beryllium disease to beryllium-exposed controls or nonberyllium exposed controls.

Animal data support the human data that genetically determined cellular immune mechanisms may be involved in chronic beryllium disease, as indicated by studies in different strains of guinea pigs and mice. Intratracheal instillation of beryllium oxide (calcined at 560 EC) resulted in the development of granulomatous lung disease in outbred Hartley and in strain 2 guinea pigs, but not in strain 13 guinea pigs (Barna et al. 1981; 1984). Granulomatous lung disease also was produced in the F_1 offspring of mated strain 2 and strain 13 guinea pigs, but the severity was milder in the hybrid strain than in the strain 2 guinea pigs (Barna et al. 1984). In addition, when guinea pigs exposed intradermally or intratracheally

to beryllium oxide were challenged by dermally applied beryllium sulfate, the strain 2 and the F_1 guinea pigs showed positive skin tests for delayed-type hypersensitivity, while strain 13 guinea pigs did not. Granulomatous lung disease was also induced in strain A/J (H-2_a haplotype) mice, but not in BALB/c (H-2_d haplotype) or C57BL/6 (H-2_b haplotype) mice, after intratracheal injection of beryllium sulfate, suggesting that genetic differences at the H-2 major histocompatibility gene complex may account for the differential responses to beryllium sulfate in mice (Huang et al. 1992). These results suggest that genetically determined factors may make some humans more susceptible to chronic beryllium disease.

Animal data indicate that females may be more susceptible than males to the effects of beryllium. Female rats exposed to 0.034 mg beryllium/m^3 as beryllium sulfate for 72 weeks had higher mortality rates and more severe weight loss than males (Reeves et al. 1967). Female rats exposed to #31 mg beryllium/kg/day as beryllium sulfate in the diet for 2 years developed a transient glucosuria; renal effects were not observed in males (Morgareidge et al. 1975). The distribution of beryllium in body tissue in female (bred and nonbred) and male rats exposed intratracheally to 0.6 mg beryllium/kg as radioactive beryllium oxide revealed the highest concentrations (other than in the lung) in the liver of female rats and in the kidney of male rats (Clary et al. 1975). This corroborates the findings of Clary et al. (1972) which suggest that translocation of beryllium from bone to liver eventually causes a systemic disease characterized by weight loss and liver necrosis. The study involves intratracheal exposure of guinea pigs and mice to radioactive beryllium oxide after hormone biosynthesis is inhibited by metyrapone injection. The results indicate that altered adrenal hormone synthesis shifts beryllium concentrations from bone to liver, causing weight loss. Therefore, any adverse effect on the adrenal gland may profoundly affect the course of beryllium disease, and a combination of adrenal dysfunction and compromised liver function could exacerbate beryllium disease. Therefore, people with lowered adrenal and/or liver functionality may be unusually susceptible to the effects of beryllium.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

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

Ellenhorn MJ, Schonwald S, Ordog G, et al., eds. 1997. Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning. Second Edition. Baltimore, MD: Williams & Wilkins, 1546-1548.

Haddad LM, Shannon MW, Winchester JF, eds. 1998. Clinical Management of Poisoning and Drug Overdose. Third Edition. Philadelphia, PA: WB Saunders, 792.

3.11.1 Reducing Peak Absorption Following Exposure

Human exposure to beryllium and its compounds occurs by inhalation, ingestion, or dermal contact. The inhalation route is of greatest concern for systemic effects because beryllium and its compounds are poorly absorbed after ingestion and dermal contact. General recommendations for reducing absorption of beryllium following acute exposure have included removing the individual from the contaminated area and removing contaminated clothing. Although beryllium is poorly absorbed from the gastrointestinal tract, administration of milk or water has been suggested to reduce the possibility of stomach irritation (HSDB 2000). Chronic granulomas observed following dermal exposure are surgically removed (HSDB 2000). Thorough washing of the skin or eyes is indicated in the case of dermal or ocular exposure, especially to irritating beryllium compounds, such as beryllium fluoride.

3.11.2 Reducing Body Burden

Beryllium is widely but slowly distributed following inhalation exposure. The highest concentration of beryllium was found in bone (13.5%) of rats following 3 hours of exposure to beryllium sulfate or beryllium chloride (Zorn et al. 1977). The percentage of beryllium in the bone was still high (6.8%) compared with other tissues following 408 hours of exposure. After inhalation exposure, beryllium that is not absorbed into the bloodstream is retained in the lung (see Section 3.4.4.1). Insoluble beryllium compounds, such as beryllium oxide, are retained in the lungs longer than soluble compounds and are associated with chronic beryllium disease. Although beryllium compounds are poorly absorbed from the gastrointestinal tract (see Section 3.4.1.2), the portion that is absorbed appears to preferentially accumulate in bone (Furchner et al. 1973; Morgareidge et al. 1975; Reeves 1965). In addition, relatively high levels of beryllium accumulated in the spleen and liver of rats after intravenous injection of beryllium sulfate (Lindenschmidt et al. 1986).

A series of studies by Mathur and associates have examined the effectiveness of several agents in reducing beryllium body burden following parenteral exposure (no additional information on exposure route was provided). Decreases in blood, liver, kidney, and/or spleen beryllium levels were observed in rats administered a single or repeated doses of beryllium followed by a 2- to 10-day exposure to Liv-52,

an alternative medicine (Mathur et al. 1994) or 5 days of N-(2-hydroxyethyl)ethylene diamine triacetic acid (HEDTA) (Mathur et al. 1993), calcium disodium ethylenediamine tetraacetic acid (CaNa-EDTA) (Mathur et al. 1993), 4,5-dihydroxy-1,3-benzene disulfonic acid (tiron) (Shukula et al. 1998) *meso*-2,3-dimercaptosuccinic acid (DMSA) (Flora et al. 1995), or 2,3-dimercaptopropane 1-sulfonate (DMPS) (Flora et al. 1995), but not after calcium trisodium diethylene triamine pentaacetic acid (CaNA-DTPA) (Mathur et al. 1993) or succinic acid (Shukula et al. 1998). For absorbed beryllium, administration of chelating agents such as aurine tricarboxylic acid increases the urinary excretion of beryllium in animals (Venugopal and Luckey 1978). However, metal chelating agents available for use in human clinical medicine have not been shown to be effective in reducing the toxicity of beryllium (Hall and Rumack 1992). Since chronic berylliosis is associated with the retention of unabsorbed beryllium compounds in the lungs, enhancing the clearance of beryllium from the lungs, perhaps by bronchoalveolar lavage, might prevent or reduce the severity of chronic beryllium disease. However, at this time there are no established methods for reducing the lung burden.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

As discussed in Section 3.9, pretreatment of rats with ferric ammonium citrate reduces mortality rates following inhalation exposure to beryllium (Sendelbach and Witschi 1978a). This protective effect has been attributed to sequestering of beryllium either through formation of a beryllium-citrate complex (Reeves 1986), or by induced ferritin (Lindenschmidt et al. 1986). Aurine tricarboxylic acid may reduce mortality by a similar mechanism (White et al. 1951). Neither of these treatments has undergone clinical trial in humans.

Parenteral administration of beryllium nitrate results in decreased hemoglobin, blood glucose, and serum protein levels, decreased serum alkaline phosphatase levels, increased serum transaminase activities, and degeneration and necrosis in the liver, kidney, and spleen. Administration of Liv-52, HEDTA, CaNa-EDTA, tiron or DMPS resulted in an improvement of these effects (Flora et al. 1995; Mathur et al. 1993, 1994; Shukula et al. 1998). The effectiveness of these treatments at lower body burdens or in humans is not known. As discussed in Section 3.2.1.2, the respiratory tract can be severely affected by inhalation of dust containing beryllium compounds. Inhalation exposure to high concentrations of soluble beryllium compounds may lead to acute chemical pneumonitis. Prolonged inhalation of low concentrations of less soluble forms are more often associated with chronic beryllium disease. Chronic beryllium disease may involve the induction of hyperplasia and hypertrophy of histiocytes (Policard 1950). Mitogenic effects may be the result of interactions of beryllium ions with lymphocyte membranes

(Price and Skilleter 1985, 1986). Hypersensitivity may be due to the formation of a beryllium-protein complex that is antigenic. Beryllium stimulates a population of CD4+ T cells, and this reaction can be blocked by antibodies to HLA Class II molecules and by antibodies to the IL-2 receptor (Saltini et al. 1989). In some cases, the manifestations of chronic beryllium disease may be reversed by corticosteroid therapy (Aronchick et al. 1987; Finkel 1983; Hardy and Stoeckle 1959). Although corticosteroids are used to control the clinical manifestations of chronic beryllium disease and to prevent further progression of the disease, steroid therapy is not without its own risks.

Ingested soluble beryllium compounds may interact with phosphate to form insoluble beryllium phosphate particles that are sequestered in Kupffer cells of the liver (Tepper 1972). Diffusion of beryllium from the deposited particulates may cause damage to these cells and necrosis of the liver. Beryllium may also be taken up by lysosomes and cause release of lysomal enzymes, and beryllium may interfere with DNA synthesis in the nucleus.

It has been established that beryllium inhibits DNA synthesis (Witschi 1968, 1970). Magnesium failed to influence the inhibitory effect of beryllium, although it had been shown that magnesium partly neutralizes the toxic effects of beryllium on fibroblasts or yeast cells (Lieben et al. 1964; Wainer 1972).

Because of the variety of effects noted for beryllium and possible mechanisms of action for those effects, it is difficult to speculate regarding therapies that will interfere with specific mechanisms of action such that net toxic effects are reduced. Given the variety of effects possible for absorbed beryllium, the most effective strategy for reducing toxic effects may be to reduce the amount of free beryllium ion through sequestering or complexing reactions as discussed in Section 3.11.2.

3.12 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of beryllium 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 beryllium.

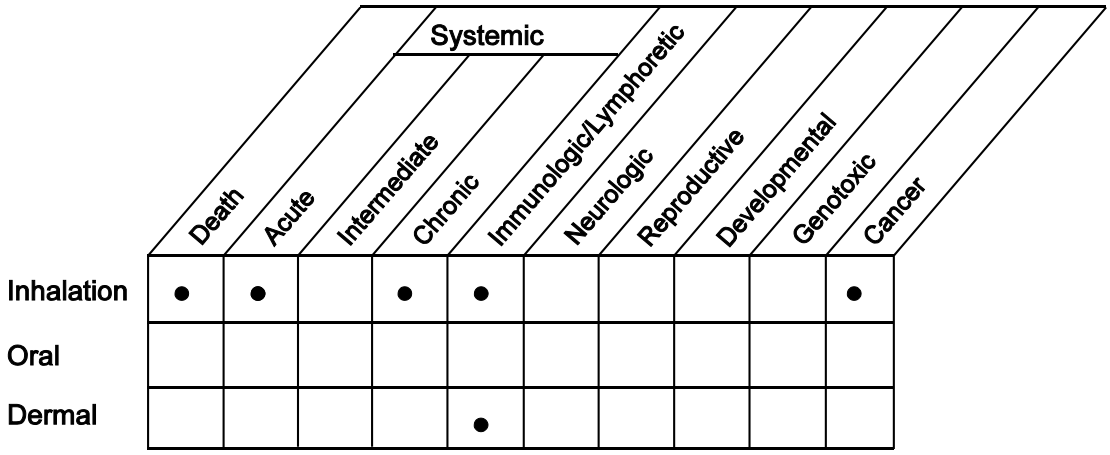
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of Beryllium

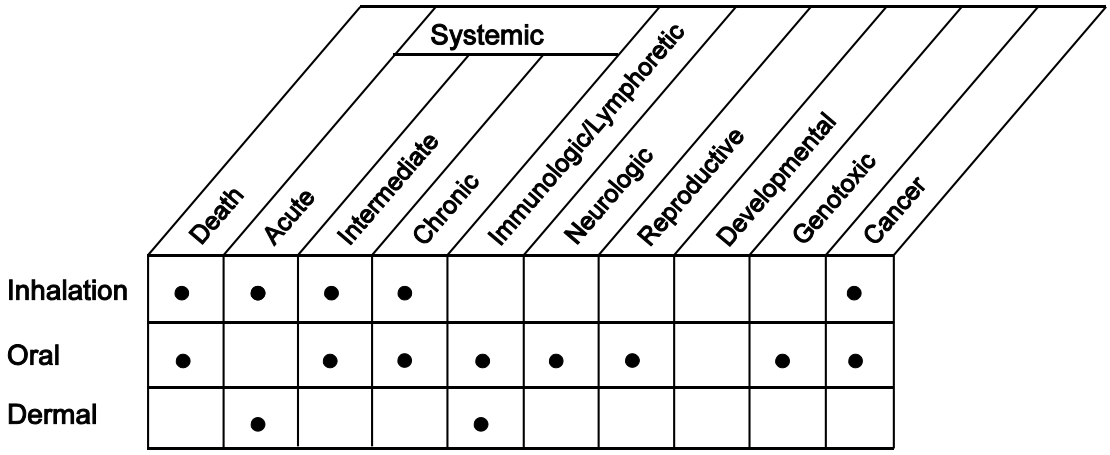
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to beryllium are summarized in Figure 3-5. The purpose of this figure is to illustrate the existing information concerning the health effects of beryllium. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Studies regarding adverse health effects in humans after exposure to beryllium or its compounds are limited (Figure 3-5). No studies were located regarding neurological, developmental, reproductive, or genotoxic effects in humans following inhalation exposure to beryllium or its compounds. Studies regarding death were limited to chronic inhalation exposure. An accidental leakage of beryllium did not cause respiratory, hepatic, or immunological effects. Most of the human data concerns respiratory effects

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



Human



Animal

● Existing Studies

and lung cancer as a result of occupational exposure to beryllium or its compounds. Immunological data indicate that beryllium induces a T-cell lymphocyte-mediated immune response in the lung and skin. No studies were located regarding any effects in humans following oral exposure to beryllium. Since beryllium is poorly absorbed through the gastrointestinal wall, effects from this route of exposure are unlikely. For dermal exposure, only skin effects (ulcerations) were reported.

The database for animals is more complete. LC_{50} values have been reported for a number of beryllium compounds. Systemic effects of acute, intermediate, and chronic exposure via inhalation include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular effects. Immunological and carcinogenic effects were observed in various species after inhalation exposure to beryllium. No studies were located regarding neurological, developmental, reproductive, or genotoxic effects in animals after inhalation exposure to beryllium or its compounds. Oral LD_{50} values were reported for many of the beryllium compounds. No other oral exposure studies were located regarding acute effects in animals exposed to beryllium or its compounds. Immunological, neurological, reproductive, genotoxic, and carcinogenic effects due to ingestion of beryllium are reported in the available literature.

No dermal studies were located regarding death, neurological, developmental, reproductive, genotoxic, or carcinogenic effects in animals. Acute dermal studies report dermatological effects of beryllium on sensitized animals. Since beryllium is a T-cell activator, exposure can cause immunological effects on the skin.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. The lung is the main target organ of inhaled beryllium and its compounds in humans (Eisenbud et al. 1948a; Van Ordstrand et al. 1945) and animals (Haley et al. 1989; Hart et al. 1984; Robinson et al. 1968; Sanders et al. 1975; Schepers 1964; Sendebach and Witschi 1987b; Sendebach et al. 1980, 1989); however, the heart, liver, kidney, adrenal (Schepers 1965), skin (Stiefel et al. 1980), and the hematopoietic tissue (Hall et al. 1950) in animals have also been identified as target organs of beryllium exposure. The effects of occupational exposure to beryllium or its compounds include acute pneumonitis as a result of inhalation exposure to more soluble beryllium compounds or chronic beryllium disease as a result of inhalation of soluble and less soluble beryllium compounds (e.g., beryllium oxide) (Cullen et al. 1987; Eisenbud and Lisson 1983; Eisenbud et al. 1948a; Rossman et al. 1988). Because an animal model that mimics all aspects of chronic beryllium disease has not been

identified, it is inappropriate to use animal data to derive an acute-duration inhalation MRL. No human acute-duration studies were identified; thus, an acute-duration inhalation MRL was not identified. No data were located regarding effects in humans after acute oral exposure to beryllium. No acute oral MRL can be derived because the only acute oral data in animals involves lethality (Ashby et al. 1990; Kimmerie 1966; Lanchow University 1978; Venugopal and Luckey 1977). The target organs of acute oral exposure of animals to low levels of beryllium are not known, but beryllium compounds are poorly absorbed from the gastrointestinal tract (Furchner et al. 1973; Le Fevre and Joel 1986; Morgareidge et al. 1975; Reeves 1965). In humans and animals sensitized to beryllium, contact with beryllium and its soluble and insoluble compounds can cause dermatitis and skin granulomas (Belman 1969; Curtis 1951; Marx and Burrell 1973; Williams et al. 1987). In general, the more soluble the compound the greater the sensitizing potential. Dermal effects usually occur on abraded skin. Dermal absorption of beryllium is assumed to be poor and would not likely cause further systemic effects. Dermal studies would be helpful to determine the amount and duration of exposure necessary for human sensitization. Additional human exposure studies that examine the potential of beryllium to cause beryllium sensitization and chronic beryllium disease after a <2 weeks of exposure would be useful for establishing an acute-duration inhalation MRL. The information regarding beryllium toxicity is useful to the general population and to populations residing at or near hazardous waste sites, who might be subject to acute exposure.

Intermediate-Duration Exposure. No studies were located regarding effects in humans after intermediate-duration inhalation exposure to beryllium or its compounds. The available occupational exposure studies provide sufficient evidence that beryllium sensitization and chronic beryllium disease would be the most sensitive end points following intermediate-duration inhalation exposure to beryllium; however, no intermediate-duration studies were identified. Several studies indicate that the lung is the main target organ in animals for intermediate exposure to soluble and insoluble beryllium compounds via inhalation (Hall et al. 1950; Schepers 1964; Schepers et al. 1957; Stokinger et al. 1950; Wagner et al. 1969). Other target organs in animals include the heart, liver, kidney, skin, and hematopoietic tissue (Hall et al. 1950; Stiefel et al. 1980; Stokinger et al. 1950). Derivation of an intermediate-duration inhalation MRL is precluded because there are no human intermediate-duration studies and an animal model that mimics all aspects of chronic beryllium disease has not been identified, thus making it inappropriate to derive an MRL from animal data. There are limited data on the toxicity of ingested beryllium following intermediate-duration exposure. The available animal data suggest that rickets is a critical end point following ingestion of beryllium carbonate (Guyatt et al. 1933; Jacobson 1933; Kay and Skill 1934). The rickets do not appear to be due to a direct effect of beryllium on the bone. Rather, the rickets are due to a phosphorus deficiency, which results from the binding of beryllium to dietary phosphorus in the gut.

Thus, the available data are insufficient for derivation of an intermediate-duration oral MRL. Additional studies involving exposure to low concentrations of several beryllium compounds would be useful for identifying critical targets of toxicity and establishing dose-response relationships. According to one study, guinea pigs were sensitized to beryllium via intradermal administration of beryllium compounds, with the sensitizing potential increasing with increasing solubility (Marx and Burrell 1973).

Chronic-Duration Exposure and Cancer. Health effects in humans and animals after chronic exposure to beryllium and its compounds are reported in the available literature. The lung is the main target organ in human (Andrews et al. 1969; Cullen et al. 1987; Eisenbud and Lisson 1983; Hardy and Tabershaw 1946; Kreiss et al. 1993a, 1996, 1997; Rossman et al. 1988; Stange et al. 1996b) and animals (Reeves et al. 1967; Vorwald and Reeves 1959; Wagner et al. 1969) after inhalation exposure to beryllium and its compounds. Occupational exposure to soluble and insoluble beryllium compounds caused delayed granulomatous disease of the lung, known as chronic beryllium disease or berylliosis (Cotes et al. 1983; Cullen et al. 1987; Eisenbud and Lisson 1983; Eisenbud et al. 1949; Kreiss et al. 1993a, 1996, 1997; Stange et al. 1996b). Acute lung inflammation was also observed after occupational exposure to soluble beryllium compounds (Eisenbud et al. 1948a). These serious respiratory effects in humans were found even at the lowest occupational exposure concentrations, which were lower than concentrations used in chronic inhalation experiments in animals. Therefore, NOAELs for respiratory effects due to occupational exposure or chronic inhalation exposure in animals have not been determined. An environmental exposure study did identify a NOAEL for chronic beryllium disease (Eisenbud et al. 1949); however, technology available at the time of the study did not allow for the detection of beryllium sensitization or subclinical chronic beryllium disease and it is not known if the identified NOAEL would be protective for these effects. Hence, derivation of a chronic inhalation MRL is precluded. Data were not located regarding effects in humans after chronic oral exposure to beryllium. The results of a chronic dog study suggests that the gastrointestinal tract is a target of beryllium sulfate toxicity (Morgareidge et al. 1976). This study is the basis for a chronic-duration oral MRL for beryllium. The MRL was derived using a benchmark dose approach and the dose-response data for small intestinal lesions in dogs (Morgareidge et al. 1976). Data regarding the effects of chronic dermal exposure to beryllium were limited to findings of dermatitis in occupationally exposed individuals (Curtis 1951; Van Ordstrand et al. 1946; Williams et al. 1987). Studies regarding inhalation and dermal exposure to low concentrations of beryllium for chronic durations would be useful for determining the respective NOAELs for respiratory and dermal effects. Studies in dogs exposed to beryllium oxide by inhalation (Finch et al. 1990) and in guinea pigs (Barna et al. 1981, 1984) and in mice (Huang et al. 1992) exposed to beryllium oxide intratracheally have been performed to identify an appropriate model to elucidate the pathogenesis of

chronic beryllium disease in humans. However, an animal model that exactly mimics chronic beryllium disease in humans has not been found. Further inhalation studies conducted in several species of animals designed to identify the most appropriate animal model that mimics chronic beryllium disease in humans would be useful to for determining mechanisms for induction and treatment of chronic beryllium disease. This work is in progress (see Section 3.12.3). This information would be useful to the general population and to populations residing at or near hazardous waste sites.

Data regarding occupational exposure to beryllium and its compounds appear to indicate an increased incidence of lung cancer (Infante et al. 1980; Mancuso 1970, 1979, 1980; Sanderson et al. 2001a; Steenland and Ward 1992; Wagoner et al. 1980; Ward et al. 1992). However, the quality of some of these studies has been severely criticized (EPA 1987). Animal studies indicate increases in lung cancer due to inhalation exposure to beryllium or its soluble and insoluble compounds (Nickell-Brady et al. 1994; Reeves et al. 1967; Vorwald 1968; Vorwald and Reeves 1959; Wagner et al. 1969), but these studies are also flawed. Nevertheless, these data and studies conducted by intratracheal, intravenous, and intramedullary routes taken as a whole support the carcinogenic potential of beryllium, and inhaled beryllium is considered a human carcinogen (IARC 2001; NTP1999, 2002); EPA considers beryllium to be a probable human carcinogen (IRIS 2002). A well-conducted chronic inhalation study in rats and mice using several exposure levels would add confidence to the database and eliminate uncertainties due to the flaws in the existing studies. Beryllium has not been found to cause cancer in animals after oral exposure (Morgareidge et al. 1975, 1976; Schroeder and Mitchener 1975a, 1975b); although, as previously noted, these studies may not have been adequate to assess carcinogenic potential. Beryllium and its compounds are poorly absorbed from the gastrointestinal tract. Therefore, conducting oral studies at doses high enough to affect plausible target organs would be difficult.

Genotoxicity. Genotoxicity data regarding exposure to beryllium or its compounds are contradictory. Forward and reverse mutation bacterial assays yielded both positive (Kanematsu et al. 1980; Ulitzur and Barak 1988) and negative (Arlauskas et al. 1985; Ashby et al. 1990; Rosenkranz and Poirier 1979; Simmon et al. 1979) results for the same compounds. The results are also contradictory for chromosomal aberrations induced by beryllium in mammalian cell cultures (Ashby et al. 1990; Brooks et al. 1989; Hsie et al. 1979; Larramendy et al. 1981; Miyaki et al. 1979; Williams et al. 1989). Studies to examine the mechanism of mutagenic activity of beryllium would be useful. Studies regarding the genotoxic potential of beryllium in occupationally exposed workers also would be useful, especially if exposure levels were related to genotoxic effects. In addition, studies regarding the *in vivo* genotoxic potential of beryllium in animals, particularly by the inhalation route, would be helpful.

Reproductive Toxicity. No studies were located regarding reproductive toxicity in humans after inhalation, oral, or dermal exposure to beryllium or its compounds. A chronic duration study that allowed continuous mating did not find any adverse reproductive effects in dogs exposed to beryllium sulfate in the diet (Morgareidge et al. 1976). A study involving histological examination of rats exposed to beryllium sulfate in drinking water for 2 years reported no alterations of the reproductive organs (Morgareidge et al. 1975); beryllium compounds are not well absorbed by the gastrointestinal tract. Another study involving intratracheal injection of beryllium oxide in rats reported no effects on reproductive function (Clary et al. 1975). Additional inhalation studies should examine reproductive organs in order to determine whether the potential for reproductive effects due to beryllium exposure exists.

Developmental Toxicity. No studies were located regarding developmental toxicity in humans after inhalation, oral, or dermal exposure to beryllium or its compounds. No developmental effects were observed in the offspring of dogs chronically exposed to beryllium sulfate in the diet (Morgareidge et al. 1976); although the usefulness of this study in establishing the potential developmental toxicity of ingested beryllium is limited by the nonconventional study design. No inhalation or dermal exposure studies examining developmental toxicity in animals were identified. Rats injected intravenously with beryllium nitrate during gestation delivered pups that died soon after birth (Mathur et al. 1987). Increased fetal mortality and fetal weight and increased abnormalities were observed after pregnant rats were injected intratracheally with beryllium oxide or beryllium chloride (Selivanova and Savinova 1986). Other studies in which beryllium salts were injected into pregnant mice indicated that beryllium can penetrate the placenta and reach the fetus and cause behavioral abnormalities in the offspring (Bencko et al. 1979; Tsujii and Hoshishima 1979). Additional animal studies would be useful to determine if developmental effects may occur after inhalation or oral exposure to beryllium.

Immunotoxicity. While beryllium has not been shown to be toxic to the immune system, beryllium and the soluble and insoluble compounds can be sensitizing and induce a cell-mediated immune response to beryllium (Cullen et al. 1987; Johnson 1983; Rossman et al. 1988; Saltini et al. 1989). This heightened immune response to beryllium is the cause of chronic beryllium disease and certain skin lesions (Williams et al. 1987). Granuloma formation and dermatitis are the principal immunological effects caused by exposure to beryllium. Although beryllium is not well absorbed by the gastrointestinal tract, studies evaluating the immunological effects of beryllium exposure to the associated lymphoid tissue would be useful to determine the local immunological reaction. Intermediate-duration studies designed to characterize the effects on the immune system would be helpful. The elucidation of the molecular

mechanisms of the immune response to beryllium and the identification of the specific T-cell families that are reactive to beryllium would aid in the identification and treatment of patients with chronic beryllium disease. In addition, identification of potential differences in allelic phenotypes between people with chronic beryllium and people exposed to beryllium but without chronic beryllium disease might help identify potentially susceptible populations based on genetic differences.

Neurotoxicity. No studies were located regarding neurotoxicity in humans after inhalation, oral, or dermal exposure to beryllium or its compounds. Histological examination of rats and dogs chronically exposed to beryllium sulfate in drinking water did not reveal any abnormalities in nerve tissues (Morgareidge et al. 1975, 1976). Beryllium is not well absorbed by the gastrointestinal tract or after dermal exposure; therefore, neurological effects are not expected to occur as a result of oral or dermal exposure. Inhalation studies involving low-level exposure to beryllium would be useful for determining its neurotoxicity.

Epidemiological and Human Dosimetry Studies. The general population is exposed to beryllium through contaminated air, water, and food. The highest exposure levels are incurred by workers in beryllium ore processing, manufacturing, or fabricating plants (Eisenbud and Lisson 1983). Few studies correlate beryllium exposure with effects on the respiratory system. Epidemiology data have been criticized for using inappropriate cohorts and including nonexposed workers. Studies that correlate occupational exposure to beryllium with cancer and other health effects would be useful and would offset the limitations of the now available studies.

Biomarkers of Exposure and Effect. There are several tests for detecting beryllium in biological fluids and tissues (Frame and Ford 1974; Foreman et al. 1970; Hurlburt 1978; IARC 1980; Martinsen and Thomassen 1986; Paschal and Bailey 1986; Shan et al. 1989). Increased levels of beryllium in urine and blood indicate exposure (Stiefel et al. 1980; Zorn et al. 1986). Beryllium has also been measured in granulomas in the lung tissue of individuals with chronic beryllium disease (Kanarek et al. 1973) and in the skin of beryllium sensitive individuals (Williams et al. 1987). Laser ion mass analysis for beryllium is the most sensitive test for identifying beryllium on histological sections from lung or skin granulomas of patients with chronic beryllium disease (Williams and Kelland 1986). A lymphocyte proliferation test has also been used to identify workers with chronic beryllium disease; positive test results rarely occur in workers who are not exposed to beryllium or its compounds (James and Williams 1985; Stokes and Rossman 1991).

Chronic exposure to beryllium can result in decreased lung function (Andrews et al. 1969; Johnson 1983). This decrease can be measured by spirometry such as forced expiratory volume in 1 second or forced vital capacity (Andrews et al. 1969; Kriebel et al. 1988a,b). Measurements of lung function cannot distinguish between chronic beryllium disease and sarcoidosis, and lung opacities are not definitively captured by x-rays (Kanarek et al. 1973). Lymphocyte proliferation assays on cells obtained from individuals by bronchoalveolar lavage are sensitive in confirming chronic beryllium disease in symptomatic individuals (James and Williams 1985; Rossman et al. 1988). The lymphocyte proliferation test also distinguishes between chronic beryllium disease and sarcoidosis. A less invasive method of determining sensitivity to beryllium would be useful, especially for monitoring health effects in individuals living at or near hazardous waste sites.

Absorption, Distribution, Metabolism, and Excretion. Beryllium and its compounds are absorbed primarily through the lungs in humans and animals (Finch et al. 1990; Reeves and Vorwald 1969; Stiefel et al. 1980; Zorn et al. 1986), but the available information is not sufficient to determine the rate and extent of pulmonary absorption. Soluble compounds are absorbed more readily than insoluble compounds (Finch et al. 1990). Information from animal studies indicates that beryllium is poorly absorbed from the gastrointestinal tract, with the majority of the dose excreted in the feces (Furchner et al. 1973; Le Fevre and Joel 1986; Morgareidge et al. 1975; Reeves 1965). Dermal absorption is also poor (Petzow and Zorn 1974). Studies regarding the rate and extent of beryllium absorption via the lungs would be useful.

The only study on the distribution of beryllium and its compounds in humans was conducted on tissue taken from autopsies (Meehan and Smythe 1967); distribution studies in animals exposed to beryllium via inhalation were more available (Finch et al. 1990; Rhoads and Sanders 1985; Sanders et al. 1975; Stiefel et al. 1980; Stokinger et al. 1950; Wagner et al. 1969; Zorn et al. 1977). The target organs identified in these studies were the lung, lymph nodes, kidney, liver, and bone. Distribution of beryllium is more widespread for the soluble compounds, reflecting the degree of absorption (Finch et al. 1990). Rats and guinea pigs achieved steady state concentrations in the lungs 36 weeks after initial exposure to beryllium sulfate (Reeves and Vorwald 1969). Steady state concentrations in the blood were reached after 8–12 hours (Stiefel et al. 1980). After oral exposure to beryllium metal, beryllium sulfate, or beryllium oxide, beryllium was distributed primarily to the liver and then to the kidneys, lymph nodes, blood, and bone (Le Fevre and Joel 1986; Morgareidge et al. 1975; Reeves 1965; Watanabe et al. 1985). Studies investigating distribution patterns of dermally absorbed beryllium would be useful to determine if sensitization to beryllium can occur after dermal exposure.

Beryllium is not biotransformed in the body. Studies involving the conversion of soluble beryllium compounds to insoluble compounds would be useful to determine the residence time of the compounds in the gastrointestinal tract. Studies investigating the binding of beryllium to proteins or nucleic acids would be useful in determining the antigenic forms of beryllium, as well as a possible mechanism for genotoxicity.

Information regarding the clearance of beryllium from serum in humans (Stiefel et al. 1980; Zorn et al. 1986) and animals (Finch et al. 1990; Rhoads and Sanders 1985; Sanders et al. 1975; Stiefel et al. 1980; Zorn et al. 1977) after inhalation exposure to beryllium compounds is reported in the available literature. Beryllium compounds are poorly absorbed by the gastrointestinal tract, and primarily eliminated in the feces (Furchner et al. 1973; Morgareidge et al. 1975; Reeves 1965). Studies regarding excretion after dermal exposure to beryllium and its compounds were not located in the available literature.

Comparative Toxicokinetics. Studies in cats, rats, monkeys, and dogs indicate quantitative and qualitative differences in the distribution of inhaled beryllium to the lung, bone, spleen, and lymph nodes (Finch et al. 1990; Rhoads and Sanders 1985; Sanders et al. 1975; Stiefel et al. 1980; Stokinger et al. 1950; Wagner et al. 1969; Zorn et al. 1977). No studies were located comparing the differences in inhalation exposures among species with respect to absorption or excretion. Since beryllium is not well absorbed by the gastrointestinal tract or after dermal exposure, comparative studies for these routes of exposure would not be particularly valuable. Additional comparative toxicokinetics studies regarding distribution, absorption, and excretion of inhaled beryllium would be helpful to determine the use of the appropriate animal model to study acute and chronic beryllium disease.

Methods for Reducing Toxic Effects. Beryllium is poorly absorbed after oral and dermal exposure, obviating the need to develop methods to reduce absorption following these routes. While beryllium is absorbed by the lungs, the major effects of inhalation exposure to beryllium are acute chemical pneumonitis, which is associated with soluble beryllium compounds and chronic berylliosis, which is associated with retention of unabsorbed less soluble beryllium compounds in the lungs (Finch et al. 1990). Testing of bronchoalveolar lavage to enhance beryllium clearance from the lungs might prevent or reduce the severity of berylliosis. The chelating agent, aurine tricarboxylic acid, by combining with beryllium ions, increases the urinary excretion of beryllium in animals (Venugopal and Luckey 1978). However, metal chelating agents available for use in human clinical medicine have not been shown to be effective in reducing the toxicity of beryllium (Hall and Rumack 1992). Effects of soluble beryllium compounds (liver necrosis due to sequestration of insoluble beryllium phosphate formed from

the interaction with phosphate, acute pneumonitis, immunological effects) are probably due to beryllium ions (Price and Skilleter 1985, 1986). Further studies on the influence of chelating agents on beryllium-induced effects would aid in establishing effective strategies for preventing or reducing the severity of these effects. Absorbed beryllium appears to preferentially accumulate in bone, and beryllium may substitute for calcium in bone, resulting in rickets or osteoporosis (Guyatt et al. 1933; Jacobson 1933). Studies could be performed to determine whether a high calcium diet would be effective in preventing the replacement of calcium by beryllium in bone.

Children's Susceptibility. No information on the toxicity of beryllium in children has been located. Studies that examine sensitive end points such as the lung, immune, and gastrointestinal effects in young animals would be useful for assessing whether children will be unusually susceptible to beryllium toxicity. The available animal data are inconclusive to determine whether the developing organism is sensitive to beryllium toxicity. As discussed in Chapter 2 and in Section 3.2.2.6, the only available oral study did not find developmental effects in the offspring of dogs chronically exposed to beryllium sulfate in the diet (Morgareidge et al. 1976). However, injection studies have found developmental effects (fetal/neonatal mortality, internal abnormalities, and behavioral effects) (Bencko et al. 1979; Mathur et al. 1987; Selivanova and Savinova 1986; Tsujii and Hoshishima 1979). Data needs relating to development are discussed in detail in the Developmental Toxicity subsection above. There are some data to suggest that beryllium can cross the placenta and be transferred to an infant via breast milk (Krachler et al. 1999a).

The available toxicokinetic data did not evaluate the potential differences between adults and children. Toxicokinetic studies examining how aging can influence the absorption, distribution, and excretion of beryllium would be useful in assessing children's susceptibility to beryllium toxicity. There are no data to determine whether there are age-specific biomarkers of exposure or effects or any interactions with other chemicals that would be specific for children. Research in adults on methods for reducing beryllium toxic effects or body burdens would also be applicable to children.

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

3.12.3 Ongoing Studies

Ongoing studies pertaining to beryllium have been identified and are shown in Table 3-6.

Table 3-6. Ongoing Studies on Beryllium

Investigator	Affiliation	Research description	Sponsor
Albertini, RJ	University of Vermont	Biomarkers for beryllium sensitization	EM
Marian, B	University of California, Los Alamos National Laboratory	Screening of beryllium worker cohorts using the immun.-flow lymphocyte proliferation test	NCR
Newman, L	University of Colorado	Immunopathogenesis of beryllium disease	NCR
Rossman, M	University of Pennsylvania	Examination of exposure-response relationship for various measures of beryllium exposure	NCR
Kotzin, BL	University of Colorado	Examination of T–cell clones in individuals with CBD and beryllium sensitized individuals	NHLBI
King, TE	National Jewish Medical and Research Center	Prevention of pulmonary fibrosis in individuals with granulomatous inflammation	NHLBI
Newman, L	National Jewish Medical and Research Center	Role of T–cells and mast cells in the development of pulmonary fibrosis	NHLBI
Mason, RJ	National Jewish Medical and Research Center	Immunologic regulation of pulmonary fibrosis	NHLBI
Warren, JS	University of Michigan	Study of oxidant-induced β-chemokines in granuloma formation	NHLBI
Fontenot, AP	University of Colorado	Pathogenic cells in beryllium-induced lung disease	NHLBI
LA Maier	National Jewish Medical and Research Center	Local angiotensin system in lung fibrogenesis	NHLBI
Bell, J	Fayetteville State University	Mutagenic effects of beryllium on the fidelity of DNA synthesis	NIGMS
Newman, L	National Jewish Medical and Research Center	Cytokine regulation in CBD	NIEHS
Finch, GL	Lovelace Biomedical and Environmental Research Institute	Mechanisms of granulomatous disease from inhaled beryllium	USDOE

CBD = chronic beryllium disease; NCR = National Center for Research Resources; NHLBI = National Heart, Lung, and Blood Institute; NIEHS = National Institute of Environmental Health and Science; NIGMS = National Institute of General Medical Sciences; USDOE = U.S. Department of Energy

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Beryllium is a naturally occurring element found in earth's surface rocks at levels of 1–15 mg/kg. It appears in Group IIA of the periodic table and has two common oxidation states, Be(0) and Be(+2). Because of its high reactivity, beryllium is not found as the free metal in nature. There are approximately 45 mineralized forms of beryllium. The important beryllium minerals in the world are beryl ($3BeO\#Al_2O_3\#6SiO_2$) and bertrandite ($Be_4Si_2O_7(OH)_2$). Beryl has been known since ancient times as the gemstones: emerald (green), aquamarine (light blue), and beryl (yellow). Information concerning the chemical identity of elemental beryllium and beryllium compounds is listed in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of beryllium and beryllium compounds are listed in Table 4-2.

Consistent with the high charge-to-radius ratio, beryllium has a strong tendency to form compounds with covalent bonds; even compounds with the most electronegative elements (e.g., BeF_2) have substantial covalent character. Although beryllium belongs to Group IIA of the periodic table, it is chemically very similar to aluminum, which also has a high charge-to-radius ratio. Like aluminum, the hydroxide of beryllium is amphoteric (Cotton and Wilkinson 1980; Drury et al. 1978; EPA 1998).

The interaction of cosmic-ray particles in the atmosphere produces a number of radionuclides including beryllium-7 (Be-7) and beryllium-10 (Be-10). The radioactive half-life of Be-7 is 53.29 days and the radioactive half-life of Be-10 is $1.51x10^6$ years (UNSCEAR 2000).

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

Characteristic	Beryllium	Beryllium chloride	Beryllium fluoride	Beryllium hydroxide	Beryllium oxide
Synonym(s)	Beryllium-9; glucinium; glucinum; beryllium metallic	Beryllium dichloride	Beryllium difluoride	Beryllium hydrate; beryllium dihydroxide	Beryllia; beryllium monoxide
Registered trade name(s)	No data	No data	No data	No data	Thermalox 995
Chemical formula	Be	$BeCl_2$	BeF_2	$Be(OH_2)$	BeO
Identification numbers:					
CAS registry	7440-41-7	7787-47-5	7787-49-7	13327-32-7	1304-56-9
NIOSH RTECS	DS1750000	DS2625000	DS2800000	DS3150000	DS4025000
EPA hazardous waste	P015[b]	No data	No data	No data	No data
OHM/TADS	72116604[c]	7217359[c]	7800049[c]	No data	No data
DOT/UN/NA/IMCO shipping	UN1567/IM06.1	NA1566/IM06.1	NA1566/IM06.1	UN1566/IM06.1	UN1566/IM06.1
HSDB	512	357	355	350	1607
NCI	No data	No data	No data	No data	No data

Table 4-1. Chemical Identity of Beryllium and Beryllium Compounds[a] (*continued*)

Characteristic	Beryllium phosphate ($3H_2O$)	Beryllium nitrate	Beryllium sulfate	Beryllium carbonate (basic)
Synonym(s)	Beryllium orthophosphate[d]	Nitric acid, beryllium salt	Sulfuric acid, beryllium salt	Basic beryllium[e] carbonate; bis[carbonato(2-)] dihydroxy triberyllium[e]
Registered trade name(s)	No data	No data	No data	No data
Chemical formula	$Be_3(PO_4)_2^{-3}H_2O$[d]	$Be(NO_3)_2$	$BeSO_4$	$(BeCO_3)_2^-$ $Be(OH)_2$[e]
Identification numbers:				
CAS registry	35089-00-0[d]	13597-99-4 (anhydrous) 13510-48-0 (tetrahydrate)	13510-49-1 (anhydrous) 14215-00-0 ($2H_2O$) 7787-56-6 ($4H_2O$)	66104-24-3[e]
NIOSH RTECS	No data	DS3675000 (anhydrous)	DS48000000 (anhydrous)	No data
EPA hazardous waste	No data	No data	No data	No data
OHM/TADS	No data	7217227[c] (anhydrous)	7217228[c] (anhydrous)	No data
DOT/UN/NA/IMCO shipping	No data	UN2464/IM05.1	UN1566/IM06.1	No data
HSDB	No data	1431	347	No data
NCI	No data	No data	No data	No data

[a]All information obtained from HSDB 2000 except where noted
[b]EPA Hazardous waste list P015 applies to beryllium powder only
[c]OHM/TADS 1990
[d]Weast 1985
[e]IARC 1980

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

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

Property	Beryllium metal	Beryllium fluoride	Beryllium hydroxide	Beryllium oxide	Beryllium carbonate (basic)
Molecular weight	9.012	47.01	43.03[b]	25.01	112.05
Color	Gray	Colorless	White[c]	White	White
Physical state	Solid; hexagonal structure[d]	Glassy, hygroscopic mass[d]	Amorphous powder or crystalline solid[d]	Light, amorphous powder[d]	Powder
Melting point	1,287–1,292 EC[e]	555 EC[b]	Decomposes (loses water) when heated[f]	2,508–2,547 EC[b]	No data
Boiling point	2,970 EC[e]	1,175 EC[b]	Not applicable	3,787 EC[b]	No data
Density	1.846 g/cm^3 [e]	1.986 g/cm^3 (25 EC)[b]	1.92 g/cm^3 [b]	3.016 g/cm^3 [c]	No data
Odor	None	None	None	None	None
Odor threshold:	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Solubility:					
Water	Insoluble[g]	Very soluble[g]	0.8x10^{-4} mol/L[g] (3.44 mg/L)	Very sparingly[g]	Insoluble (cold) decomposes (hot)
Other solvent(s)	Soluble in dilute acid and alkali	Slightly soluble in alcohol[d]	Soluble in hot concentrated acid and alkali[d]	Soluble in concentrated acids[d]	Soluble in acid, alkali
Partition coefficients:					
Log K_{ow}	No data	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data	No data
Vapor pressure	1 mmHg (1,520 EC)	No data	No data	No data	No data
Henry's law constant	No data	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data	No data
Conversion factors[h]					
Explosive limits	No data	No data	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Beryllium and Beryllium Compounds[a] *(continued)*

Property	Beryllium chloride	Beryllium nitrate (tetrahydrate)	Beryllium phosphate (trihydrate)	Beryllium sulfate	Beryllium sulfate (tetrahydrate)
Molecular weight	79.92	205.08[b]	271.03	105.07	177.13
Color	Colorless	White[b]	White[b]	Colorless[b]	Colorless[b]
Physical state	Needles	Crystals[b]	Solid[b]	Tetragonal crystals	Tetragonal crystals
Melting point	405 EC	60.5 EC[b]	100 EC (loses H_2O) (decomposes)[b]	550–600 EC (decomposes)	100 EC (loses $2H_2O$)
Boiling point	520 EC	142 EC (decomposes)[b]	No data	Not applicable	400 EC (loses $4H_2O$)
Density	1.899 g/cm^3 (25 EC)	1.557 g/cm^3 [b]	No data	2.443 g/cm^3	1.713 g/cm^3 (10.5 EC)
Odor	None	None[b]	None[b]	None	None
Odor threshold:	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Solubility:					
Water	Very soluble	166 parts/100 parts H_2O (20 EC)[b] ($1.66x10^6$ mg/L)	Soluble	Insoluble	39.1 parts/100 parts H_2O (20 EC)[b] ($3.91x10^5$ mg/L)
Other solvent(s)	Very soluble in alcohol, ether, pyridine; slightly soluble in benzene and chloroform	No data	Soluble in acetic acid	No data	Slightly soluble in H_2SO_4, insoluble in alcohol
Partition coefficients:					
Log K_{ow}	No data	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data	No data
Vapor pressure	No data	No data	No data	No data	No data
Henry's law constant	No data	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Beryllium and Beryllium Compounds[a] *(continued)*

Property	Beryllium chloride	Beryllium nitrate (tetrahydrate)	Beryllium phosphate (trihydrate)	Beryllium sulfate	Beryllium sulfate (tetrahydrate)
Flammability limits	No data	No data	No data	No data	No data
Conversion factors	[h]	[h]	[h]	[h]	[h]
Explosive limits	No data	No data	No data	No data	No data

[a]All information obtained from Weast 1985 except where noted
[b]Dean 1985
[c]Hawley 1981
[d]Windholz 1983
[e]Ballance et al. 1978
[f]Walsh and Rees 1978
[g]EPA 1987
[h]These compounds do not exist in the atmosphere in the vapor phase; therefore, an air conversion factor is not applicable.

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

5.1 PRODUCTION

Beryllium is an element that is present in the earth's surface rocks in amounts ranging from <1–15 mg/kg. The beryllium minerals of commercial interest are beryl (i.e., $3BeO·Al_2O_3·6SiO_2$) and bertrandite (i.e., $Be_4Si_2O_7(OH)_2$). In the United States, bertrandite, which contains <1% beryllium, is the principal mineral mined. Outside the United States, beryl is the principal beryllium mineral mined. In 1999, the U.S. Geological Survey (USGS) estimated that United States resources of bertrandite ore in Utah and Texas contained 21,000 metric tons of beryllium (Cunningham 1999). Only one company, Brush Wellman, Inc. of Elmore, Ohio, produced beryllium in the United States in 1998. The bertrandite ore was mined using open-pit methods from deposits near Spor Mountain, Utah. In 1998, 230 metric tons of beryllium were mined in the United States (Cunningham 1999). Beryllium hydroxide is the basic raw material for the production of beryllium metal, alloys, and compounds. Bertrandite ore is wet milled, leached with sulfuric acid, and then extracted from the acid leachate with di(2-diethylhexyl) phosphate in kerosene at elevated temperature. The beryllium is then treated with aqueous ammonium carbonate to form an aqueous ammonium beryllium carbonate complex, which is then heated to precipitate beryllium as carbonate. Continued heating liberates carbon dioxide and beryllium hydroxide (i.e., $Be(OH)_2$). Beryllium hydroxide is then recovered by filtration. Beryllium hydroxide is the feed material for products such as beryllium metal, beryllium alloys, and beryllium oxide (Ballance et al. 1978; Drury et al. 1978).

Beryllium metal is produced by Brush Wellman Inc. in Elmore, Ohio using the Schenzfeier-Pomelee purification process. The hydroxide is initially reacted with ammonium fluoride to form ammonium fluoroberyllate (e.g., $(NH_4)_2BeF_4$), which is then heated to produce an amorphous beryllium fluoride (e.g., BeF_2), which is reduced by magnesium metal at 900–1,300 EC to yield beryllium metal and a beryllium fluoride-magnesium fluoride slag. The slag is removed by leaching with water, leaving 97% pure beryllium metal. Beryllium metal may be further electrorefined to produce a higher purity material (Ballance et al. 1978; Drury et al. 1978). Beryllium oxide (i.e., BeO) is the most important high purity commercial beryllium chemical. It is produced by dissolving technical-grade beryllium hydroxide in sulfuric acid, precipitating out hydrated beryllium sulfate, which is then calcined at 1,150–1,450 EC (Ballance et al. 1978; Drury et al. 1978).

Copper-beryllium alloy is commercially the most important beryllium alloy. Copper-beryllium master alloy is manufactured by an arc-furnace method in which beryllium oxide is reduced by carbon in the presence of molten copper at 1,800–2,000 EC. The resulting master alloy usually contains 4.0–4.25% beryllium by weight. Other copper-beryllium alloys are produced by melting the master alloy together with virgin copper, copper scrap, and possibly other metals (Ballance et al. 1978; Drury et al. 1978).

Brush Wellman, Inc. of Elmore, Ohio is the only processor of beryllium ores in the United States. Brush Wellman, Inc. is also the leading producer and consumer of beryllium metal, alloys, and oxide. NGK Metals Corporation in Reading, Pennsylvania is also a major U.S. manufacturer of beryllium alloys. U.S. mine shipments steadily increased from 173 metric tons in 1994 to 230 metric tons in 1998 of beryllium metal equivalent. Including imports of beryllium ore, stockpiling, and inventory uses, the apparrent U.S. consumption of beryllium from 1994 to 1998 has increased from 198 to 240 metric tons of beryllium equivalent (Cunningham 1999). Tables 5-1 and 5-2 list the number of facilities in each state that manufacture or process beryllium and beryllium compounds, respectively. Included in these tables are the activities and uses of beryllium and beryllium compounds and the range of maximum amounts of beryllium and beryllium compounds that are stored on site (TRI99 2002).

5.2 IMPORT/EXPORT

In 1998, 13% of the beryllium ore and metal consumed in the United States (35 metric tons) was imported from other countries. All imports of beryllium ore originated from Canada. Exports of beryllium metal were 60 metric tons in 1998, up from 29 metric tons in 1994. Japan, France, the United Kingdom, and Germany were the major recipients of beryllium exports during this period (Cunningham 1999).

5.3 USE

In 1998, the use of beryllium (as an alloy, metal, or oxide) in the electronic and electrical components, aerospace, and defense applications accounted for >80% of its consumption (Cunningham 1999).

Beryllium metal is used in aircraft disc brakes, x-ray transmission windows, space vehicles optics and instruments, aircraft/satellite structures, missile guidance systems, nuclear reactor neutron reflectors, nuclear warhead triggering devices, fuel containers, precision instruments, rocket propellants,

Table 5-1. Facilities that Produce, Process, or Use Beryllium

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
CA	2	0	999	8, 10
IN	2	100	999,999	9, 12
LA	1	0	99	1, 5, 9, 13
MO	1	1,000	9,999	8, 10
NC	1	100,000	999,999	10, 13
OH	1	10,000	99,999	1, 4
OK	2	100	99,999	1, 5, 9
PA	1	10,000	99,999	10
SC	1	100	999	9
UT	1	1,000	9,999	8
WI	1	10,000	99,999	8

Source: TRI99 2002

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

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

Table 5-2. Facilities that Produce, Process, or Use Beryllium Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	4	1,000	99,999	1, 3, 4, 5, 6, 9, 1, 13
AR	1	1,000	9,999	1, 5
AZ	3	10,000	9,999,999	1, 3, 4, 5, 6, 9, 1
FL	2	0	9,999	1, 3, 4, 5, 6, 1
GA	3	10,000	99,999	1, 3, 4, 5, 6, 1, 13
IL	1	1,000	9,999	1, 5, 1
IN	3	100	99,999	1, 5, 6, 9, 1, 13
KY	5	0	99,999	1, 2, 3, 5, 6, 9, 1, 13
MI	2	10,000	99,999	1, 5, 9, 1
MO	1	1,000	9,999	9
MS	1	100	999	1, 5
MT	1	10,000	99,999	1, 3, 5, 6, 13
NC	2	10,000	99,999	1, 3, 4, 5, 6, 1
NM	3	100	99,999	1, 3, 4, 5, 6, 1, 13
NY	1	100	999	1, 5
OH	4	1,000	99,999	1, 3, 4, 5, 6, 8, 1, 13
PA	4	100	999,999	1, 2, 3, 4, 5, 6, 7, 9, 1
TN	2	10,000	99,999	1, 5, 8, 9
TX	1	10,000	99,999	1, 3, 4, 5, 6, 1, 13
UT	4	1,000	49,999,999	1, 4, 7, 8, 13
WI	1	1,000	9,999	9
WV	3	1,000	99,999	1, 3, 4, 5, 6, 1, 13
WY	1	0	99	1, 5, 6

Source: TRI99 2002

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

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

navigational systems, heat shields, mirrors, high speed computer, and audio components, as well as other uses (Ballance et al. 1978; Cunningham 1998).

Beryllium oxide is used in high technology ceramics, electronic heat sinks, electrical insulators, microwave oven components, gyroscopes, military vehicle armor, rocket nozzles crucibles, thermocouple tubing, laser structural components, substrates for high-density electrical circuits, automotive ignition systems, and radar electronic countermeasure systems (Ballance et al. 1978, Cunningham 1998).

Beryllium-copper alloys are used in a wide variety of applications because of their electrical and thermal conductivity, high strength and hardness, good corrosion and fatigue resistance, and nonmagnetic properties. Beryllium-copper alloys are manufactured into: springs; electrical connectors and relays; precision instruments; bushings and bearings in aircraft and heavy machinery; nonsparking tools; submarine cable housing and pivots; wheels and pinions; switches in automobiles; molds for injection molded plastics; radar; telecommunications; factory automation; computers; home appliances; instrumentation and control systems; tubing in oil and drilling equipment; connectors for fiber optics; and integrated circuits, as well as many other uses (Ballance et al. 1978; Cunningham 1998).

5.4 DISPOSAL

The most significant amount of beryllium waste results from pollution control methods such as solid particulates scrubbers. Since beryllium is a valuable element, the most desirable method of handling beryllium wastes is to recycle them to the producers. Metal scrap, aqueous suspensions, and particulates are routinely recycled by Brush Wellman, Inc. at their production facility in Ohio (Brush Wellman 2000a).

The EPA has classified beryllium powder as a hazardous waste material (40 CFR Section 261.33). Under the Resource Conservation and Recovery Act (RCRA), compliance with labeling and disposal procedures as well as obtaining permits for discharges into air and water are required for beryllium powder. EPA standards require that atmospheric emissions from stationary sources be <10 g of beryllium over a 24-hour period, and that the ambient concentration of beryllium near the stationary source be <0.01 $\mu g/m^3$. Beryllium solid waste should be placed into impermeable, sealed bags or containers (e.g., drums) that are labeled in accordance with the requirements of EPA regulations (Fishbein 1981). The EPA has also issued final regulations under the Clean Water Act for specific nonferrous metal manufacturing operations including beryllium processing facilities. These regulations limit the discharge

of beryllium containing pollutants into navigable waters and into publically-owned treatment works (POTWs). Waste waters containing beryllium may therefore require treatment to reduce the concentration of beryllium. A typical treatment method for beryllium involves steps such as chemical precipitation, settling clarification, neutralization, filtration, and sludge dewatering (EPA 1982, 1988a). Waste waters that contain permissible levels of beryllium may be discharged into streams and POTW facilities (EPA 1982, 1988a).

A significant amount of beryllium waste results from pollution control methods such as containment of solid particulates or aqueous suspensions resulting from air-scrubbing processes. According to the TRI99 (TRI99 2002), a total of 54,097 and 838,373 pounds of beryllium and beryllium compound wastes, respectively, were released to the environment by various industries in 1999 (see Chapter 6). Of the total release of beryllium, 98.5% was disposed on land (on-site), 1.4% was released to air, and 0.1% was released to surface water. Likewise, of the total release of beryllium compounds, 98.2% was disposed on land (on-site), 0.9% was released to air, 0.4% was released to surface water, and 0.5% was injected underground. An additional 20,081 and 72,118 pounds of beryllium and beryllium compound wastes, respectively, were transferred to off-site locations within the United States. Data regarding the trend in disposal practices for beryllium wastes in recent years were not located.

6. POTENTIAL FOR HUMAN EXPOSURE

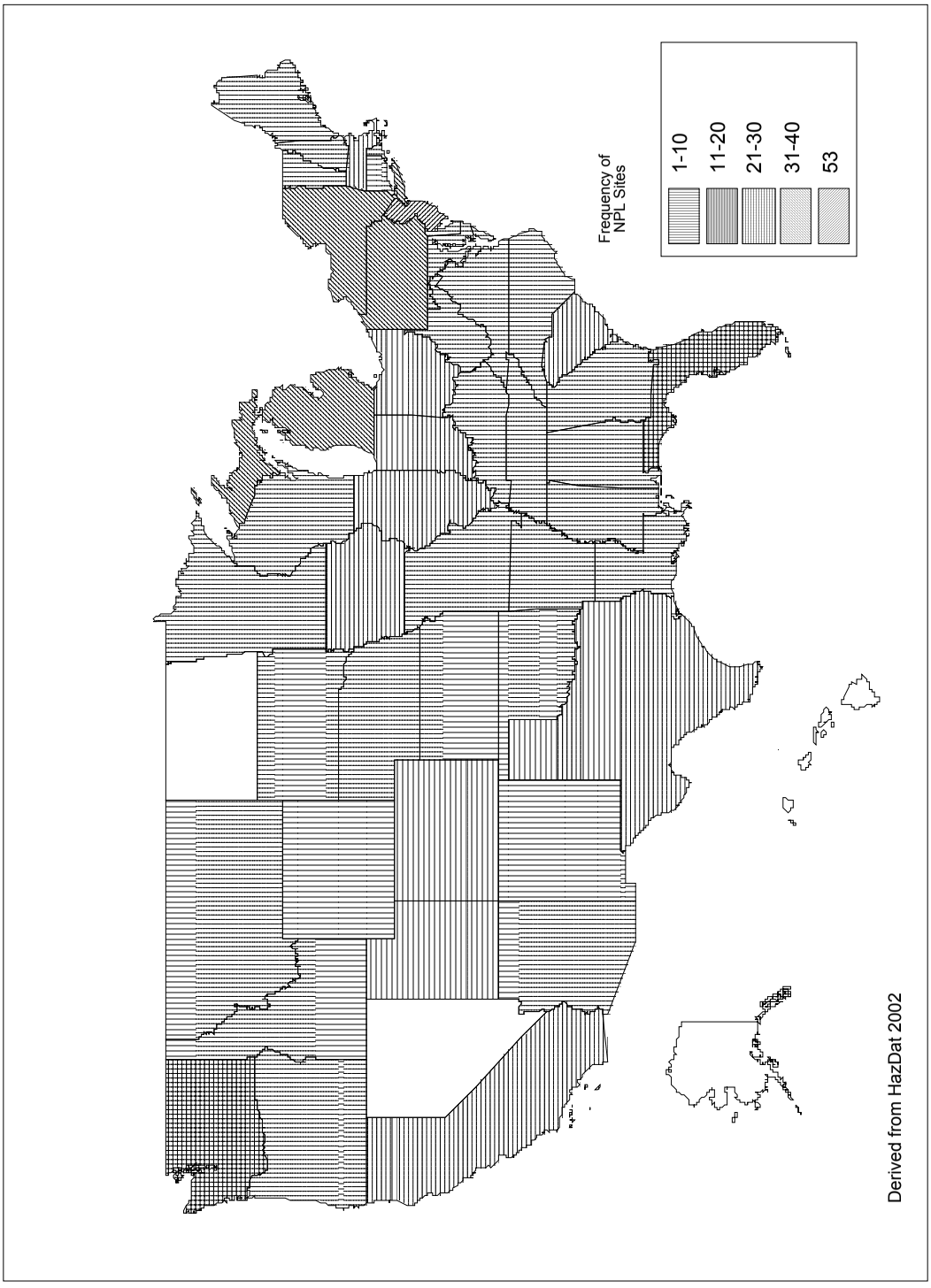
6.1 OVERVIEW

Beryllium has been identified in at least 535 of the 1,613 hazardous waste sites that have been proposed for inclusion on the EPA NPL (HazDat 2002). However, the number of sites evaluated for beryllium is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 524 are located within the United States, 2 are located in the Territory of Guam, 2 are located in the U.S. Virgin Islands, and 7 are located in the Commonwealth of Puerto Rico (not shown).

Beryllium is naturally emitted to the atmosphere by windblown dusts and volcanic particles (EPA 1987). The major anthropogenic emission source to the environment is the combustion of coal and fuel oil, which releases particulates and fly ash that contain beryllium into the atmosphere (DOE 1996). Other anthropogenic processes, such as ore processing, metal fabrication, beryllium oxide production and use, and municipal waste combustion, release only a fraction of the amounts emitted from coal and oil combustion (Cleverly et al. 1989; EPA 1987; Fishbein 1981). Beryllium naturally enters waterways through the weathering of rocks and soils (EPA 1980). The sources of anthropogenic release of beryllium to surface waters include treated waste water effluents from beryllium or related industries and the runoff from beryllium-containing waste sites (EPA 1980, 1981). Deposition of atmospheric beryllium aerosols from both natural and anthropogenic sources is also a source of beryllium in surface waters. Some beryllium compounds are naturally present in soil, but the concentration of beryllium in localized soils can be increased because of the disposal of coal ash, municipal combustor ash, industrial wastes that contain beryllium, and deposition of atmospheric aerosols.

Beryllium released to the atmosphere from combustion processes and ore processing will probably be present as beryllium oxide. Atmospheric beryllium particulates will eventually settle to the earth's surface by dry deposition or may be removed from the atmosphere by wet deposition (i.e., precipitation). Upon reaching water and soil, beryllium will probably be retained in an insoluble form in sediment and soil and will be generally immobile. Although chemical reactions may transform one beryllium compound into another, beryllium cannot be degraded by environmental reactions. However, the data regarding transformation reactions of beryllium in water and soil are limited. Bioconcentration of beryllium in plants and animals is low. In plants, uptake of beryllium appears to be restricted to the root

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



system; no significant translocation of beryllium to the above ground parts of the plant has been observed. Beryllium is not expected to bioconcentrate in aquatic animals (EPA 1980).

The average concentration of beryllium in air in the United States is 0.03 ng/m^3, but the median concentration in cities is 0.2 ng/m^3 (Bowen 1979; EPA 1987). Dissolved beryllium was detected in groundwater at 352 of 504 sites in the United States (6.4% of sites) with an average concentration of 13.6 µg/L. In surface water, dissolved beryllium was detected at 85 of 504 sites in the United States (16.1%) with an average concentration of 23.8 µg/L (EPA 2000a). The mean concentration of beryllium in U.S. soils is 0.6 mg/kg (Eckel and Langley 1988). The beryllium concentrations in both raw carrots and field corn grown in the United States were <25 µg/kg (fresh weight) (Wolnik et al. 1984).

The general population is exposed to beryllium through inhalation of air and consumption of food and drinking water. The total beryllium intake by the general U.S. population cannot be estimated due to the lack of data regarding beryllium content in food. People who work in beryllium manufacturing, fabricating, and reclaiming industries are exposed to higher levels of beryllium than the general population. Smokers may also be exposed to higher levels of beryllium than nonsmokers because cigarette smoke contains beryllium (Reeves 1986).

6.2 RELEASES TO THE ENVIRONMENT

Releases of beryllium and beryllium compounds are required to be reported under Superfund Amendments and Reauthorization Act Section 313; consequently, data are available for this compound in the Toxics Release Inventory (TRI) (EPA 1995). According to the TRI, a total of 74,178 pounds (33,647 kg) of beryllium and 910,491 pounds (412,990 kg) beryllium compounds were released to the environment in 1999 (TRI99 2002). The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

Beryllium has been identified in a variety of environmental media (air, surface water, leachate, groundwater, soil, and sediment) collected at 535 of 1,613 current or former NPL hazardous waste sites (HazDat 2002).

6.2.1 Air

Anthropogenic and natural emissions of beryllium to the atmosphere from various sources are reported in Table 6-1. In addition to ore processing, beryllium is also released into the atmosphere during the production and use of beryllium alloys and chemicals. Beryllium is released into the atmosphere from anthropogenic sources including the combustion of coal and fuel oil, the incineration of municipal solid waste (MSW), the production, use, and recycling of beryllium alloys and chemicals, and, to a minor extent, the burning of solid rocket fuel. According to the TRI data (TRI99 2002) shown in Tables 6-2 and 6-3, 769 and 7,816 pounds of beryllium and beryllium compounds, respectively, were released in the atmosphere from alloys, chemicals, and user industries in 1999.

Beryllium emissions from coal and fuel oil combustion account for a majority of the U.S. beryllium emissions from natural and anthropogenic sources (EPA 1987). The average beryllium concentration in coal is between 1.8 and 2.2 μg/g (EPA 1987). A study by the Department of Energy (DOE) and the University of North Dakota examined the emissions of toxic trace elements from coal-fired power plants (DOE 1996). The data in this study show that stack concentrations are 2–3 orders of magnitude greater than the range of ambient air concentrations for beryllium (DOE 1996). The median stack concentration for beryllium was 0.8 μg Be/m^3, and the average emission from the nine coal-fired power plants was 22.6 pounds/year (range 0.49–55.8 pounds/year). The estimated total emissions of beryllium in 1990 from the 3,266 fuel oil-fired power plants in the United States was 0.45 tons (0.41 metric tons) (DOE 1999a). TRI release data for electric utilities of 6,988 pounds of beryllium compounds were reported for 1999 (EPA 1987; TRI99 2002). The largest atmospheric releases of beryllium compounds were reported by Roxboro Steam Electric Plant in Person, North Carolina; Mt. Storm Power Station in Grant, West Virginia; and FirstEnergy Power Plant in Beaver, Pennsylvania with 487, 680, and 1,250 pounds (0.22, 0.31, and 0.57 metric tons), respectively, for the year 1999. The TRI99 data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list (TRI99 2002).

In 1986, there were 494 of 7,835 incinerated municipal waste streams containing beryllium in the United States (Behmanesh et al. 1992). There are 58 municipal Waste-to-Energy (WTE) facilities in the United States (DOE 1999a). At a municipal WTE facility in Commerce, California, stack emissions for

Table 6-1. Anthropogenic and Natural Emissions of Beryllium and Beryllium Compounds to the Atmosphere[a]

Emission source	Emission (tons/year)[b]
Natural	
Windblown dust	5
Volcanic particles	0.2
Anthropogenic[c,d]	
Industry	0.6
Metal Mining	0.2
Electric utilities	3.5
Waste and Solvent Recovery (RCRA)	0.007
Total	9.507

[a]Adapted from Drury et al. 1978; EPA 1987; TRI99 2002
[b]Units are metric tons.
[c]Data in TRI are maximum amounts released by each industry.
[d]The sum of fugitive and stack releases are included in releases to air by a given industry.

RCRA = Resource Conservation and Recovery Act; TRI = Toxic Release Inventory

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

		Reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Underground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on and off-site release
CA	3	0	No data	No data	No data	0	No data	0
IN	3	0	No data	No data	2,650	2,650	2,415	5,065
LA	1	2	No data	No data	No data	2	No data	2
MO	1	0	No data	No data	10	10	0	10
NC	1	38	No data	No data	No data	38	No data	38
OH	6	721	27	No data	50,532	51,280	9,870	61,150
OK	2	No data	23	No data	5	28	6,830	6,858
PA	1	1	7	No data	No data	8	966	974
SC	1	7	No data	No data	74	81	No data	81
TN	1	No data	No data	No data	No data	No data	No data	No data
UT	1	0	No data	No data	0	0	No data	0
WI	1	No data	No data	No data	No data	No data	No data	No data
Total	22	769	57	0	53,271	54,097	20,081	74,178

Source: TRI99 2002

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

Table 6-3. Releases to the Environment from Facilities that Produce, Process, or Use Beryllium Compounds

		Reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Underground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on and off-site release
AL	6	419	250	No data	62,691	63,360	326	63,686
AR	2	197	48	No data	9,130	9,375	1	9,376
AZ	4	50	No data	No data	16,421	16,471	1,630	18,101
FL	3	390	250	No data	5,745	6,385	5	6,390
GA	5	764	0	No data	76,925	77,689	No data	77,689
IL	1	79	850	No data	8,500	9,429	No data	9,429
IN	4	340	63	No data	40,019	40,422	3,808	44,230
KY	5	351	1,221	No data	27,730	29,302	No data	29,302
MD	1	No data	No data	No data	No data	No data	No data	No data
MI	2	313	17	No data	15,000	15,330	250	15,580
MO	3	10	No data	No data	No data	10	555	565
MS	1	2	20	4,100	19	4,141	0	4,141
MT	1	250	No data	No data	6,900	7,150	750	7,900
NC	4	817	403	No data	51,010	52,230	260	52,490
NM	4	112	77	No data	47,724	47,913	39,000	86,913
NY	1	20	0	No data	400	420	No data	420
OH	4	450	30	No data	25,846	26,326	11,422	37,748
PA	4	1,580	16	No data	8,700	10,296	6,411	16,707
TN	2	256	250	No data	14,100	14,606	640	15,246
TX	1	19	0	No data	31,400	31,419	No data	31,419
UT	4	366	No data	No data	299,952	300,318	5	300,323
WI	1	10	5	No data	No data	15	255	270

Table 6-3. Releases to the Environment from Facilities that Produce, Process, or Use Beryllium Compounds *(continued)*

		Reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Underground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on and off-site release
WV	9	861	10	No data	70,765	71,636	6,800	78,436
WY	1	160	No data	No data	3,970	4,130	No data	4,130
Total	73	7,816	3,510	4,100	822,947	838,373	72,118	910,491

Source: TRI99 2002

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

beryllium were measured at 0.2 μg/m^3 (Hasselriis and Licata 1996). The stack emissions from individual municipal WTE facilities are about the same order of magnitude as stack emissions from individual coal fired power plants; however, the number of municipal WTE facilities in the United States is a factor of 20 less than the number of coal fired power plants.

Natural emission sources of beryllium include windblown dusts and volcanic particles. The beryllium amounts released to the atmosphere from these sources are comparable with anthropogenic sources (see Table 6-1).

Beryllium has been identified in 9 air samples collected from 535 current or former NPL hazardous waste sites where it was detected in some environmental media (HazDat 2002).

6.2.2 Water

Anthropogenic sources of beryllium release to water include industrial waste water effluents. A compilation of data for the beryllium levels in raw and treated waste water from various industrial sources is available (EPA 1981). The concentrations of beryllium compounds are the highest in waste waters from electric utility industries (TRI99 2002). The total reported amounts of beryllium and beryllium compounds released to surface water for 1999 were 57 pounds (26 kg) and 3,510 pounds (1,592 kg), respectively, as shown in Tables 6-2 and 6-3 (TRI99 2002).

Deposition of atmospheric beryllium is also a source in surface waters; however, the relative significance of the contribution from this source, compared to industrial discharge to surface water, cannot be assessed. Beryllium also enters the waterways from the weathering of rocks and soils (EPA 1980). Since coal contains beryllium, it is also likely that beryllium will enter surface water via leaching of coal piles.

The industrial releases of beryllium and beryllium compounds into surface water are shown in Tables 6-2 and 6-3, respectively. The largest releases to water were reported by electric utility facilities such as St. Johns River Power Park (Duval, Florida), U.S. TVA Widows Creek Fossil Plant (Jackson, Alabama), Baldwin Power Station (Randolph, Illinois), and U.S. TVA Cumberland Fossil Plant (Stewart, Tennessee), which reported releases of 250, 250, 850, and 1,000 pounds (0.11, 0.11, 0.39, and 0.45 metric tons), respectively (TRI99 2002).

Beryllium has been identified in 92 surface water and 376 groundwater samples collected from 535 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2002).

6.2.3 Soil

Beryllium is naturally present in soils and sediments. Releases of beryllium and beryllium compounds to U.S. soils in 1999 as reported to the TRI are shown in Tables 6-2 and 6-3, respectively. According to the TRI, 53,271 pounds (52 metric tons) of beryllium and 822,947 pounds (179 metric tons) of beryllium compounds were released on-site to land by facilities that manufacture or process beryllium and beryllium compounds (TRI99 2002). An additional 20,081 pounds (9 metric tons) of beryllium and 72,118 pounds (33 metric tons) of beryllium compounds were released off-site to locations within the United States in 1999 (TRI99 2002).

Coal fly ash and municipal solid waste incinerator ash are disposed of in landfills and used in building materials (Kalyoncu 1998). Coal fly ash contains beryllium at levels of 46 mg beryllium/kg ash (Stadnichenko et al. 1961). About 100 million tons of coal fly ash containing various levels of beryllium are generated each year (Kalyoncu 1998). This translates to about 420 metric tons of beryllium disbursed as coal fly ash.

Land application of sewage sludge containing higher than background concentrations of beryllium can be source of beryllium contamination of soil. Deposition of atmospheric aerosols on terrestrial surfaces is another source of beryllium in soil. Valberg et al. (1996) estimated the amount of time that it would take to double the ambient soil concentration of beryllium by dry deposition (at the point of maximum impact) near a MSW incinerator in Vermont. Their estimate was between 468 and 2,275 years, depending upon the ambient concentration of beryllium in the soil. Other quantitative data regarding the relative significance of these sources was not available.

Beryllium has been identified in 353 soil and 193 sediment samples collected from 535 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2002).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Beryllium in air is attached to particulate matter whose residence time in air is dependant upon particle size. A study of stack emissions from coal combustion reported that most beryllium is found on particles with diameters of <2.5 μm (Gladney and Owens 1976). Particles of this size can remain airborne for approximately 10 days (Gladney and Owens 1976). The transport of beryllium from the atmosphere to terrestrial and aquatic surfaces occurs through wet and dry deposition (EPA 1987). By analogy to other elements, a typical dry deposition velocity may be estimated for beryllium particles over vegetative surfaces as 0.25 cm/second (EPA 1987). The dry deposition rate of aerosol particles is a function of particle size, wind speed, and surface roughness. The process of wet deposition of airborne beryllium consists of wash-out and rain-out; wash-out involves the scrubbing of particles from the air by rain and rain-out involves their attachment to aerosols in clouds. The portion of beryllium particles transported from the atmosphere by wet deposition has not been estimated. Beryllium was detected but not quantified in rainwater from Fresno, California, which suggests that transport of beryllium from the atmosphere to terrestrial and aquatic surfaces occurs by wet deposition (Salo et al. 1986). Beryllium containing soil can be resuspended in the atmosphere as a result of wind action.

Beryllium is carried to rivers, lakes, and oceans by the process of land erosion. The amount of beryllium transported to surface waters from the land by wind-blown soil is estimated to be relatively small (Merrill et al. 1960). Acid deposition has been shown to accelerate chemical weathering of soil and bedrock into drainage outflow, increasing the mobility of beryllium (Jagoe et al. 1993). The estimated residence time of beryllium in ocean water, before it is removed from the aquatic phase by sedimentation or other removal processes, is between 150 and 570 years (Bowen 1979; Merrill et al. 1960).

Beryllium binds strongly to soil fulvic acid; binding increases with increasing pH. Beryllium also forms complexes with marine fulvic acids at nearly neutral pH values (Esteves Da Silva et al. 1996a). However, beryllium has a much stronger affinity for clay minerals than for organic matter. Beryllium is usually associated in soil with aluminum sites on clay minerals rather than with iron oxides (Lum and Gammon 1985). It tends to displace divalent cations with smaller charge-to-ionic radius ratios (Fishbein 1981). For pH values #6, the distribution of beryllium between solution and solids is related to sorption at surface sites. At pH values >6, the solute concentration of beryllium is strongly controlled by the solubility of $Be(OH)_2$ (Aldahan et al. 1999).

The sediment-water distribution coefficients (K_d) for beryllium are very high indicating a very low mobility in sediments. At pH values >6, K_d values are very high for most soils and sediments. For Lake Michigan sediments, K_d ranged between 105 and 106 (Hawley et al. 1986). Beryllium may accumulate in the surface organic layer of the sediment profile; however, there is no indication as to whether the organic matter content of sediment affects K_d (Lum and Gammon 1985). The presence of organic matter did not significantly affect the K_d for saline systems (You et al. 1989); in seawater, K_d is, on average, between 316,000 and 794,000 (Hawley et al. 1986).

In highly alkaline soils, the mobility of beryllium may increase as a result of the formation of soluble hydroxide complexes, such as $[Be(OH)_4]^{2-}$ (Callahan et al. 1979; Cotton and Wilkinson 1980). In acidic soils (e.g., forest ecosystems), dissolved Be^{2+} has been found to be the prevailing beryllium species in the soil solution, and it should be relatively mobile in these environments (Krám et al. 1998). However, leaching would not be expected to occur in less acidic soils (Hayes and Traina 1998).

The concentration of beryllium in plants is very low (see Section 6.4.4). Soluble forms of beryllium must be present for uptake to occur in plants. For collard seedlings, beryllium remains in the roots, and only small portions were translocated to above ground portions (Kaplan et al. 1990). Romney and Childress (1965) examined uptake of ^7Be in beans, barley, sunflowers, and tomato plants. Over 95% of ^7Be was found in the roots; very little was translocated to the foliage and fruits (Romney and Childress 1965). The Enrichment Ratio (ER) of beryllium in oat grain and in alfalfa grown in both microcosms and field plots amended with beryllium containing fly ash was 1 (Tolle et al. 1983).

Beryllium does not bioconcentrate in aquatic organisms. A measured bioconcentration factor (BCF) of 19 was reported for beryllium in bluegill fish (EPA 1980). Other investigators have reported a BCF of 100 for freshwater and marine plants, vertebrates, and fish (Callahan et al. 1979). Comparisons of the beryllium levels in bottom-feeding biota and surfaces sediments from Lake Pontchartrain, Louisiana, indicate similar, but somewhat lower, beryllium concentrations in biota (Byrne and DeLeon 1986). Very low bioaccumulation for beryllium was observed in southern toads (*Bufo terrestris*) exposed directly to elevated levels of beryllium and other trace metals from a coal fly ash basin (Hopkins et al. 1998). No evidence of the bioaccumulation of beryllium in the food chain of humans was located in the literature (Fishbein 1981).

6.3.2 Transformation and Degradation

As an element, beryllium does not degrade in the environment; it can only change its form.

6.3.2.1 Air

The atmospheric emission of beryllium during ore processing is likely to occur as: beryllium, beryllium ore dust, beryllium hydroxide, $Be(OH)_2$; beryllium oxide, BeO; sodium fluoroberyllate, $(NH_4)_2BeF_4$; and beryllium fluoride, BeF_2 (Fishbein 1981); from ceramic plants, atmospheric emissions are typically beryllium or beryllium oxide (Fishbein 1981). The form of beryllium emitted into the atmosphere from thermal processes is typically beryllium oxide (EPA 1998). It is unlikely that beryllium oxide in air will react with sulfur or nitrogen oxides to produce beryllium sulfates or nitrates.

6.3.2.2 Water

Beryllium exhibits only the +2 oxidation state in water. The reaction of beryllium in water is controlled by chemical speciation by which one species is converted to another. Beryllium is highly hydrated in acid solutions, which is a consequence of its high charge to size ratio. The speciation of beryllium in solution is: $[Be(H_2O)_4]^{2+}$, $Be_2(OH)^{3+}$, $Be_3(OH)_3^{3+}$, and possibly $Be_5(OH)_7^{3+}$ in acid solution (i.e., pH#6); and $[Be(OH)_4]^{2-}$ in basic solution (i.e., pH>8) (Cotton and Wilkinson 1980). In the pH range of 6–8, typical of most waters, the speciation of beryllium is controlled by the formation solid beryllium hydroxide, $Be(OH)_2$, which has a very low solubility (solubility product, $K_{sp}=10^{-21}$). Table 6-4 illustrates several precipitation reactions for beryllium under a neutral environment.

Other transformations of environmental importance are the formation of insoluble basic carbonates, such as $(BeCO_3)_2Be(OH)_2$, formed by reaction of dissolved carbonate with beryllium solutions and the formation of beryllium sulfate (i.e., $BeSO_4$) formed by reaction of soluble sulfates with beryllium solutions.

Table 6-4. Precipitation of Beryllium Compounds in a Neutral (pH 6.5–9.5) Environment

Ammonium tetrafluoroberyllate (Ammonium beryllium fluoride) $(NH_4)_2BeF_4$ —> $2[NH4]^+_{aq} + [BeF_4]^{2-}_{aq}$ Excess H_2O pH 7	Remains soluble in a neutral environment
Beryllium oxide $BeO + H_2O$ —> $Be(OH)_2$ Excess H_2O pH 7	Forms insoluble beryllium hydroxide in a neutral environment
Beryllium hydroxide $Be(OH)_2$ —> no reaction Excess H_2O pH 7	Beryllium hydroxide is insoluble in a neutral environment
Beryllium fluoride $BeF_2 + 2\ H_2O$ —> $[BeF_2(H_2O)_2]_{aq}$ and other complexes Excess H_2O pH 7	Remains soluble in a neutral environment
Beryllium nitrate trihydrate $Be(NO_3)_2\#3H_2O + 2MOH^a$ —> $Be(OH)_2 + 2[M]^+_{aq} + 2[NO_3]^-_{aq} + 3H_2O$ Excess H_2O pH 7	Forms insoluble beryllium hydroxide in a neutral environment
Beryllium sulfate tetrahydrate $BeSO_4\#4H_2O + 2MOH^a$ —> $Be(OH)_2 + 2[M]^+_{aq} + [SO_4]^{2-}_{aq} + 4H_2O$ Excess H_2O pH 7	Forms insoluble beryllium hydroxide in a neutral environment

Table 6-4. Precipitation of Beryllium Compounds in a Neutral (pH 6.5–9.5) Environment *(continued)*

Beryllium oxalate trihydrate $BeC_2O_4\#3H_2O + 2MOH^a \longrightarrow Be(OH)_2 + 2[M]^+_{aq} + [C_2O_4]^{2-}_{aq} + 3H_2O$ Excess H_2O pH 7	Forms insoluble beryllium hydroxide in a neutral environment
Beryllium Basic Acetate[b] $Be_4O(C_2H_3O_2)_6 + 6MOH^a + H_2O \underset{aq}{\longrightarrow} 4Be(OH)_2 + 6[M]^+_{aq} + 6[C_2H_3O_2]^-$ Excess H_2O pH 7	Forms insoluble beryllium hydroxide in a neutral environment

Source: EPA 1998

[a]MOH is a base; M in MOH signifies a cation such as sodium (Na) or potassium (K).
[b]Beryllium basic acetate is not a true basic salt; it is a covalent compound.

6.3.2.3 Sediment and Soil

Typical transformation processes for beryllium in soil include precipitation, complexation, and anion exchange. Important factors affecting the transformation of beryllium in soils and sediments include: pH, ionic strength (i.e., salinity), concentration and distribution of species, composition of the mineral matrix, organic matter, biological organisms, and temperature (see Section 6.3.1). Data suggesting the biotransformation of beryllium or its compounds in soil were not located.

6.3.2.4 Other Media

No data were located on the transformation of beryllium in media other than air, water, sediment, and soil in the literature.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

6.4.1 Air

Beryllium in the ambient air is measured at many local, state, and national air monitoring stations across the United States. The data are available from the Storage and Retrieval of Aerometric Data database (EPA 1987). The detection limit for aerometric determination of beryllium is 0.03 ng/m^3, and annual averages at most of these monitoring stations are listed below this concentration. Measurements at 100 U.S. locations indicated an average daily beryllium concentration of <0.5 ng/m^3 (Drury et al. 1978; Fishbein 1981). Between 1982 and 1992, annual averages of beryllium in air ranged from 0.02 to 2 ng/m^3 in the urban Detroit, Michigan area. The ambient concentrations of beryllium were quite similar for all land use categories (e.g., residential, commercial, and industrial). In 1985, in Jacksonville, Florida, beryllium was below the limit of detection in air (Del Delumyea et al. 1997).

The ambient concentration of beryllium found in air near power stations in Castellon, Spain ranged from not detected to 1.61 ng/m^3 (Boix et al. 2001). Beryllium concentrations in atmospheric particulate samples in and around a beryllium processing facility near Navi Mumbai, India were 0.48±0.42 ng/m^3 (N#397). The levels of beryllium during the monsoon season were comparatively lower and often were below the detection limit (Thorat et al. 2000).

6.4.2 Water

Beryllium was detected in 2,760 out of 50,000 U.S. Geological Survey ambient surface water monitoring stations through the year 1988 with a mean concentration of 1.9 µg/L (Eckel and Jacob 1988). The National Drinking Water Contaminant Occurrence Database (NDOD), which contains data from ambient water supplies, lists the number of detections of beryllium in surface water at several locations around the United States. In lakes/reservoirs, dissolved beryllium was detected at 13 of 137 sites (9.5% of sites) with an average concentration of 1.1±0.4 µg/L (EPA 2001). In spring waters, dissolved beryllium was detected at 4 of 66 sites (6.1% of sites) with an average concentration of 99.3±42.1 µg/L (EPA 2000a). In other surface waters, dissolve beryllium was detected at 227 of 1,539 sites (14.7% of sites) with an average concentration of 20.8±36.1 µg/L; total beryllium was detected at 182 of 943 sites (19.3% of sites) with an average concentration of 4.4±35.1 µg/L (EPA 2001). The median total beryllium concentration of Great Lakes water samples ranged from <4 to 120 ng/L. The percentage of beryllium in suspended particulates of Great Lakes water samples ranged from 2 to 88% and averaged about 50% (Rossmann and Barres 1988). Beryllium concentrations measured in the Houston Ship Channel ranged from 8 to 24 ng/L (Saleh and Wilson 1999). The concentration of total beryllium in seawater ranges from 0.02 to 0.9 ng/L, with an average of <0.5 ng/L (Measures and Edmond 1986; Merrill et al. 1960).

The NDOD lists the number of detections of beryllium in groundwater water at several locations around the United States. In groundwater, dissolved beryllium was detected at 262 of 4,177 sites (6.6% of sites) with an average concentration of 13.0±50.3 µg/L; total beryllium was detected at 30 of 334 sites (9.0% of sites) with an average concentration of 1.7±1.8 µg/L (EPA 2000a). The median concentration of beryllium in groundwater samples taken around the Denver, Colorado metropolitan area in 1993 was measured at <1 µg/L (Bruce & McMahon 1996). Beryllium has been identified in 376 groundwater samples collected from 535 NPL hazard waste sites, where it was detected in some environmental media (HazDat 2002).

Rainwater in Australia had an average beryllium concentration of 0.05–0.08 µg/L (Meehan and Smythe 1967) and an upland environment in Great Britain had an average concentration of <0.06 µg beryllium/L (Neal et al. 1992).

The average concentrations of beryllium in bottled and tap water in the United States were <0.1 and 0.013 µg/L, respectively. Table 6-5 summarizes some selected data on the beryllium content of drinking water (Vaessen and Szteke 2000).

6.4.3 Sediment and Soil

Beryllium is the 44th most abundant element in the Earth's crust. The average beryllium concentration in the Earth's crust is approximately 2–5.0 mg/kg (Drury et al. 1978; Griffitts and Skilleter 1990; Krám et al. 1998; Mason and Moore 1982; Reeves 1986). Beryllium occurs in silicate minerals and feldspar minerals. The greatest known concentrations of beryllium are found in certain pegmatite bodies. Beryllium ores can contain several thousand mg beryllium per kg solid (Fishbein 1981). Shacklette and Boerngen (1984) reported the average and range of beryllium concentrations in soils and other surficial materials in the conterminous United States as 0.63 and <1–15 mg/kg, respectively. Frink (1996) summarized several different studies and reported that the most likely concentration of beryllium in uncontaminated soils (in the Northeast United States) ranges from <1 to 7 mg/kg. The average concentrations of beryllium in the O or A horizons (sandy loam) and the B horizon (clay) in Maryland were 0.71 and 0.46 mg/kg respectively (Sparling and Lowe 1996). The average and range of beryllium concentrations in Florida soils were 0.46 mg/kg and 0.01–5.92, respectively (Chen et al. 1999). The average beryllium concentration in California soils was measured as 1.14 mg/kg (Chen et al. 1999). There are few beryllium rich soils in the United States, and these areas are in sparsely settled areas that are not important for food production (Griffitts and Skilleter 1990). The concentration of beryllium in soil around beryllium processing facilities in Navi Mumbai, India ranged from 1.42 to 2.75 µg/g (Thorat et al. 2000). These levels were comparable to background levels reported in the literature.

In bottom sediments of the Detroit River and western Lake Erie, concentrations of beryllium ranged from 0.1 to 3.8 µg/g beryllium (Lum and Gammon 1985). The beryllium levels in the sediments of Lake Pontchartrain, Louisiana were 0.05–0.5 µg/kg (dry weight) (Byrne and DeLeon 1986). The concentration of beryllium in sediments from the Neosho River in southeastern Kansas ranged from 0.52 to 1.1 µg/g dry weight in 1992 (Allen et al. 2001). Beryllium has been identified in 353 soil and 193 sediment samples collected from 535 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2002).

Table 6-5. Beryllium Content of Drinking Water

Product	Number of samples	Content (µg/kg) Mean	Range	Technique	Reference
Mineral water (bottled)					
Spain:					
Lanjaron	3	—	0.12±0.01	IEF	Capitan et al. 1989
Ortigosa del Monte	3	<0.6	<0.06	IEF	Capitan et al. 1989
United States:					
All samples	72	<0.1	<0.1–5.2	ICP	Allen et al. 1989
Domestic samples[a]	18	<0.1	<0.1–0.2	ICP	Allen et al. 1989
European samples[b]	54	<0.1	<0.1–5.2	ICP	Allen et al. 1989
Poland:					
Nieszawa	3	0.17	—	ET-AAS	Szczepaniak and Szymanski 1996
Zywiec Zdrój	3	0.15	—	ET-AAS	Szczepaniak and Szymanski 1996
Tap Water					
Spain-Granada	3	—	0.09±0.01	IEF	Capitan et al. 1989
Germany-Mainz	—	0.008[c]	<0.005±0.009	ET-AAS	Reichert 1973
Germany-Weisbeden	—	—	0.034±0.002	ET-AAS	Sauer and Lieser 1986

Table 6-5. Beryllium Content of Drinking Water *(continued)*

Product	Number of samples	Content (µg/kg) Mean	Range	Technique	Reference
Saudi Arabia-Riyadh (schools)	59	1.24[c]	0.4–2.17	ICP-MS	Al-Saleh 1996
The Netherlands	266	<0.1	<0.1–0.2	—	Fonds et al. 1987
	91	<0.05	<0.05–0.21	ICP-MS	Van de Veld-Koerts et al. 1994
United States	—	0.013[c]	0.01–0.7	—	APHA 1992

Source: Vaessen and Szteke 2000

[a]nine brands
[b]28 brands
[c]arithmetic mean

— = Not specified; ET-AAS = electrothermal atomic absorption spectrometry; ICP = inductively coupled plasma spectroscopy; ICP-MS = inductively coupled plasma mass spectrometry; IEF = ion exchange fluorimetry

6.4.4 Other Environmental Media

The beryllium concentration in several foods, fruits, and fruit juices from around the world are shown in Tables 6-6 and 6-7. The median concentration of beryllium in the 38 foods listed in Table 6-6 is 22.5 µg/kg fresh weight (excluding kidney beans) and the range of concentrations is <0.1–2,200 µg/kg fresh weight. The highest concentrations (in µg/kg fresh weight) were reported for kidney beans (2,200), crisp bread (112), garden peas (109), parsley (77), and pears (65). The average concentration of beryllium in fruit and fruit juices listed in Table 6-7 is 13.0 µg/L, and the concentrations ranged from not detected to 74.9 µg/L.

The beryllium concentration in the tissue of bottom fish (e.g., English sole or *Parophrys vetulus*) from Commencement Bay, Tacoma, Washington was 6 µg/kg (Nicola et al. 1987). Beryllium levels in oysters and clams in Lake Pontchartrain, Louisiana were 0.051 and 0.083–0.38 µg/g dry weight, respectively (Byrne and DeLeon 1986). A U.S. FDA survey of concentrations of beryllium and other elements in oysters and clams collected from U.S. coastal areas in use for shellfish production ranged from not detected to 0.002 mg/kg wet weight (Capar and Yess 1996). In 1991, the concentration of beryllium in mussels species from the Neosho River, Kansas were 0.02–0.04, not detected–0.02, 0.03, and 0.02–0.04 µg/g dry weight for pimpleback (n=3) sampled at Cottonwood River; Kansas, monkeyface (n=2) sampled at Humboldt, Kansas; monkeyface (n=1) sampled at Leroy, Kansas; and monkeyface (n=4) sampled at Oswego, Kansas, respectively (Allen et al. 2001).

The concentration of beryllium in pipping black-crowned night herons from Pea Patch Island in Delaware Bay, a major shipping area that receives anthropogenic releases of toxic substances, ranged from not detected to 0.028 µg/g dry weight. At Middle Island (a coastal reference site without contamination located in Rehoboth Bay, Delaware), the concentration of beryllium in pipping black-crowned night herons ranged from not detected to 0.021 µg/g dry weight (Ratter et al. 2000).

Beryllium has been detected in orchard leaves and in various trees and shrubs in the United States at concentrations of 26 and <1 µg/kg, respectively (IARC 1980). The beryllium content of macrohydrophytes derived from various habitats in Poland ranged from 0.7 to 136.6 µg/g. The beryllium concentrations varied with the plant species and the particular degree of water contamination in their respective environments (Sarosiek and Kosiba 1993). Beryllium levels were below detection limits (not

Table 6-6. Beryllium Content of Various Fresh Foods

Product	Number of samples	Concentration (µg Be/kg fresh weight) Mean	Range	Technique	Reference
Bananas, pulp	400	4.2	ND–18	—	Cowgill 1981
Beans	3	0.07	ND–0.07	F	Meehan and Smythe 1967
Beans, kidney	—	2,200[a]	—	ICP-AES	Awadallah et al. 1986
Cabbage	1	0.2	—	F	Meehan and Smythe 1967
Cabbage	95	0.091	ND–0.50	ICP-MS	Bibak et al. 1999
Cane sugar:					
brown	—	30	—	—	Hamilton and Minski 1973
demerara	—	6	—	—	Hamilton and Minski 1973
refined	—	2	—	—	Hamilton and Minski 1973
granulated	—	0.2	—	—	Hamilton and Minski 1973
Carrots, raw	—	<25	—	—	Wolnik et al. 1984
Clams, hardshell	31	2±3	—	ICP-AES	Caper and Yess 1996
Clams, softshell	10	<2	—	ICP-AES	Caper and Yess 1996
Crabs	6	15	10–20	F	Meehan and Smythe 1967
Crisp bread	—	112[a]	—	Flame AAS	Zorn and Diem 1974[b]
Coriander	—	34[a]	—	ICP-AES	Awadallah et al. 1986
Corn, field	—	<25	—	—	Wolnik et al. 1984
Dill	—	59[a]	—	ICP-AES	Awadallah et al. 1986
Egg plant (aubergine)	—	26[a]	—	ICP-AES	Awadallah et al. 1986
Fish, whole:					
Mullet	8	11	1.6–19	F	Meehan and Smythe 1967
Blackfish	4	11	3.7–18	F	Meehan and Smythe 1967
Fish, whole:					
Mullet	2	1.5	ND–2.6	F	Meehan and Smythe 1967
Blackfish	1	0.4	—	F	Meehan and Smythe 1967
Garden pea	—	109[a]	—	ICP-AES	Awadallah et al. 1986
Green pepper	—	42[a]	—	ICP-AES	Awadallah et al. 1986
Hen eggs, yolk	1	0.2	—	F	Meehan and Smythe 1967
Hen eggs, yolk, and white	1	0.06	—	F	Meehan and Smythe 1967
Honey					
Eucaliptus	—	0.18±0.09	—	ICP-MS	Bettinelli et al. 2000
Robinia	—	0.38±0.02	—	ICP-MS	Bettinelli et al. 2000

Table 6-6. Beryllium Content of Various Fresh Foods (*continued*)

Product	Number of samples	Concentration (µg Be/kg fresh weight) Mean	Range	Technique	Reference
Lettuce	—	16[a]	—	Flame AAS	Zorn and Diem 1974
Meat	3	4	4–5	GC-ECD	Kaiser et al. 1972
Milk	100	0.2	ND–0.7	F	Meehan and Smythe 1967
Mushrooms	1	1.6	—	F	Meehan and Smythe 1967
Mushrooms, European wild	1,303	9	<5–36	ET-AAS	Seeger et al. 1984
Orange juices	—	<1	—	—	McHard et al. 1980
Oysters	59	0.6	0.2–5.4	F	Meehan and Smythe 1967
Oysters, east coast United States	93	<2	—	ICP-AES	Capar and Yess 1996
Oysters, west coast United States	40	<2	—	ICP-AES	Capar and Yess 1996
Parsley	—	77[a]	—	ICP-AES	Awadallah et al. 1986
Peanuts, kernels	2	0.5	0.3–0.8	F	Meehan and Smythe 1967
Pears	—	65[a]	—	ICP-AES	Awadallah et al. 1986
Potatoes	—	59[a]	—	ICP-AES	Awadallah et al. 1986
Potatoes	—	33[a]	—	Flame AAS	Zorn and Diem 1974
Potatoes	41	0.4–0.6	0.2–1.4	ET-AAS	Hofele et al. 1994
Rice	3	4	3–5	GC-ECD	Kaiser et al. 1972
Rice, peeled	—	72[a]	—	Flame AAS	Zorn and Diem 1974
Tomatoes	1	0.2	—	F	Meehan and Smythe 1967
Tomatoes		17[a]	—	Flame AAS	Zorn and Diem 1974
Vegetable marrow (pumpkin)	—	20[a]	—	ICP-AES	Awadallah et al. 1986

[a]Original data based on dry weight; concentrations are recalculated to fresh weight.

— = not specified; AAS = atomic absorption spectroscopy; AES = atomic emission spectroscopy; ET-AAS = electrothermal atomic absorption spectrometry; F = fluorimetry; GC-ECD = gas chromatography electron capture detection; ICP-AES = inductively coupled plasma-atomic emission spectroscopy; ICP-MS = inductively coupled plasma-mass spectrometry; ND = not detected

Table 6-7. Beryllium Content of Various Fruits and Fruit Juices

Product	Number of samples	Mean (µg/L)	Range
Apple juice	4	22.5	ND–43.6
Citrus fruit			
Ruby red grapefruit	1	1.3	—
Lime	1	ND	—
Tangerine	1	0.8	—
Grape cultivars	3	4.4	<0.1–7
Lemon products			
CA lemon	1	17.4	—
Bottled lemon	1	17.0	—
Lemonade	1	55.3	—
Orange juice	5	2.8	ND–2.8
Papaya (pulp)	3	74.9	64.5–84.1
Pear (pulp)	1	37.3	—
Red currant	1	1.1	—
Stone fruit (pulp)			
Apricot	1	<0.1	—
Peach	1	ND	—
Plum	1	1.6	—
Prune	1	3.6	—
Sour cherry	1	1.5	—
Tomato sauce	2	42.4	39.8–45.0
Tropical fruit			
Banana	1	1.5	—
Kiwi	1	3	—
Mango	1	4.5	—
Pineapple	1	<0.1	—

Source: Barnes 1997

— = not specified; ND = not detected

specified) in vegetation in the immediate vicinity of a municipal solid waste (MSW) incinerator near Catalonia, Spain (Meneses et al. 1999).

Beryllium levels of 0.47–0.74 µg per cigarette have been detected in three brands of German cigarettes; 2–10% of the beryllium was found in the cigarette smoke (Reeves 1986). In a literature review undertaken by Smith et al. 1997, yields of 0–0.0005 µg beryllium per cigarette have been reported for domestic cigarette brands. Beryllium was detected in only 4 of 12 studies in which it was a target element (Smith et al. 1997).

The beryllium concentration in coal ash is on average 46 mg/kg in the United States (Stadnichenko et al. 1961). Beryllium concentrations in ammonia, nitrate, and phosphorus fertilizers used in agriculture ranged from <0.2 to 13.5 µg/g (Raven and Loeppert 1997).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population is exposed to trace amounts of beryllium by inhalation of air and ingestion of drinking water and food. If the average concentration of beryllium in air is assumed to be <0.03 ng Be/m^3 (see Section 6.4.1), and it is further assumed that a normal U.S. adult inhales approximately 20 m^3 of air per day, then the inhalation exposure for a U.S. adult would be approximately <0.6 ng Be/day. This value may be somewhat higher for persons living near sources of beryllium emission. Similarly, if the concentration of beryllium in average U.S. drinking water is 0.5 µg/L (see Section 6.4.2), and the consumption rate of drinking water by a normal adult is assumed to be 2 L/day, the exposure from drinking water would be 1 µg per day. Reliable data regarding the daily exposure rate to beryllium from food consumption are lacking. It has been estimated that the daily intake of beryllium from U.S. food is 0.12 µg (EPA 1987). This estimate is based on an arbitrary value for beryllium content of a total diet sample of 0.1 ng per g food and a daily consumption of 1,200 g of food (EPA 1987). In a study examining the trace element concentrations of foodstuffs in Tarragona, Spain, beryllium was below the detection limit (0.02 µg/g) in the following food groups: meat, seafood, cereals, seeds, vegetables, roots/tubers, fruits, milk, dairy products, eggs, and sugar (Llobet et al. 1998). In another study examining, the trace element concentrations of food samples via hospital diets in Japan, the average daily intake of beryllium was determined to be 84.4 µg/day (Muto et al. 1994). Other investigators have reported the total daily intake of beryllium in the range of 5–100 µg/day (Emsley 1998; Tsalev and Zaprianov 1984; Vaessen and Szteke 2000).

The mean concentration of beryllium in urine of about 500 nonoccupationally exposed individuals in the United States according to the 3rd National Health and Nutrition Examination Survey was 0.22 µg/g of creatinine (Paschal et al. 1998). Other studies reported mean urinary beryllium concentrations ranging from <0.03 to 0.4 µg/L for persons not occupationally exposed (Apostoli and Schaller 2001). Tsalev and Zaprianov (1984) reported that approximately 10 µg Be/day is excreted (on average) in human feces. Using the estimated daily fecal concentration, the exposure to beryllium by this method is within the range of estimates determined from total diet studies as discussed previously. Beryllium concentrations in other human tissues and fluids are: blood 0.01–3.6 µg/L, bone 3 µg/kg, hair 5–8 µg/kg, liver 2 µg/kg, muscle 0.8 µg/kg, nails <10 µg/kg, plasma or serum <4 µg/L, and tooth <0.01 µg/kg (Emsley 1998; Tsalev and Zaprianov 1984).

In a study of German cigarettes, tobacco was found to contain 0.47–0.74 µg beryllium per cigarette and 2–10% passes into the smoke during smoking (Reeves 1986). Some cigarettes contain small amounts of beryllium, and increases of blood and urine beryllium have been associated with smoking (Tsalev and Zaprianov 1984). In another review focusing on cigarettes from the United States, yields of 0–0.0005 µg Be per cigarette have been reported in 4 of 12 studies of smoke measurements; however, 8 of 12 studies failed to detect beryllium at any concentration (Smith et al. 1997). Nevertheless, smokers may have a higher probability of exposure to beryllium than the nonsmoking population.

People who work in industries where beryllium is present have a greater probability of inhalation exposure than nonoccupational groups. The estimated daily-weighted average beryllium exposure levels for some workers in a plant that extracted and produced beryllium metal were >50 µg/m^3 during the mid-1960s. Beryllium exposure levels were >30 µg/m^3 during the mid-1970s. After 1977, this plant complied with the OSHA maximum TWA concentration of 2 µg/m^3 (Kriebel et al. 1988a). The TWA personal air concentration for beryllium in a precious metal refinery in 1983 ranged from 0.22 to 42.3 µg/m^3 (Cullen et al. 1987). Recent occupational exposure measurements of beryllium at the Rocky Flats Environmental Technology Site in Colorado were conducted in the main beryllium production building. Mean concentrations of beryllium were measured for area and breathing zone monitors as 0.16 and 1.04 µg/m^3, respectively (Stange et al. 1996a). At the Cardiff Atomic Weapons Establishment in the United Kingdom, annual mean area and personal sampling concentration ranges of beryllium were from 0.02–0.32 and 0.09–0.72 µg/m^3, respectively, over the period from 1961 to 1997 (Johnson et al. 1999).

Workers who do not change their work clothes at the end of the work day can increase the probability of home contamination with beryllium. Fabrics experimentally exposed at a beryllium production worksite contained up to 2.8 mg Be/m^2 (NIOSH 1995). Workers' family members may be exposed when workers come home wearing beryllium-contaminated clothing. Resuspended beryllium dust concentrations in air from unwashed clothing can reach levels of 0.64 µg/m^3. The shaking of contaminated clothes can administer an inhalation dose of approximately 17 µg beryllium (NIOSH 1995). In another study, beryllium concentrations in machine shop workers' personal vehicles were measured. The highest concentrations of beryllium were measured on the driver's floor of the workers' vehicles at 19 µg/Be/$foot^2$ (Sanderson et al. 1999).

It is likely that dental technicians who work with beryllium-containing dental alloys without using appropriate handling safeguards may be exposed to higher levels of beryllium than the normal population (Bauer et al. 1988).

A National Occupational Exposure Survey conducted by NIOSH during 1981–1983 estimated that 13,869 workers were potentially exposed to beryllium and 7,045 workers to beryllium compounds in the workplace (NIOSH 1989a).

6.6 EXPOSURES OF CHILDREN

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

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

Specific information on the exposure of children to beryllium is limited. An x-ray health survey was conducted in 1948 in the neighborhood surrounding a beryllium manufacturing facility in Lorain, Ohio.

In this survey, 2,000 children were examined, and none of the children exhibited signs of chronic berylliosis disease (AEC 1948). As with adults in the general population, small exposures in children occur from normal ingestion of food and drinking water and inhaling air. These exposures may be higher in areas with naturally high beryllium soil levels, and near beryllium processing sites, electric power plants, and waste sites containing beryllium. A study by Krachler et al. (1999a) provides suggestive evidence that beryllium is transferred across the placenta and excreted via breast milk. The levels of beryllium in umblical cord serum and in colostrum were higher than in maternal serum. The average concentrations of beryllium in the umbilical cords of healthy newborn children were measured for arterial (1.3 µg/L), venous (0.8 µg/L), and mixed (0.6 µg/L) sera (Krachler et al. 1999b). No information on beryllium levels in amniotic fluid, meconium, or neonatal blood was located.

At waste sites, beryllium that is found in excess of natural background levels is most likely to be in soil, and presents a special hazard for young children. Hand-to-mouth activity and eating contaminated dirt will result in oral exposure to beryllium. The hazard in this case depends on the form of beryllium present at the waste site. Beryllium in soil at waste sites is almost entirely in the form of insoluble oxides and hydroxides of beryllium which would be expected to be less available than more soluble forms (see Section 6.3.1).

Other home exposures are unlikely since no household products or products used in crafts, hobbies, or cottage industries contain significant amounts of beryllium except in copper-beryllium wire, which is used in and around the home in electronics or other electrical devices.

Beryllium exposure to children from parents' work clothes, skin, hair, tools, or other objects from the workplace is possible if the parent uses beryllium at work. In a report to Congress by NIOSH, several historical cases of home contamination by beryllium were reported (NIOSH 1995). The most recent case was in 1992, suggesting that cases of beryllium home contamination may still be occurring. The majority of these cases were from the contamination of machinist workers' clothing with beryllium dust (NIOSH 1995).

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Several populations are at high risk for beryllium exposure. Individuals with the highest risk include people who are occupationally exposed to beryllium from manufacturing, fabricating, or reclaiming industries. There have been no reports of diseases attributable to beryllium exposure as a result of beryllium ore mining operations (Eisenbud and Lisson 1983; EPA 1987; Hamilton and Hardy 1974). People living near beryllium-emitting industries may be at a slightly increased risk of beryllium exposure due to contact with beryllium-contaminated dust within the household, as opposed to ambient air levels. Occupationally exposed workers who carry beryllium dust on their clothes from the workplace to their home may increase the risk of beryllium exposure to their family members (EPA 1987). However, it is common today for beryllium industries to provide and launder employee's work clothes. The National Emission Standard for Hazardous Air Pollutants (NESHAPS) restricts the amount of beryllium emitted into the environment by industries that process beryllium ores, metals, oxides, alloys, or wastes. The NESHAPS can be met by complying with either a 10 g per 24-hour emission limit or by meeting an ambient air concentration of 0.01 μg/m^3 of air averaged over a 30-day period (EPA 1982). Machine shops machining alloys containing #5% beryllium by weight are excluded from regulation under the NESHAPS emission standard (see 40 CFR Part 61, subpart C 61.30(b) 2001). No new cases of beryllium disease in people living near beryllium-processing industries have been reported in the past several years, probably because the past exposures were relatively high compared to present levels of beryllium in the ambient and workplace air (EPA 1987; NIOSH 1995).

Individuals may be exposed to high levels of beryllium from implanted dental prostheses (EPA 1987). The highest concentration of beryllium released from base metal alloy used as dental crowns measured in an artificial oral environment was 8 μg/day per crown (Tai et al. 1992). The mantles of some lanterns used by campers contain approximately 600 μg of beryllium, and most of the beryllium becomes airborne during the first 15 minutes when a new mantle is used (Fishbein 1981). Therefore, people who camp outdoors and use these mantles are possibly exposed to higher than normal levels of beryllium. A small percentage of the population is sensitive to very low concentrations of beryllium, but there is no evidence that sensitivity develops at beryllium concentrations present in food or water, or that sensitivity is aggravated by ingestion of beryllium. No other special groups at risk were identified (EPA 1980).

6.8 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of beryllium 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 beryllium.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The relevant physical and chemical properties of beryllium are known (see Section 4.2). Additional information regarding the chemical forms of beryllium in coal fly ash and aerosols produced by specific industrial processes, and the mode by which beryllium compounds are incorporated into biological systems would be useful. Additional information about the chelation of beryllium (especially about chelating agents that may be used in the development of beryllium-specific chelation therapy) would also be useful.

Production, Import/Export, Use, Release, and Disposal. Data regarding the production, import/export, and use of beryllium and beryllium compounds are available (see Sections 5.1 through 5.3). 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 TRI is updated yearly and provides a list of industrial production facilities and emissions.

As reported in Tables 6-2 and 6-3, the most significant amount of beryllium and beryllium compounds from production and use facilities is disposed of on land. Little is known about the methods used for land disposal of beryllium, except that small amounts of beryllium waste are discharged into public sewers

(TRI99 2002). Additional data examining the method used for land disposal of beryllium waste and the routes by which beryllium might find its way from land disposal sites into groundwater would be useful.

Environmental Fate. For solids, there is a need to determine uptake factors into edible portions of plants and not just adherence to the root structure. Dry or wet deposition from the atmosphere to soil and water can occur. Little experimental data on the particle size and residence time of beryllium and beryllium compounds present in the ambient atmosphere are available. Additional data examining the possible chemical transformation reactions of beryllium and its half-life in air would be useful. Data regarding the dominant types of sorption mechanisms for beryllium (e.g., ion exchange vs. chemical sorption) for different mineral and environmental conditions are limited. Additional information elucidating the fate of beryllium with respect to its chemical speciation in soil is necessary.

Bioavailability from Environmental Media. Although the absorption of specific beryllium compounds from skin contact, inhalation, and ingestion have been studied in animals (see Section 3.3.1), the bioavailability of beryllium or its compounds from contaminated air, water, soil, or plant material may differ significantly from the studied values. Additional information on the dependence of absorption of beryllium on such parameters as chemical form, extent of sorption in the host medium, and other possible variables would be useful.

Food Chain Bioaccumulation. Beryllium does not bioconcentrate to high levels in aquatic animals (EPA 1980), although the bioconcentration in bottom-dwelling animals may be higher than non bottom-dwelling animals (Byrne and DeLeon 1986). There is no evidence of biomagnification of beryllium within terrestrial or aquatic food chains (Fishbein 1981). Further studies establishing the biomagnification potential for beryllium would be useful. Data regarding the intake of beryllium from food are lacking (Vaessen and Szteke 2000; Wolnik et al. 1984). The accuracy of the available database of beryllium in foods is questionable (Vaessen and Szteke 2000). More reliable concentration information is needed on levels of beryllium in food stuff to reduce or eliminate the uncertainties in estimating the dietary intake of beryllium (Vaessen and Szteke 2000). Such information would be important in assessing the contribution of food to the total intake of beryllium from different pathways.

Exposure Levels in Environmental Media. Some data on the levels of beryllium in air and drinking water are available. Limited data regarding the ambient concentration of beryllium near beryllium-containing hazardous waste sites in the United States are available. These monitoring data are important for assessing the potential health risk for individuals living near the waste sites (Eckel and

Langley 1988). Nationwide monitoring data determining the levels of beryllium in U.S. drinking water at a detection limit <10 ng/L would be useful. Reliable and more recent monitoring data for the levels of beryllium in air, drinking water, soil (particularly at NPL sites), and food would be useful in estimating exposure from each source. Remedial investigations and feasibility studies conducted at the NPL sites contaminated with beryllium will add to the available database on exposure levels in environmental media. Investigations at these sites will also increase the current knowledge regarding the transport and transformation of beryllium at hazardous waste sites.

Exposure Levels in Humans. Beryllium levels in the urine and lung of both the control and occupationally exposed populations are available (Kanarek et al. 1973; Stiefel et al. 1980). No data on the beryllium levels in body tissues or fluids of populations living near hazardous waste sites or coal-fired power plants are available. Such information would be useful in assessing exposure levels for this population. Further studies regarding the possibility of increased exposure to beryllium via dental implants may be useful.

Exposures of Children. Children will be exposed to beryllium in the same manner as adults in the general population (i.e., ingestion of food and water, and inhalation of air).

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

Exposure Registries. The Beryllium Case Registry (BCR) was established at Massachusetts General Hospital, Boston, Massachusetts in 1952 and taken over by NIOSH in the late 1970s. Since its transfer to NIOSH, no additional cases were added. Presently, the BCR is not an active registry. This element is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The element will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this element.

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2001) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1. These studies are summarized in Table 6-8.

Table 6-8. Ongoing Studies on Human Exposure to Beryllium

Investigator	Affiliation	Subject	Sponsor
Peters, EL	Chicago State University	Fluctuating asymmetry in isopods as indicator of hazardous metals in urban area	National Institute of General Medical Sciences
Grew, ES	University of Maine	Beryllium in antarctic ultrahigh-temperature granulite-facies rocks and its role in partial melting of the lower continental crust	NSF

Source: FEDRIP 2001

NSF = National Science Foundation

7. ANALYTICAL METHODS

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

7.1 BIOLOGICAL MATERIALS

Methods used for the analysis of beryllium in biological materials are reported in Table 7-1. Reviews of beryllium analysis methods in biological media have been published (Delves 1981; Tsalev and Zaprianov 1984). Although the level of beryllium in urine may be informative of the current exposure level, it is not useful for quantitative exposure analysis. In contrast, the level of beryllium in blood, serum, or plasma is predictive of the intensity of current exposure from certain beryllium compounds (Tsalev and Zaprianov 1984; see Section 3.4.2). Neither flame atomic absorption spectroscopy (AAS) nor atomic emission spectroscopy (AES) have adequate sensitivity for measuring beryllium concentrations found in body fluids and tissues. The determination of beryllium levels in these matrices using the preceding techniques requires elimination of spectral interferences. Graphite furnace (or electrothermal) atomic absorption spectroscopy with background correction (deuterium or Zeeman effect) and inductively coupled plasma atomic emission spectroscopy (ICP-AES) are common analytical methods for beryllium. These techniques have the sensitivity and accuracy to determine the content of beryllium in body fluids and tissues (Delves 1981). To avoid sample contamination, stainless steel needles should be avoided for the collection of whole blood samples. Certain polyethylene sample collection tubes with added heparin as an anticoagulant may contaminate whole blood samples (Paudyn et al. 1989). A gas chromatographic method to detect beryllium in whole blood down to a concentration level of 0.02 µg/mL is available (Taylor and Arnold 1971). Krachler et al. (1999b) measured beryllium in umbilical cord serum, colostrum, and maternal serum at concentrations to <1 µg/L using inductively coupled plasma mass

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood	Add EDTA; acidify	GC/EC	~20 µg/L	44–117%	Taylor and Arnold 1971
Blood (dog)	Add sodium hydroxide; dissolve by heating; chelate with tri-fluoroacetylacetone; extract with benzene	GC/EC	No data	95–117%	Frame and Ford 1974
Urine	Dilute with nitric acid	ICP-MS	0.1 µg/L	No data	Paschal et al. 1998
Urine	Acidified urine precipitated with excess ammonium hydroxide; centrifuge, dissolve in nitric acid and add lanthanum	GFAAS	0.01 µg/L	94–110%	Hurlburt 1978
Urine	Dilute with a matrix modifier	GFAAS	0.05 µg/L	107%; 94–98%	Paschal and Bailey 1986; Shan et al. 1989
Urine (human and rat)	Add EDTA to aqueous sample; adjust to pH 6; add trifluoro-acetylacetone in benzene; extract	GC/EC	1 µg/L	68–123%	Foreman et al. 1970
Feces	Digest; dry ash; dissolve residue in acid	GFAAS	1 µg/kg; ~2 µg/kg	108%; 90–110%	Delves 1981; Hurlburt 1978
Fingernails	Acid digestion; dry ash; dissolve in acid	GFAAS	~2 µg/kg	90–110%	Delves 1981
Hair-fingernails	Dissolve in nitric acid-perchloric acid (1:1)	GFAAS	<1 µg/kg	98–105%	Hurlburt 1978

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Liver (bovine)	Wet-ash tissue in a mixture of acids; chelate with acetylacteone; extract (chloroform); acidify chelate with 2-hydroxy-3-naphthoic acid reagent	Fluorescence spectroscopy	No data	No data	IARC 1980
Lung tissue	Sample subjected to dry or wet ashing	ICP-AES	0.075 mg/kg	No data	Martinsen and Thomassen 1986
Lung tissue	Dry; acid digestion; dilute in acid; standard addition	GFAAS	No data	No data	Baumgardt et al. 1986

EDTA = ethylenediaminetetraacetic acid; GC/EC = gas chromatography-electron capture; GFAAS = graphite furnace atomic absorption spectrometry; ICP-AES = inductively coupled plasma-atomic emission spectrometry; ICP-MS = inductively coupled plasma-mass spectrometry

spectroscopy (ICP-MS). Another relative method for the detection of beryllium is Laser Ion Mass Analysis (LIMA). This analysis method uses a laser beam to ionize elements (e.g., beryllium) in a small section of tissue and detects the elements by time-of-flight mass spectrometry (MS) (Williams and Kelland 1986).

Standard reference materials (SRMs) are useful to determine the accuracy of an analytical method. A standard reference urine (SRM=2,670) with a certified beryllium concentration is available from National Institute of Standards and Technology (Shan et al. 1989).

7.2 ENVIRONMENTAL SAMPLES

Methods used to analyze beryllium in environmental media are presented in Table 7-2. The standard test methods approved by EPA and NIOSH for beryllium analysis in ambient and occupational samples are included in Table 7-2. Environmental samples analyzed by atomic absorption spectroscopy and gas chromatography (GC) require pretreatment to remove interfering substances and increase sensitivity (EPA 1987). At high concentrations (500 mg/kg), aluminum and silicon interfere with the analysis of beryllium by atomic absorption spectroscopy. Separation of these elements is achieved by chelation and extraction with an organic solvent. High concentrations of iron interfere with the 243.86 nm beryllium emission line used in ICP-AES (Vaessen and Szteke 2000). A method using laser spark spectroscopy has been used for the direct determination of trace quantities of airborne beryllium collected on filters (Cremers and Radziemski 1985). A recent analytical advance is laser induced breakdown spectroscopy (LIBS), a real time technique (Langner et al. 1997). This technique has been used to monitor worker exposure to beryllium in 30-second sample intervals (Langner et al. 1997).

The following SRMs for beryllium in environmental samples are available from the National Institute of Standards and Technology: San Joaquin soil, SRM=2,709; Montana soil 1, SRM=2,710; Montana soil 2, SRM=2,711; coal, SRM=1,632; fly ash, SRM=1,633; trace elements in water, SRM=1,643; orchard leaves, SRM=1,571; and filter media, SRM=2,676 (Chang et al. 1982; Epstein et al. 1978; Gladney and Owens 1976; Namiesnik and Zygmunt 1999). SRMs are available for beryllium in soils and sediments from Canadian Certified Reference Materials Project (CCRMP), National Research Council of Canada

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Wet ash collection filter with mixture of HNO_3/HCl mixture; concentrate; add HNO_3/LiCl solution	Optical emission spectroscopy	5.3 µg/L (in dissolved particles)	96–108%	Scott et al. 1976
Air	Dissolve collection filter matrix in HF; add HNO_3; water; boil; dilute	GFAAS FAAS	0.05ng/m^3 2.5 ng/m^3	No data	Zdrojewski et al. 1976
Air	None	Laser spark technique	0.45 ng/cm^{-2}	No data	Cremers and Radziemski 1985
Occupational air	Dry collection filter; add HNO_3 and sulfuric acid; solubilize with concentrated HCl	Direct current plasma AES	0.0036 µg/sample	100%	Chang et al. 1982
Occupational air	Filter collection, acid digestion	GFAAS (method 7102)	5 pg/sample	107%	NIOSH 1989b
Occupational air	Filter collection, acid digestion	GFAAS (method 7300)	1 pg/sample	No data	NIOSH 1989b
Water	Acidify with HNO_3; evaporate under heat; add HCl or HNO_3	AAS (aspiration-method 210.1)	0.005 mg/L	97–100%	EPA 1983
		AAS (furnace method 210.2)	0.2 µg/L	No data	
Water	Acidify with HNO_3	GFAES GFAAS	2 µg/L 0.06 µg/L	112% (average) 98% (average)	Epstein et al. 1978
Water	Digest; acidify; dilute	ICP-AES (method 3500-BE-C); ICP-AES (method D1976)	1 µg/L No data	No data No data	APHA 1992 ASTM 1999

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Digest; acidify; dilute	ICP-MS (method 933.14)	0.1 µg/L	No data	AOAC 1995
Seawater	Add specific volumes of EDTA, sodium acetate, benzene and Hfta to collected seawater; rinse organic phase with NaOH; UV oxidize	GC/EC	0.02 ng/L	93–104%	Measures and Edmond 1986
Sediment	Extract dry sample with HCl solution	DCP-AES	0.02 µg/g	No data	Lum and Gammon 1985
Soil and sediment	Acid digest in bomb; dilute	ICP-AES (method D1971-A)	No data	No data	ASTM 1999
Soil, sludge, sediments, and other solid wastes	Acid digestion of sample	ICP-AES (method 6010)	0.3 µg/L	97.7–100%	EPA 1988c
Solid (coal ash)	Acid digest in bomb; dilute with acid	GFAAS	0.14–4.8 µg/L	No data	Pougnet et al. 1985
Oils and waxes	Add potassium permanganate with heat; acidify; digest with heat; filter; dilute	FAAS or ICP-AES (method 3031)	No data	No data	OSW 2000

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Food	Dissolve in HNO_3; dry, then treat with HCl-$HClO_4$ and heat; filter	ICP-AES	No data	No data	Awadallah et al. 1986
Food	Freeze-dry or blender-grind food composites; solubilize with	ICP-AES	2.5 µg/kg	No data	Wolnick et al. 1984
	HNO_3, $HClO_4$, H_2SO_4, or HCl		2 µg/kg	98%	Capar and Yess 1996

AAS = atomic absorption spectrometry; AES = atomic emission spectrometry; AOAC = Association of Official Analytical Chemists; APHA = American Public Health Association; ASTM = American Society for Testing and Materials; DCP-AES = direct current plasma-atomic absorption spectroscopy; EDTA = ethylenediamine tetraacetic acid; FAAS = flame atomic absorption spectrometry; GC/EC = gas chromatography-electron capture; GFAAS = graphite furnace atomic absorption spectrometry; GFAES = graphite furnace atomic emission spectrometry; HCl = hydrochloric acid; $HClO_4$ = perchloric acid; HF = hydrogen fluoride; Hfta = 1,1,1-trifluoro-2,4-pentanedione; HNO_3 = nitric acid; H_2SO_4 = sulfuric acid; ICP-AES = inductively coupled plasma-atomic emission spectrometry; ICP-MS = inductively coupled plasma-mass spectrometry; LiCl = lithium chloride; NaOH = sodium hydroxide; NIOSH = National Institute for Occupational Safety and Health; OSW = Office of Solid Waste of the U.S. Environmental Protection Agency; UV = ultraviolet

NRCC and the U.S. Geological Survey (USGS): soil, SO 1; soil-sandy, SO 2; soil-limestone til, SO 3; soil-silty, SO 4; arable soil, TILL 2; Lake sediment, IKSD 4; sediment MESS-1; sediment BCSS-1; and marine sediment, MAG 1 (Namiesnik and Zygmunt 1999; Waldichuk et al. 1987).

7.3 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of beryllium 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 beryllium.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. As discussed in Section 3.8.1, the beryllium level in blood/serum/plasma is an accurate biomarker of exposure to certain forms of beryllium (James and Williams 1985; Stokes and Rossman 1991; Zorn et al. 1986). The level of beryllium in normal blood is 1 µg/kg (Zorn et al. 1986). No analytical method capable of determining beryllium in blood at or below this level has been reported in the literature. The routine analytical methods presently available are useful for detecting beryllium levels in the blood of occupationally exposed persons.

Effect. There are several methods for measuring effects due to beryllium exposure (see Section 3.8.2). An antigen-specific lymphocyte proliferation test confirms exposure and may be useful in early diagnosis of individuals with chronic beryllium disease; several methods for the lymphocyte proliferation test have been reported (Bobka et al. 1997; Kreiss et al. 1989; Mroz et al. 1991; Rossman et al. 1988; Stokes and

Rossman 1991). Another method that can be used for the positive diagnosis of chronic beryllium disease when other symptoms are evident is LIMA of histological sections of lung or skin granulomas. LIMA can detect parts per million (or mg/kg) levels of beryllium in these tissues (Williams and Kelland 1986).

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. The concentration of beryllium in approximately 95% of drinking waters in the United States is <0.01 µg/L (EPA 1980; Iwan 1987). Although a few methods are available (see Table 7-2) to detect beryllium at such low concentrations, no routine methods are available to quantify beryllium concentrations in most U.S. drinking waters. Similarly, the detection limit for beryllium in fresh vegetables by the commonly used analytical method (see Table 7-2) is 2.5 µg/kg. At this detection limit, beryllium was not found in two foods tested (Wolnik et al. 1984). Developing a routine analytical method to detect low levels of beryllium in foods would be useful. The data on the levels of beryllium in drinking water and total diet samples from ambient sources are significant in determining background levels of daily intake from these routes.

7.3.2 Ongoing Studies

The FEDRIP database lists an ongoing National Institute of Environmental Health and Sciences study by Jolly et al. at ELS Technology, Inc. (Lakewood, Colorado) that is investigating a portable low-cost analyzer for the detection of beryllium in toxic metal aerosols (FEDRIP 2001).

8. REGULATIONS AND ADVISORIES

A chronic-duration oral MRL of 0.002 mg beryllium/kg/day was derived for beryllium. This MRL is based on a benchmark dose (defined as the 95% lower confidence limit of the dose corresponding to a 10% increase in the incidence of small intestine lesions compared to controls) of 0.56 mg beryllium/kg/day. The benchmark dose was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for intrahuman variability) and a modifying factor of 3 (to account for the lack of a study that supports the gastrointestinal effects found in the Morgareidge et al. [1976] dog study and the uncertainty as to whether the benchmark dose level is the NOAEL).

A chronic oral reference dose (RfD) of 0.002 mg beryllium/kg/day has been derived and verified by EPA for beryllium (IRIS 2002). The RfD is based on a benchmark dose of 0.46 mg beryllium/kg/day for small intestine lesions in dogs exposed to beryllium sulfate in the diet for 33–172 weeks (Morgareidge et al. 1976). This benchmark concentration was divided by an uncertainty factor of 300 to account for extrapolation from animals to humans (10), human variability (10), and database gaps (3), particularly adequate reproductive and developmental toxicity studies and studies examining immunological end points. The chronic-duration oral MRL and the RfD were both derived using a benchmark analysis and the same incidence data set. The difference in the benchmark doses is due to the differences in the mathematical model fit to the incidence data (ATSDR used a probit model with a chi-square goodness-of-fit statistic p-value of 0.9999 and EPA used a weibull model with a chi-square goodness of fit statistic p-value of 0.96) and the higher number of significant figures that EPA used to express beryllium doses.

A chronic inhalation reference concentration (RfC) of 0.02 $\mu g/m^3$ has been derived for beryllium (IRIS 2000). The RfC is based on two human studies finding chronic beryllium disease in workers at a facility manufacturing beryllia ceramics (Kreiss et al. 1996) and in residents living near a beryllium manufacturing facility (Eisenbud et al. 1949). The Kreiss et al. (1996) study identified a LOAEL of 0.55 $\mu g/m^3$ for beryllium sensitization and subclinical chronic beryllium disease, and the Eisenbud et al. (1949) study identified a NOAEL of 0.01–0.1 $\mu g/m^3$ for chronic beryllium disease. The LOAEL identified in the Kreiss et al. (1996) study was used for the operational derivation of the RfC. This LOAEL was divided by an uncertainty of 10 to account for less-than-chronic exposure duration (1), use of a LOAEL (3), human variability (1), and database limitations (3), particularly the poor quality of exposure monitoring in the co-principal studies and other epidemiology studies.

NTP (1999, 2002) lists beryllium and certain beryllium compounds (beryllium-aluminum alloy, beryllium chloride, beryllium fluoride, beryllium hydroxide, beryllium oxide, beryllium phosphate, beryllium sulfate, beryllium zinc silicate, and beryl ore) as substances reasonably anticipated to be carcinogens. IARC (2001) has classified beryllium and beryllium compounds in Group 1, carcinogenic to humans, and EPA classifies inhaled beryllium in Group B1, a probable human carcinogen (IRIS 2002).

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

Table 8-1. Regulations and Guidelines Applicable to Beryllium

Agency	Description	Information	Reference
INTERNATIONAL Guidelines:			
IARC	Carcinogenicity classification—beryllium and beryllium compounds	Group 1[a]	IARC 2001
NATIONAL Regulations and Guidelines:			
a. Air			
ACGIH	Beryllium and compounds (as Be) TLV (8-hour TWA) STEL (15-minute TWA)	 0.002 mg/m^3 0.01 mg/m^3	ACGIH 2001
DOD	Requires notification to the EPA when conducting operations, construction, or modification of a source of hazardous air pollutants—beryllium		DOD 2001 32CFR650.132
EPA	National emission standards for hazardous air pollutants—beryllium emissions to the atmosphere from rocket-motor test sites	Shall not exceed 75 µg minutes/m^3 of air within the limits of 10–60 minutes, accummulated during any 2 consecutive weeks, in any area in which an effect adverse to public health could occur	EPA 2001i 40CFR61.42
	National emission standards for hazardous air pollutants—if combustion products from the firing of beryllium propellant are collected in a closed tank	Emissions from such tank shall not exceed 2 g/hour and a maximum of 10 g/day	EPA 2001i 40CFR61.42
	National emission standards for hazardous air pollutants Beryllium emissions to the atmosphere from stationary sources Request approval from the Administrator to meet an ambient concentration limit on beryllium in the vicinity of the stationary source	 Shall not exceed 10 grams over a 24-hour period 0.01 µg/m^3, averaged over a 30-day period	EPA 2001l 40CFR61.32

Table 8-1. Regulations and Guidelines Applicable to Beryllium *(continued)*

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
NIOSH	Beryllium and beryllium compounds (as Be) REL (10-hour TWA)[b] IDLH	 $5x10^{-4}$ mg/m^3 4 mg/m^3	NIOSH 2001
OSHA	PEL (8-hour TWA)—beryllium and beryllium compounds (as Be)	2 µg/m^3	OSHA 2001a 29CFR1910.1000 Table Z-1
	Acceptable ceiling concentration—beryllium and beryllium compounds	5 µg/m^3	OSHA 2001a 29CFR1910.1000 Table Z-2
	Acceptable maximum peak above the acceptable ceiling concentration for an 8-hour shift for a maximum duration of 30 minutes—beryllium and beryllium compounds	25 µg/m^3	OSHA 2001a 29CFR1910.1000 Table Z-2
	PEL (8-hour TWA) for construction workers—beryllium and beryllium compounds (as Be)	2 µg/m^3	OSHA 2001c 29CFR1926.55
	PEL (8-hour TWA) for shipyard workers—beryllium and beryllium compounds (as Be)	2 µg/m^3	OSHA 2001b 29CFR1915.1000
	Welding or cutting indoors, outdoors, or in confined spaces involving beryllium-containing base or filler metals shall be done using local exhaust ventilation and airline respirators		OSHA 2001d 29CFR1910.252 (c)(8)
USC	Listed as a hazardous air pollutant—beryllium compounds		USC 2001 42 USC 7412
b. Water			
EPA	Groundwater monitoring—beryllium (total) Suggested methods 6010 7090 7091	 PQL 3 µg/L 50 µg/L 2 µg/L	EPA 2001b 40CFR264, Appendix IX

Table 8-1. Regulations and Guidelines Applicable to Beryllium *(continued)*

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Land disposal restrictions; universal treatment standards for beryllium		EPA 2001e 40CFR268.48
	Wastewater standard	0.82 mg/L[2]	
	Non-wastewater standard	1.22 mg/L TCLP	
	MCLG—beryllium	0.004 mg/L	EPA 2001g 40CFR141.51(b)
	MCL—beryllium	0.004 mg/L	EPA 2001f 40CFR141.62(b)
	National recommended water quality criteria for human health for consumption of beryllium	EPA has not calculated human health criteria for this contaminant	EPA 1999a
	Water and organism		
	Organism only		
	Health Advisories for beryllium		EPA 2000a
	10-kg child		
	1-day	30 mg/L	
	10-day	30 mg/L	
	DWEL[c]	0.07 mg/L	
c. Food			
FDA	Bottled water allowable limit—beryllium	0.004 mg/L	FDA 2001 21CFR165.110
d. Other			
ACGIH	Carcinogenicity classification—beryllium and compounds	A1[d]	ACGIH 2001
DOE	Chronic beryllium disease prevention program		DOE 2001 10CFR850
EPA	Beryllium and compounds		IRIS 2001
	Carcinogenicity classification	B1[e]	
	RfC	$2X10^{-2}$ µg/m^3	
	RfD	$2x10^{-3}$ mg/kg/day	
	Health based limits for exclusion of waste-derived residue—beryllium		EPA 2001c 40CFR266, Appendix VII
	TCLP extract concentration limits	$7x10^{-3}$ mg/L	

Table 8-1. Regulations and Guidelines Applicable to Beryllium *(continued)*

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Identification and listing of beryllium powder as a hazardous waste—hazardous waste number	P015	EPA 2001d 40CFR261.33(e)
	Reportable quantity regarded as a CERCLA hazardous substance under Section 307(a) of the Clean Water Act		EPA 2001a 40CFR302.4
	Beryllium and compounds	1 pound	
	Beryllium chloride, beryllium fluoride, and beryllium nitrate	5,000 pounds	
	Standards for management of hazardous waste		EPA 2001j 40CFR266, Appendix V
	Unit risk	2.4×10^{-3} µg/m^3	
	Risk specific doses	4.2×10^{-3} µg/m^3	
	Toxic chemical release reporting; community right-to-know, effective date for reporting—beryllium	01/01/87	EPA 2001k 40CFR372.65
	Toxic pollutant designated pursuant to Section 307(a)(1) of the Clean Water Act—beryllium and compounds		EPA 2001l 40CFR401.15
NTP	Carcinogenicity classification-beryllium and compounds	Known human carcinogens	NTP 1999, 2002
STATE Regulations and Guidelines:			
a. Air			
North Carolina	Toxic air pollutant—beryllium		BNA 2001
	Chronic toxicant (24 hours)	4.1×10^{-6} mg/m^3	
Vermont	Hazardous ambient air standard[f]—beryllium, total	1.3×10^{-3} µg/m^3	VT Agency of Natural Resources 1998
Washington	Acceptable source impact levels (at 10^{-6} risk), annual average—beryllium and compounds	4.2×10^{-4} µg/m^3	WA Dept. of Ecology 1998
Wisconsin	Hazardous air contaminants without acceptable ambient concentrations requiring application of best available control technology—beryllium and beryllium compounds (as Be)	25 pounds/year[2]	WI Dept. of Natural Resources 1997

Table 8-1. Regulations and Guidelines Applicable to Beryllium *(continued)*

Agency	Description	Information	Reference
STATE *(cont.)*			
b. Water			
Alaska	Primary MCL—beryllium	0.004 mg/L	AK Dept. of Environ. Conservation 1999
Arizona	Aquifer water quality standard—beryllium	0.004 mg/L	BNA 2001
	Drinking water guideline—beryllium	0.007 µg/L	HSDB 2001
California	Primary MCL—beryllium	0.004 mg/L	CA Dept. of Health Services 2000
Hawaii	MCL—beryllium	0.004 mg/L	HI Dept. of Health 1999a
	Toxic pollutant standards—beryllium		HI Dept. of Health 1999b
	Freshwater		
	Acute	43 mg/L	
	Chronic	No standard	
	Saltwater		
	Acute	No standard	
	Chronic	No standard	
	Fish Consumption	0.038 mg/L	
Kansas	Water quality standards—beryllium, total		KS Dept. of Health and Environ. 1999
	Aquatic life	130 mg/L	
	Acute	5.3 mg/L	
	Chronic		
	Public health	0.13 mg/L	
	Food procurement	4.0 mg/L	
	Domestic water supply		
Kentucky	Domestic water supply use—beryllium concentration	0.04 µg/L	BNA 2001
Minnesota	Drinking water guideline—beryllium	0.08 µg/L	HSDB 2001
New Jersey	Groundwater standards—beryllium		NJ Dept. of Environ. Protection 1993
	Groundwater quality criteria	0.008 µg/L	
	PQL	20 µg/L	

Table 8-1. Regulations and Guidelines Applicable to Beryllium *(continued)*

Agency	Description	Information	Reference
STATE *(cont.)*			
Rhode Island	Beryllium		BNA 2001
	Groundwater quality standard	0.004 mg/L	
	Preventive action limit	0.002 mg/L	
South Dakota	MCL for community and non-transient non-community water systems—beryllium	0.004 mg/L	SD Dept. of Environ. & Natural Resources 1998
Vermont	Groundwater quality standard—beryllium		BNA 2001
	Enforcement standard	4.0 µgL	
	Preventive action level	1.0 µg/L	
c. Food	No data		
d. Other			
Connecticut	Direct exposure criteria for soil—beryllium		BNA 2001
	Residential criteria	2 mg/kg	
	Industrial/commercial criteria	2 mg/kg	
Massachusetts	Human health-based toxicity values—beryllium		BNA 2001
	Chronic oral RfD	2.0×10^{-3} mg/kg/day	
	Oral cancer slope factor	$4.3\ (mg/kg/day)^{-1}$	
Minnesota	Health risk limits		BNA 2001
	Slope factor	$4.3\ (mg/kg/day)^{-1}$	
	Health risk limit	0.08 µg/L	

[a]Group 1: carcinogenic to humans
[b]Potential occupational carcinogen
[c]DWEL: A lifetime exposure concentration protective of adverse, non-cancer health effects that assumes all of the exposure to a contaminant is from a drinking water source.
[d]A1: confirmed human carcinogen. The agent is carcinogenic to humans based on the weight of evidence from epidemiologic studies.
[E]B1: probable human carcinogen
[f]Indicates value derived using an inhalation cancer potency factor

ACGIH = American Conference of Governmental Industrial Hygienists; BNA = Bureau of National Affairs; CERCLA = Comprehensive Environmental Response Compensation and Liability Act; CFR = Code of Federal Regulations; DOD = Department of Defense; DOE = Department of Energy; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure level; PQL = practical quantitation limits; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; STEL = short-term exposure limit; TCLP = toxicity characteristic leaching procedure; TLV = threshold limit value; TWA = time-weighted average; USC = United States Code

9. REFERENCES

ACGIH. 1990. Threshold limit values for chemical substances and physical agents and biological exposure indices for 1990-1991. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

ACGIH. 1999. Threshold limit values for chemical substances and physical agents and biological exposure indices for 1999. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

*ACGIH. 2001. Threshold limit values for chemical substances and physical agents and biological exposure indices. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

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

*Adlercreutz H. 1995. Phytoestrogens: Epidemiology and a possible role in cancer protection. Environ Health Perspect Suppl 103(7):102-112.

*AL Dept of Environ Conservation. 1999. Alaska Department of Environmental Conservation. Beryllium. Current regulations. Title 18 Environmental Conservation.

*Aldahan A, Haiping Y, Possnert G. 1999. Distribution of beryllium between solution and minerals (biotite and albite) under atmospheric conditions and variable pH. Chem Geo 156:209-229.

Allen GT, Blackford SH, Tabor VM, et al. 2001. Metals, boron, and selenium in Neosho madtom habitats in the Neosho River in Kansas, USA. Environ Monit Assess 66:1-21.

*Altman PL, 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.

*American College of Chest Physicians. 1965. Beryllium disease: report of the section on nature and prevalence. Dis Chest 48:550-558.

*Andersen ME, Krishnan K. 1994. Relating in vitro to in vivo exposures with physiologically based tissue dosimetry and tissue response models. In: Salem H, ed. Animal test alternatives: Refinement, reduction, replacement. New York: Marcel Dekker, Inc., 9-25.

*Andersen ME, Clewell HJ III, Gargas ML, et al. 1987. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. Toxicol Appl Pharmacol 87:185-205.

*Andrews JL, Kazemi H, Hardy HL. 1969. Patterns of lung dysfunction in chronic beryllium disease. Am Rev Respir Dis 100:791-800.

---

*Cited in text

9. REFERENCES

AOAC. 1995. Volume 1: Metals and other Elements. Official Methods of Analysis of AOAC International, 16th Edition. Association of Official Analytical Chemists (USA). Method 933.1.

*APHA 1992. Beryllium. Standard Methods for the Examination of Water and Wastewater, 18th Edition. American Public Health Association. Methods 3500-BE-C, 3500-BE-D.

*Apostoli P, Schaller KH. 2001. Urinary beryllium-a suitable tool for assessing occupational and environmental beryllium exposure. Int Arch Occup Environ Health 74:162-166.

*Arlauskas A, Baker RSU, Bonin AM, et al. 1985. Mutagenicity of metal ions in bacteria. Environ Res 36:379-388.

*Aronchick JM, Rossman MD, Miller WT. 1987. Chronic beryllium disease: Diagnosis, radiographic findings, and correlation with pulmonary function tests. Radiology 163:677-682.

*Ashby J, Ishidate J Jr., Stoner GD, et al. 1990. Studies on the genotoxicity of beryllium sulphate in vitro and in vivo. Mutat Res 240:217-225.

ASTM. 1999. Annual Book of ASTM Standards. American Society for Testing and Materials (ASTM). Volume 11.01-2 Water (I, II). Methods D1971-A, D1976, D3645-A, D3645-B, D4190.

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

*ATSDR. 1989. Agency for Toxic Substances and Disease Registry. Decision guide for identifying substance-specific data needs related to toxicological profiles: Notice. Federal Register 54(174):37618-37634.

*Awadallah RM, Sherif MK, Amrallah AH, et al. 1986. Determination of trace elements of some Egyptian crops by instrumental neutron activation, inductively coupled plasma-atomic emission spectrometric and flameless atomic absorption spectrophotometric analysis. Journal of Radioanalytical and Nuclear Chemistry 98:235-246.

Balachandran S, Bharat RM, Khillare PS. 2000. Particle size distribution and its elemental composition in the ambient air of Delhi. Environ Int 26:49-54.

Balkissoon RC, Newman LS. 1999. Beryllium copper alloy (2%) causes chronic beryllium disease. J Occup Environ Med 41(4):304-308.

*Ballance J, Stonehouse AJ, Sweeney R, et al. 1978. Beryllium and beryllium alloys. In: Grayson M, Eckroth D, eds. Kirk-Othmer encyclopedia of chemical technology, 3rd ed. Vol. 3. New York, John Wiley & Sons, Inc., 803-823.

Barg E, Lal D, Pavich MJ, et al. 1997. Beryllium geochemistry in soils: evaluation of 10Be/9Be ratios in authigenic minerals as a basis for age models. Chem Geol 140:237-258.

Bargon J, Kronenberger H, Bergmann L, et al. 1986. Lymphocyte transformation test in a group of foundry workers exposed to beryllium and non-exposed controls. Eur J Respir Dis 69:211-215.

9. REFERENCES

*Barna BP, Chiang T, Pillarisetti SG, et al. 1981. Immunological studies of experimental beryllium lung disease in the guinea pig. Clin Immunol Immunopathol 20:402-411.

*Barna BP, Deodhar SD, Chiang T, et al. 1984. Experimental beryllium-induced lung disease. I. Differences in immunologic response to beryllium compounds in strains 2 and 13 guinea pigs. Int Arch Allergy Appl Immunol 73:42-48.

Barnes KW. 1997. Trace metal determinations in fruit, juice, and juice products using an axially viewed plasma. Atom Spectrosc 18(3):84-101.

*Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessment. Regul Toxicol Pharmacol 8:471-486.

*Barnes JM, Denz FA, Sissons HA. 1950. Beryllium bone sarcomata in rabbits. Br J Cancer IV:212-222.

Bartell SM, Ponce RA, Takaro TK, et al. 2000. Risk estimation and value-of-information analysis for three proposed genetic screening programs for chronic beryllium disease prevention. Risk Anal 20(1):87-99.

Bashir W, Paull B. 2001. Sensitive and selective ion chromatographic method for the determination of trace beryllium in water samples. J Chromatogr 910:301-309.

Baskaran M, Shaw GE. 2001. Residence time of arctic haze aerosols using the concentrations and activity ratios of ^{210}Po ^{210}Pb and ^{7}Be. J Aerosol Sci 32:443-452.

*Bauer S, Hohmann W, Kronenberger H, et al. 1988. Frequency of use and health risk implications of beryllium-containing dental alloys in West German dental laboratories. In: Proceedings of the 7th Congress of the European Society of Pneumology: Symposium on lung and infection prevention and screening, Budapest, Hungary, September 5-9, 1988. Eur Respir J 1(Suppl. 2):248S.

Baumgardt B, Jackwerth E, Otto H, et al. 1986. Trace analysis to determine heavy metal load in lung tissue a contribution to substantiation of occupational hazards. Int Arch Occup Environ Health 58:27-34.

*Bayliss DL. 1970. Written communication (November 12) to William H Foege, Center for Disease Control, regarding the article entitled “Beryllium: An etiologic agent in the induction of lung cancer, nonneoplastic respiratory disease, and heart disease among industrially exposed workers”. Atlanta, GA.

*Bayliss DL, Lainhart WS, Crally LJ, et al. 1971. Mortality patterns in a group of former beryllium workers. In: Proceedings of the American Conference of Governmental Industrial Hygienists 33rd Annual Meeting, Toronto, Canada, 94-107.

*Behmanesh N, Allen DT, Warren JL. 1992. Flow rates and compositions of incinerated waste streams in the United States. J Air Waste Manage Assoc 42(4):437-442.

*Belman S. 1969. Beryllium binding of epidermal constituents. J Occup Med 11(4):175-183.

*Bencko V, Brezina M, Benes B, et al. 1979. Penetration of beryllium through the placenta and its distribution in the mouse. J Hyg Epidemiol Microbiol Immunol 23:361-367.

9. REFERENCES

Bennett GF. 1989. Impact of toxic chemicals on local wastewater treatment plant and the environment. Environmental Geology and Water Science 13:201-212.

Benson JM, Holmes AM, Barr EB, et al. 2000. Particle clearance and histopathology in lungs of C3H/HeJ mice administered beryllium/copper alloy by intratracheal instillation. Inhal Toxicol 12:733-749.

*Berger GS. 1994. Epidemiology of endometriosis. In: Berger GS, ed. Endometriosis: Advanced management and surgical techniques. New York, NY: Springer-Verlag.

Bertinelli M, Baroni U, Spezia S, et al. 1921. 6. Atom Spectrosc 21(6):195-204.

Bibak A, Sturup S, Knudsen L, et al. 1999. Concentrations of 63 elements in cabbage and sprouts in Denmark. Commun Soil Sci Plant Anal 30(17&18):2409-2418.

*BNA. 2001. Environment and Safety Library on the Web. States and Territories. Bureau of National Affairs, Inc. Washington, D.C. http//www.esweb.bna.com/.

*Bobka CA, Stewart LA, Engelken GJ, et al. 1997. Comparison of *in vivo* and *in vitro* measures of beryllium sensitization. J Occup Environ Med 39(6):540-547.

Boix A, Jordan MM, Querol X, et al. 2001. Characterization of total suspended particles around a power station in an urban coastal area in eastern Spain. Environ Geol 40:891-896.

Bost T, Newman L, Riches D. 1993. Increased TNF-alpha and IL6 mRNA expression by alveolar macrophages in chronic beryllium disease. Chest 103(Suppl. 2):138S.

*Bost TW, Riches DWH, Schumacher B, et al. 1994. Alveolar macrophages from patients with beryllium disease and sarcoidosis express increased levels of mRNA for tumor necrosis factor-alpha and interleukin-6 but not interleukin-1beta. Am J Respir Cell Mol Biol 10(5):506-513.

*Bowen HJM. 1979. Environmental chemistry of the elements. New York, NY, Academic Press.

*Brancaleone P, Weynand B, DeVuyst P, et al. 1998. Lung granulomatosis in a dental technician. Am J Ind Med 34(6):628-631.

Brooks GH. 1989. The comparative uptake and interaction of several radionuclides in the trophic levels surrounding the Los Alamos Meson Physics Facility (LAMPF) waste water ponds. Los Alamos National Laboratory. LA-11487-T.

*Brooks AL, Griffith WC, Johnson NF, et al. 1989. The induction of chromosome damage in CHO cells by beryllium and radiation given alone and in combination. Radiat Res 120:494-507.

*Bruce BW, McMahon. 1996. Shallow ground-water quality beneath a major urban center: Denver, Colorado, USA. Journal of Hydrology 186:129-151.

*Brush Wellman. 2000a. Corporate Website Factsheet. http://www.brushwellman.com.

*Brush Wellman. 2000b. Material Safety Data Sheet (MSDS) for beryllium copper alloy: CAS Number 55130-107-21.

9. REFERENCES

*Brush Wellman. 2000c. Material Safety Data Sheet (MSDS) for beryllium aluminum alloy: CAS Number 12770-50-2.

*Brush Wellman. 2000d. Material Safety Data Sheet (MSDS) for beryllium nickel alloy: CAS Number 37227-61-5.

Buchholz BA, Landsberger S. 1993. Trace metal analysis of size-fractioned municipal solid waste incinerator fly ash and its leachates. J Environ Sci Health Part A A28(2):423-441.

*Byrne CJ, DeLeon IR. 1986. Trace metal residues in biota and sediments from Lake Pontchartrain, Louisiana USA. Bull Environ Contam Toxicol 37:151-158.

*CA Dept Health Services. California Department of Health Services. 2000. Division of drinking water and environmental management. California Department of Health Services. http://www.dhs.cahwnet.gov/ps/ddwem/.

*Callahan MA, Slimak MW, Gabel NW, et al. 1979. Water-related environmental fate of 129 priority pollutants. Washington, DC: U.S. Environmental Protection Agency. EPA-440/4-79-029a

*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(5):553-560.

CELDS. 1990. Computer-aided Environmental Legislative Data System. July, 1990.

*Chang AE, Morse R, Harley NH, et al. 1982. Atomic emission spectrometry of trace levels of beryllium in industrial aerosols. Am Ind Hyg Assoc J 43:117-119.

*Chen M, Ma LQ, Harris WG. 1999. Baseline concentrations of 15 trace elements in Florida surface soils. J Environ Qual 28(4):1173-1181.

*Chesner C. 1950. Chronic pulmonary granulomatosis in residents of a community near a beryllium plant: three autopsied cases. Ann Int Med 20(6):1028-1048.

*Clarke SM. 1991. A novel enzyme-linked immunosorbent assay (ELISA) for the detection of beryllium antibodies. Journal of Immunological Methods 137:65-72.

Clarke SM, Barrick CW. 1988. A human cell beryllium acute toxicity assay. Toxicol Ind Health 4:1-9.

*Clary JJ, Bland LS, Stokinger HE. 1975. The effect of reproduction and lactation on the onset of latent chronic beryllium disease. Toxicol Appl Pharmacol 33:214-221.

*Clary JJ, Hopper CR, Stokinger HE. 1972. Altered adrenal function as an inducer of latent chronic beryllium disease. Toxicol Appl Pharmacol 23:365-375.

*Cleverly DH, Morrison RM, Riddle BL, et al. 1989. Regulatory analysis of pollutant emissions, including polychlorinated dibenzo-p-dioxins (CDDs) and dibenzofurans (CDFs), from the stacks of municipal waste combustors). Chemosphere 18:1143-1153.

*Clewell HJ III, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1(4):111-131.

9. REFERENCES

CLPSD. 1989. Contract Laboratory Program Statistical Database. July 12, 1989.

*CO Dept of Public Health and Environ. 1999. Colorado Department of Public Health and Environment Department regulations. Air quality control commission (ACC)-1001.

*Colborn T, Clement C, eds. 1992. Chemically-induced alterations in sexual and functional development: The wildlife-human connection. In: Advances in modern environmental toxicology, Vol. XXI, Princeton, NJ: Princeton Scientific Publishing.

Comhair SAA, Lewis MJ, Bhathena PR, et al. 1999. Increased glutathione and glutathione peroxidase in lungs of individuals with chronic beryllium disease. Am J Respir Crit Care Med 159(6):1824-1829.

Conradi C, Burri PH, Kapanci Y, et al. 1971. Lung changes after beryllium inhalation. Arch Environ Health 23:348-358.

*Cotes JE, Gilson JC, McKerrow CB, et al. 1983. A long-term follow-up of workers exposed to beryllium. Br J Ind Med 40:13-21.

*Cotton FA, Wilkinson G. 1980. Advanced Inorganic Chemistry. New York: John Wiley & Sons, Inc., 271-280.

CRC. 1986. Physical Constants of Inorganic Compounds. In: CRC Handbook of Chemistry and Physics. Ed By: Weast RC. CRC Press Inc. Boca Raton, FL.

*Creamers DA, Radziemski LJ. 1985. Direct detection of beryllium on filters using the laser spark. Appl Spectroscopy. 39(1):57-63.

CRISP. 1990. Crisp Data Base, National Institutes of Health. July, 1990.

*Cullen MR, Kominsky JR, Rossman MD, et al. 1987. Chronic beryllium disease in a precious metal refinery. Am Rev Respir Dis 135:201-208.

*Cunningham LD. 1998. Beryllium, Mineral Yearbook. U.S. Geological Survey, K1-K4.

*Cunningham LD. 1999. Beryllium, Mineral Commodity Summary. U.S. Geological Survey, 34-35.

*Curtis GH. 1951. Cutaneous hypersensitivity due to beryllium: a study of thirteen cases. AMA Archives of Dermatology and Syphilology 64:470-482.

*Curtis GH. 1959. The diagnosis of beryllium disease, with special reference to the patch test. AMA Archives of Industrial Health 19:150-153.

*Dattoli JA, Lieben J, Bisbing J. 1964. Chronic beryllium disease: a follow-up study. J Occup Med 6:189-194.

Dawson R, Duursma EK. 1974. Distribution of radioisotopes between phytoplankton, sediment and sea water in a dialysis compartment system. Neth J Sea Res 8(4):339-353.

*Dean JA, ed. 1985. Lange's Handbook of Chemistry. 13th ed. New York, McGraw-Hill Book Co., 4-28 and 4-29.

9. REFERENCES

Dearman RJ, Basketter DA, Kimber I. 1999. Local lymph node assay: Use in hazard and risk assessment. J Appl Toxicol 19(5):299-306.

*Del Delumyea R, McKay T, Horowitz J. 1997. Trends in air quality research in northeast Florida, 1945-1995 and comparison of air quality in Jacksonville,Fl with nine other cities in the United States, 1972-1992. Fla Sci 60(3):175-192.

*Delves HT. 1981. The analysis of biological and clinical materials. Progress in Analytical Atomic Spectroscopy 4:1-48.

Deubner DC, Goodman M, Iannuzzi J. 2001a. Variability, predictive value, and uses of the beryllium blood lymphocyte proliferation test (BLPT): Preliminary analysis of the ongoing workforce survey. Appl Occup Environ Hyg 16(5):521-526.

*Deubner D, Kelsh M, Shum M, et al. 2001b. Beryllium sensitization, chronic beryllium disease, and exposures at a beryllium mining and extraction facility. Appl Occup Environ Hyg 16(5):579-592.

Deubner DC, Lowney YW, Paustenbach DJ, et al. 2001c. Contribution of incidental exposure pathways to total beryllium exposures. Appl Occup Environ Hyg 16(5):568-578.

*DOD. 2001. Special authorizations. U.S. Department of Defense. Code of Federal Regulations. 32 CFR 650.132. http://frwebgate.access.gpo.gov/cgi-bin/...PART=650&SECTION=132&YEAR=2001&TYPE=TEXT. December 13, 2001.

*DOE. 1996. A comprehensive assessment of toxic emissions from coal-fired power plants-topical report. U.S. Department of Energy. DOE/MC/30097-5321.

*DOE. 1999a. Existing capacity and planned capacity additions at U.S. electric utilities by energy source, as of January 1, 1999. Department of Energy. http://www.eia.doe.gov/cneaf/electricity/ipp/t1p01.txt

DOE. 1999b. Grant of specific authorization. U.S. Department of Energy. Code of Federal Regulations. 10 CFR 810.10.

*DOE. 2001. Chronic beryllium disease prevention program. U.S. Department of Energy. Code of Federal Regulations. 10 CFR 850. Http://www.access.gpo.gov/nara/waisidx_01/10cfr850_01.html. December 13, 2001.

Domingo JL, Schumacher M, Agramunt MC, et al. 2001. Levels of metals and organic substances in blood and urine of workers at a new hazardous waste incinerator. Int Arch Occup Environ Health 74:263-269.

DOND. 1999a. Special authorizations. U.S. Department of National Defense. Code of Federal Regulations. 32 CFR 650.132.

DOND. 1999b. Implementing guidelines. U.S. Department of National Defense. Code of Federal Regulations. 32 CFR 650.130.

DOND. 1999c. Standards. U.S. Department of National Defense. Code of Federal Regulations. 32 CFR 650.88.

9. REFERENCES

DOS. 1999. Military explosives and propellants. U.S. Department of State. Code of Federal Regulations. 22 CFR 122.12.

DOT. 1999. Purpose and use of hazardous materials table. U.S. Department of Transportation. Code of Federal Regulations. 49 CFR 172.101.

Dougherty CP, Holtz SH, Reinert JC, et al. 2000. Dietary exposures to food contaminants across the United States. Environ Res 84(Sect A):170-185.

*Drury JS, Shriner CR, EG Lewis, et al. 1978. Reviews of the environmental effects of pollutants: VI. Beryllium. U.S. Environmental Protection Agency, Cincinnati, OH, 1-191. EPA-600/1-78-028.

*Eckel WP, Jacob TA. 1988. Ambient levels of 24 dissolved metals in U.S. surface and ground waters. Abstracts of Papers, Division of Environmental Chemistry. Presented before the 196th American Chemical Society National Meeting, Los Angeles, California. September 25-30, 1988. 371-372.

*Eckel WP, Langley WD. 1988. A background-based ranking technique for assessment of elemental enrichment in soils at hazardous waste sites. In: Proceedings of the 9th National Conference: Superfund '88, Washington, DC, November 28-30, 1988.

*Eisenbud M. 1993. Lung cancer incidence among patients with beryllium disease [letter comment]. J Natl Cancer Inst 85(20):1697-1699.

*Eisenbud M. 1997. Is beryllium carcinogenic in humans? JOEM 39(3):205-208.

Eisenbud M. 1998. The standard for control of chronic beryllium disease. Appl Occup Environ Hyg 13(1):25-31.

*Eisenbud M, Lisson J. 1983 Epidemiological aspects of beryllium-induced nonmalignant lung disease: A 30-year update. J Occup Med 25:196-202.

*Eisenbud M, Berghout CF, Steadman LT. 1948a. Environmental studies in plants and laboratories using beryllium: the acute disease. J Ind Hyg Toxicol 30:282-285.

Eisenbud M, Berghout CF, Steadman LT. 1948b. Non-occupational berylliosis in Lorain, Ohio. U.S. Atomic Energy Commission, Office of New York Directed Operations, Medical Division. August 5, 1948.

*Eisenbud M, Wanta C, Dustan LT, et al. 1949. Non-occupational berylliosis. J Ind Hyg Toxicol 31:282-294.

*Ellenhorn MJ, Schonwald S, Ordog G, et al., eds. 1997. Ellenhorn's medical toxicology: Diagnosis and treatment of human poisoning. Second Edition. Baltimore, MD: Williams & Wilkins. 1546-1548.

EMSLC. 1991. Methods for the Determination of Metals in Environmental Samples. Environmental Monitoring Systems Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati. EPA-600/4-91-010. Methods 200.0, 200.8, 200.11, 200.15.

*Emsley J. 1998. The Elements. Third Edition. Clarendon Press, Oxford, 34-35.

9. REFERENCES

*EPA. 1980. Ambient water quality criteria for beryllium. Washington, DC: Office of Water Regulations and Standards, Criteria and Standards Division, U.S. Environmental Protection Agency. EPA-440/5-80-024.

*EPA. 1981. Treatability manual. Vol. 1. Treatability data. U.S. Environmental Protection Agency. EPA-600/8-80-042, I.4.4-1 to I.4.4-4.

*EPA. 1982. National emission standards for hazardous air pollutants. U.S. Environmental Protection Agency. Code of Federal Regulations 40:61.30-61.34.

*EPA. 1983. Methods for chemical analysis of water and wastes. March, 1983. Cincinnati, OH: Environmental Monitoring Support Laboratory, Office of Research and Development, U.S. Environmental Protection Agency. EPA-600/4-79-020, 210.2-1 to 210.2-2.

EPA. 1986. Quality criteria for water 1986. Washington, DC: Office of Water Regulations and Standards, U.S. EPA. EPA 440/5-86-001.

*EPA. 1987. Health assessment document for beryllium. Prepared by Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, U.S. Environmental Protection Agency, Research Triangle Park, NC for Office of Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC. EPA/600/8-84/026F.

*EPA. 1988a. U.S. Environmental Protection Agency. CFR 40 part 421.152 to 421.156.

EPA. 1988b. Analysis of the Clean Water Act Effluent Guidelines Pollutants. Summary of the chemicals regulated by industrial points source categories. 40 CFR Parts 400-475. Draft. Washington, DC: Office of Water Regulations and Standards, Division of Water, U.S. Environmental Protection Agency.

*EPA. 1988c. Method 6010: Inductively coupled plasma atomic emissions spectroscopy. In: Test methods for evaluating solid waste. SW846. Washington, DC: Office of Solid Waste and Emergency Response, U.S. Environmental Protection Agency, 6010-1 to 6010-15.

EPA. 1988d. Emissions standard for beryllium. Code of Federal Regulations. U.S. Environmental Protection Agency. 40 CFR 61.32.

EPA. 1989a. Interim methods for development of inhalation reference doses. U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. Washington, DC. EPA 600/8-88-066F.

EPA. 1989b. Environmental Protection Agency. Reportable quantity adjustments; Delisting of ammonium thiosulfate. U.S. Environmental Protection Agency: Final Rule. Federal Register 54:33426-33483.

*EPA. 1990. Interim methods for development of inhalation reference concentrations. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Office of Research and Development, Environmental Criteria and Assessment Office. EPA 600/8-90/066A.

EPA. 1996. Drinking water regulations and health advisories. Washington, DC. United States Environmental Protection Agency, Office of Water 4304. EPA 822-B-96-002.

9. REFERENCES

*EPA. 1997a. Special report on environmental endocrine disruption: An effects assessment and analysis. Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. EPA/630/R-96/012.

*EPA. 1997b. Profile of the fossil fuel electric power generation industry: EPA Office of Compliance Sector Notebook Project. U.S. Environmental Protection Agency. EPA/310-R-97-007.

EPA. 1997c. Automated Form R for Windows: User's guide (RY97). Washington, DC: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics.

*EPA. 1998. Toxicological review of beryllium and compounds. U.S. Environmental Protection Agency, Washington DC.

*EPA. 1999a. National recommended water quality criteria-correction. Washington, DC. U.S. Environmental Protection Agency, Office of Water 4304. EPA 822-Z-99-001. April, 1999.

*EPA. 1999b. Inorganic chemical sampling and analytical requirements. United States Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.23.

EPA. 1999c. Universal treatment standards. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 268.48.

EPA. 1999d. Emission standard. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 61.32.

EPA. 1999e. Designation of hazardous substances. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4.

*EPA. 1999f. Prevention of significant deterioration of air quality. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 51.166.

*EPA.. 1999g. Subpart D- Transfer, modification, revocation and reissuance and termination of permits. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 122 Subpart D.

EPA. 1999h. Emission standard. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 61.42.

EPA. 1999i. Subpart C- National emission standard for beryllium. Applicability. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 61.30.

EPA. 1999j. Subpart A- General provisions. Lists of pollutants and applicability of part 61. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 61.01.

EPA. 1999k. Treatment standards expressed as specific technologies. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.42.

EPA. 1999l. Subpart D- Lists of hazardous wastes. General. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261 Subpart D.

EPA. 1999m. Comparable/syngas fuel exclusion. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261,38.

EPA. 1999n. Discarded commercial chemical products, off-specification species, container residues, and spill residues thereof. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261.33.

EPA. 1999o. Definition of hazardous waste. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261.3.

EPA. 1999p. Standards to control metals emissions. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 266.106.

EPA. 1999q. Interim status standards for burners. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 266.103.

EPA. 1999r. Permit standards for burners. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 266.102.

EPA. 1999s. Applicability: Description of the primary beryllium subcategory. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 421.150.

EPA. 1999t. Toxic pollutants. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 401.15.

EPA. 1999u. Variances and exemptions from the maximum contaminant levels for organic and inorganic chemicals. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 142.62.

EPA. 1999v. Maximum contaminant levels for inorganic contaminants. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.62.

EPA. 1999w. Maximum contaminant level goals for inorganic contaminants. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.51.

EPA. 1999x. Subpart D- Specific toxic chemical listings. Chemicals and chemical categories to which this part applies. Code of Federal Regulations. U.S. Environmental Protection Agency. 40 CFR 372.65.

*EPA. 2000a. Drinking water standards and health advisories. U.S. Environmental Protection Agency. Office of Water. EPA 822-B-00-001.

*EPA. 2000b. National Drinking Water Contaminant Occurrence Database (NCOD). U.S. Environmental Protection Agency. http://www.epa.gov/ncodwork/html/ncod/ncod_query.html.

EPA. 2000c. Superfund hazardous waste site query data source. Office of Emergency and Remedial Response, U.S. Environmental Protection Agency. http://www.epa.gov/superfund/sites/query/basic.htm.

*EPA. 2001a. Designation, reportable quantities, and notification. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4. http://ecfr.access.gpo.gov/otcgi/cfr/otfilter.cgi?DB=I&QUERY=438159&RGN=BSECCT&SUBSET=SUBSET&FROM=1&ITEM=1. December 18, 2001.

*EPA. 2001b. Groundwater monitoring list. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 264, Appendix IX. http://ecfrback.access.gpo.gov/otcgi/cfr/otfilter.cgi...nd&QUERY=49673&RGN=BAPPCT&SUBSET=SUBSET&FROM=1&ITEM=1. December 18, 2001.

*EPA. 2001c. Health based limits for exclusion of waste-derived residues. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 266, Appendix VII. http://ecfrback.access.gpo.gov/otcgi/cfr...0&RGN=BAPPCT&SUBSET=SUBSET&FROM=1&ITEM=1. December 18, 2001.

*EPA. 2001d. Identification and listing of hazardous waste. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261.33(e). http://ecfrback.access.gpo.gov/otcgi/cfr...8&RGN=BSECCT&SUBSET=SUBSET&FROM=1&ITEM=1. December 18, 2001.

*EPA. 2001e. Land disposal restrictions. Universal treatment standards. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.48. http://ecfr.access.gpo.gov/otcgi/cfr...1&RGN=BSECCT&SUBSET=SUBSET& FROM=1&ITEM=1. December 18, 2001.

*EPA. 2001f. Maximum contaminant levels for inorganic contaminants. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.62(b). http://ecfr.access.gpo.gov/otcgi/cfr/otf...8&RGN=BSECCT&SUBSET=SUBSET& FROM=1&ITEM=1. December 18, 2001.

*EPA. 2001g. Maximum contaminant level goals for inorganic contaminants. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.51(b). http://ecfr.access.gpo.gov/otcgi/cfr/otf...3&RGN=BSECCT&SUBSET=SUBSET& FROM=1&ITEM=1. December 18, 2001.

*EPA. 2001h. National emission standards for hazardous air pollutants. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 61.32. http://ecfr.access.gpo.gov/otcgi/cfr...4&RGN=BSECCT&SUBSET=SUBSET& FROM=1&ITEM=1. December 18, 2001.

*EPA. 2001i. National emission standards for hazardous air pollutants. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 61.42. http://ecfr.access.gpo.gov/otcgi/cfr...4&RGN=BSECCT&SUBSET=SUBSET& FROM=1&ITEM=1. December 18, 2001.

*EPA. 2001j. Risk specific doses. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 266, Appendix V. http://ecfrback.access.gpo.gov/otcgi/cfr/otfilter.cgi...and&QUERY=9974&RGN=BAPPCT&SUBSET=SUBSET&FROM=1&ITEM=1. December 18, 2001.

*EPA. 2001k. Toxic chemical release reporting; Community right-to-know. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.65. http://ecfrback.access.gpo.gov/otcgi/cfr...4&RGN=BSECCT&SUBSET=SUBSET&FROM=1&ITEM=1. December 18, 2001.

9. REFERENCES

*EPA. 2001l. Toxic pollutant. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 401.15. http://ecfr.access.gpo.gov/otcgi/cfr/otf...1&RGN=BSECCT&SUBSET=SUBSET&FROM=1&ITEM=1. December 18, 2001.

Epner EP, Vancil MA. 1989. Locating and estimating air toxics emissions from municipal waste combustors. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, Research Triangle Park, NC. NTIS PB89-195226.

*Epstein MS, Rains TC, Brady TJ, et al. 1978. Determination of several trace metals in simulated fresh water by graphite furnace atomic emission spectrometry. Anal Chem 50(7):874-880.

*Epstein PE, Dauber JH, Rossman MD et al. 1982. Bronchoalveolar lavage in a patient with chronic berylliosis: evidence for hypersensitivity pneumonitis. Ann Intern Med 97:213-216.

*Epstein WL. 1983. Commentary and update: Beryllium granulomas of the skin: A small window to understanding. Cleveland Clinic Quarterly 50:73-75.

Esteves Da Silva JCG, Machado AASC. 1996b. Characterization of the Binding Sites for Al(III) and Be(II) in a sample of marine fulvic acids. Marine Chemistry 54:293-302.

*Esteves Da Silva JCG, Machado AASC,, et al. 1996a. Quantitative study of Be(ii) complexation by soil fulvic acids by molecular fluorescence spectroscopy. Environ Sci Technol 30(11):3155-3160.

Farris GM, Newman LS, Frome EL, et al. 2000. Detection of beryllium sensitivity using a flow cytometric lymphocyte proliferation test: the Immuno-Be-LPT. Toxicology 143:125-140.

FDA. 1999. Subpart B- Requirements for specific standardized beverages. Bottled water. Food and Drug Administration, HHS. Code of Federal Regulations. 21 CFR 165.110.

*FDA. 2001. Bottled water. Food and Drug Administration. Code of Federal Regulations. 21 CFR 165.110. http://frwebgate.access.gpo.gov/cgi-bin/...PART=165&SECTION=110&YEAR=2001&TYPE=TEXT. December 18, 2001.

*FEDRIP. 2000. Federal Research in Progress. July 1990.

Finch GL. 1992. Written communication (September 3) to Agency for Toxic Substances and Disease Control in peer review comments on draft toxicological profile for beryllium. Lovelace Inhalation Toxicology Research Institute, Albuquerque, NM.

Finch GL. 2000. Beryllium. In: Cohen MD, Zelikoff JT, Schlesinger RB, eds. Pulmonary Immunotoxicology. Boston: Kluwer Academic Publishers, 213-239.

Finch GL, Haley PJ, Hoover MD, et al. 1994. Responses of rat lungs to low lung burdens of inhaled beryllium metal. Inhal Toxicol 6(3):205-224.

Finch GL, Hoover MD, Hahn FF, et al. 1996. Animal models of beryllium-induced lung disease. Environ Health Perspect 104(Suppl. 5):973-979.

Finch GL, March TH, Hahn FF, et al. 1998a. Carcinogenic responses of transgenic heterozygous p53 knockout mice to inhaled $^{239}Pu0_2$. Toxicol Pathol 26(4):484-491.

Finch GL, Mewhinney JA, Eidson AF, et al. 1988. In vitro dissolution characteristics of beryllium oxide and beryllium metal aerosols. J Aerosol Sci 19:333-342.

*Finch GL, Mewhinney JA, Hoover MD, et al. 1990. Clearance, translocation, and excretion of beryllium following acute inhalation of beryllium oxide by beagle dogs. Fundam Appl Toxicol 15:231-241.

Finch GL, Nikula KJ, Hoover MD. 1998b. Dose-response relationships between inhaled beryllium metal and lung toxicity in C3H mice. Toxicol Sci 42(1):36-48.

*Fishbein L. 1981. Sources, transport and alterations of metal compounds: An overview. I. Arsenic, beryllium, cadmium, chromium, and nickel. Environ Health Perspect 40:43-64.

Fiskesjo G. 1988. The allium test - an alternative in environmental studies: the relative toxicity of metal ions. Mutat Res 197:243-260.

*Flora SJ, Mathur S, Mathur R. 1995. Effects of meso-2,3-dimercaptosuccinic acid or 2,3-dimercaptopropane 1-sulfonate on beryllium-induced biochemical alterations and metal concentration in male rats. Toxicology 95(1-2):167-175.

*Fomon SJ. 1966. Body composition of the infant: Part 1: 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 10 years. Am J Clin Nutr 35:1169-1175.

*Fontenot AP, Falta MT, Freed BM, et al. 1999. Identification of pathogenic T cells in patients with beryllium-induced lung disease. J Immunol 163(2):1019-1026.

*Fontenot AP, Kotzin BL, Comment CE, et al. 1998. Expansions of T-cell subsets expressing particular T-cell receptor variable regions in chronic beryllium disease. Am J Respir Cell Mol Biol 18(4):581-589.

*Fontenot AP, Torres M, Marshall WH, et al. 2000. Beryllium presentation to CD4+ T cells underlies disease-susceptibility HLA-DP alleles in chronic beryllium disease. Proc Natl Acad Sci U S A 97(23):12717-12722.

*Foreman JK, Gough TA, Walker EA. 1970. The determination of traces of beryllium in human and rat urine samples by gas chromatography. Analyst 95:797-804.

*Frame GM, Ford RE. 1974. Trace determination of beryllium oxide in biological samples by electron-capture gas chromatography. Anal Chem 46:534-539.

*Freiman DG, Hardy HL. 1970. Beryllium disease. The relation of pulmonary pathology to clinical course and prognosis based on a study of 130 cases from the U.S. Beryllium Case Registry. Hum Pathol 1:25-44.

*Freundt KJ, Ibrahim HA. 1990. Growth of rats during a subchronic intake of the heavy metals Pb, Cd, Zn, Mn, Cu, Hg, and Be. Pol J Occup Med 3:227-232.

*Frink CR. 1996. A perspective on metals in soils. J Soil Contam 5(4):329-359.

9. REFERENCES

Frome EL, Smith MH, Littlefield LG, et al. 1996. Statistical methods for the blood beryllium lymphocyte proliferation test. Environ Health Perspect 104(Suppl. 5):957-968.

FSTRAC. 1990. Summary of state and federal drinking water standards and guidelines. Chemical Communication Subcommittee, Federal-State Toxicology and Regulatory Alliance Committee.

FSTRAC. 1998-1999. Summary of state and federal drinking water standards and guidelines. U.S. Environmental Protection Agency, Office of Science and Technology, Office of Water. Data Bank Update Committee Federal-State Toxicology and Risk Analysis Committee.

*Furchner JE, Richmond CR, London JE. 1973. Comparative metabolism of radionuclides in mammals. VIII. Retention of beryllium in the mouse, rat, monkey and dog. Health Phys 24:293-300.

Galbraith GMP, Pandey JP, Schmidt MG, et al. 1996. Tumor necrosis factor alpha gene expression in human monocytic THP-1 cells exposed to beryllium. Arch Environ Health 51(1):29-33.

Garry VF, Nelson RL, Whorton EP, et al. 1989. Chromosomal aberrations and sister-chromatid exchanges in tool and die workers. Mutat Res 225:1-9.

*Giwercman A, Carlsen E, Keiding N, et al. 1993. Evidence for increasing incidence of abnormalities of the human testis: A review. Environ Health Perspect Suppl 101(2):65-71.

*Gladney ES, Owens JW. 1976. Beryllium emissions from a coal-fired power plant. J Environ Sci Health ll:297-311.

Goel KA, Agrawal VP, Garg V. 1980. Pulmonary toxicity of beryllium in albino rat. Bull Environ Contam Toxicol 24:59-64.

Gore BJ, Gericke G, Delport. 1999. Pisces: Power industry integrated systems, chemical emissions study. Water Sci Technol 39(10-11):361-366.

*Griffitts WR, Skilleter DN. 1990. Beryllium. In: Merian E, ed. Metals and their compounds in the environment. New York: VCH, 775-787.

Griggs K. 1973. Toxic metal fumes from mantle-type camp lanterns. Science 181:842-843.

Groth DH, Kommineni C, MacKay GR. 1980. Carcinogenicity of beryllium hydroxide and alloys. Environ Res 21:64-84.

*Guyatt BL, Kay HD, Branion HD. 1933. Beryllium "rickets." J Nutr 6:313-324.

*Guzelian PS, Henry CJ, Olin SS, eds. 1992. Similarities and differences between children and adults: Implications for risk assessment. Washington, DC: International Life Sciences Institute Press.

Haberman AL, Pratt M, Storrs FJ. 1993. Contact dermatitis from beryllium in dental alloys. Contact Dermatitis 28(3):157-162.

*Haddad LM, Shannon MW, Winchester JF, eds. 1998. Clinical Management of Poisoning and Drug Overdose. Third Edition: Philadelphia, PA: WB Saunders, 792.

9. REFERENCES

*Haley PJ, Finch GL, Hoover, MD, et al. 1990. The acute toxicity of inhaled beryllium metal in rats. Fundam Appl Toxicol 15:767-778.

Haley PJ, Finch GL, Hoover MD, et al. 1992. Beryllium-induced lung disease in the dog following two exposures to BeO. Environ Res 59:400-415.

*Haley PJ, Finch GL, Mewhinney JA, et al. 1989. A canine model of beryllium-induced granulomatous lung disease. Lab Invest 61:219-227.

Haley P, Pavia KF, Swafford DS, et al. 1994. The comparative pulmonary toxicity of beryllium metal and beryllium oxide in cynomolgus monkeys. Immunopharmacol Immunotoxicol 16(4):627-644.

Hall AH, Rumack BH, eds. 1992. TOMES(R) information system. Denver, CO: Micromedex Inc.

*Hall RH, Scott JK, Laskin S, et al. 1950. Acute toxicity of inhaled beryllium. Arch Ind Hyg Occup Med 12:25-48.

*Hall TC, Wood CH, Stoeckle, et al. 1959. Case data from the Beryllium Registry. AMA Arch Ind Health 19:100-103.

Hamada H, Sawyer RT, Kittle LA, et al. 2000. Beryllium-stimulation does not activate transcription factors in a mouse hybrid macrophage cell line. Toxicology 143:249-261.

*Hamilton A, Hardy HL. 1974. Beryllium. In: Industrial toxicology, 3rd ed. Acton, MA: Publishing Sciences Group, Inc., 49-58

*Hamilton A, Hardy HL. 1983. In:. Hamilton and Hardy's industrial toxicology. 4th ed. Finkel AJ, ed. 4th Ed., Boston, MA: John Wright PSG Inc, 26-36.

*Hamilton EI, Minski MJ. 1973. Abundance of the chemical elements in man’s diet and possible relation with environmental factors. Science of the Total Environment. 1:375-394.

*Hardy HL, Stoeckle JD. 1959. Beryllium disease. J Chronic Disease 9:152-160.

*Hardy HL, Tabershaw IR. 1946. Delayed chemical pneumonitis occurring in workers exposed to beryllium compounds. J Ind Hyg Toxicol 28:197-211.

9. REFERENCES

Harmsen AG, Finch GL, Mewhinney JA, et al. 1986. Lung cellular response and lymphocyte blastogenesis in beagle dogs exposed to beryllium oxide. In: Muggenburg BA, Sun JD, eds. Annual report of the Inhalation Toxicology Research Institute, October 1, 1985 through September 30, 1986. Lovelace Biomedical and Environmental Research Institute, Albuquerque, New Mexico, 291-295.

Harris J, Bucher Bartelson B, Barker E, et al. 1997. Serum neopterin in chronic beryllium disease. Am J Ind Med 32:21-26.

Harris KM, McConnochie K, Adams H. 1993. The computed tomographic appearances in chronic berylliosis. Clin Radiol 47(1):26-31.

*Hart BA, Harmsen AG, Low RB, et al. 1984. Biochemical, cytological and histological alterations in rat lung following acute beryllium aerosol exposure. Toxicol Appl Pharmacol 75:454-465.

*Hasselriis F, Licata A. 1996. Analysis of heavy metal emission data from municipal waste combustion. J Hazard Mater 47:77-102.

*Hawley GG. 1981. The condensed chemical dictionary. 10th ed. New York, NY: Van Nostrand Reinhold Co., 126-127.

*Hawley N, Robbins JA, Eadie BJ. 1986. The partitioning of ^{7}beryllium in fresh water. Geochim Cosmochim Acta 50:1127-1131.

*Hayes KF, Traina SJ. 1998. Metal ion speciation and its significance in ecosystem health. Soil chemistry and ecosystem health. Special publication 52. Soil Science Society of America. Madison, WI, 45-84.

HazDat. 1992. Agency of Toxic Substances and Disease Registry (ATSDR), Atlanta, GA. October 20, 1992.

HazDat. 2000. Agency of Toxic Substances and Disease Registry (ATSDR), Atlanta, GA. March, 2000.

HazDat. 2001. Agency of Toxic Substances and Disease Registry (ATSDR), Atlanta, GA. December, 2001.

*HazDat. 2002. Agency of Toxic Substances and Disease Registry (ATSDR), Atlanta, Ga. March 2001.

Helmsers RA, Hunninghake GW. 1987. Bronchoalveolar lavage in the nonimmunocompromised patient. Chest 96:1184-1190.

*Henneberger PK, Cumro D, Deubner DD. 2001. Beryllium sensitization and disease among long-term and short-term workers in a beryllium ceramics plant. Int Arch Occup Health 74:167-176,

*Herr M. 1997. Defense programs beryllium good practice guide. Lawrence Livermore National Laboratory. UCRL-ID-127871.

*HI Dept of Health. 1999a. Hawaii Department of Health. Administrative Rules. Environmental Health. Safe drinking water rules.

*HI Dept of Health. 1999b. Hawaii Department of Health. Administrative Rules. Environmental Health. Clean Water Rules.

Hill SJ. 1997. Speciation of trace metals in the environment. Chem Soc Rev 26:291-298.

*Hoagland MB, Grier RS, Hood MB. 1950. Beryllium and growth. I. Beryllium-induced osteogenic sarcomata. Cancer Res:629-635.

*Hoel DG, Davis DL, Miller AB, et al. 1992. Trends in cancer mortality in 15 industrialized countries, 1969-1986. J Natl Cancer Inst 84(5):313-320.

Holcombe LJ, Eynon BP, Switzer P. 1985. Variability of elemental concentrations in power plant ash. Environ Sci Technol 19:615-620.

Holtzman NA. 1996. Medical and ethical issues in genetic screening- An academic view. Environ Health Perspect 104(Suppl. 5):987-998.

Hoover MD, Eidson AF, Mewhinney JA, et al. 1988. Generation and characterization of respirable beryllium oxide aerosols for toxicity studies. Aerosol Science and Technology 9:83-92.

*Hopkins WA, Mendonça MT, Rowe CL, et al. 1998. Elevated trace element concentrations in southern toads, *Bufo terrestris*, exposed to coal combustion waste. Arch Environ Contam Toxicol. 35:325-329.

*HSDB. 2000. Hazardous Substance Data Bank. National Library of Medicine, National Toxicology Information Program, Bethesda, MD. July 16, 1990.

*HSDB. 2001. Beryllium. Hazardous Substances Data Bank. http://toxnet.nlm.nih.gov/cgi-bin/sis/search. September 05, 2001.

*Hsie AW, Johnson NP, Couch DB, et al. 1979. Quantitative mammalian cell mutagenesis and a preliminary study of the mutagenic potential of metallic compounds. In: Kharasch N, ed. Trace metals in health and disease: New roles of metals in biochemistry, the environment, and clinical/nutritional studies. New York, NY: Raven Press, 55-69.

*Huang H, Meyer KC, Kubal L, et al. 1992. An immune model of beryllium-induced pulmonary granulomata in mice: Histopathology, immune reactivity, and flow-cytometric analysis of bronchoalveolar lavage-derived cells. Lab Invest 67:138-146.

Hubert AM, Vaessen AMGV, Szteke B. 2000. Beryllium in food and drinking water-a summary of available knowledge. Food Addit Contam 17(2):149-159.

*Hurlburt JA. 1978. Determination of beryllium in biological tissues and fluids by flameless atomic absorption spectroscopy. Atomic Absorption Newsletter 17:121-124.

*IARC. 1980. IARC monographs on the evaluation of carcinogenic risk of chemicals to humans. Volume 23: Some metals and metallic compounds. World Health Organization, Lyon, France., 143-172.

IARC. 1987. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Supplemental 7: Beryllium and beryllium compounds. World Health Organization, Lyon, France, 127-128.

*IARC. 1993. IARC monographs of the evaluation of the carcinogenic risk of chemicals to humans. World Health Organization, Lyon, France.

9. REFERENCES

*IARC. 1997. IARC monographs of the evaluation of the carcinogenic risk of chemicals to humans. Beryllium and beryllium compounds. http.//193.51.164.11/htdocs/Monographs/Vol58/MONO58-1.HTM.

*IARC. 2001. Overall evaluations of carcinogenicity to humans. International Agency for the Research on Cancer. http://193.51.164.11/monoeval/crthgr01.html. December 18, 2001.

*Infante PF, Wagoner JK, Sprince NL. 1980. Mortality patterns from lung cancer and nonneoplastic respiratory disease among white males in the beryllium case registry. Environ Res 21:35-43.

Inoue Y, Barker E, Daniloff E, et al. 1997. Pulmonary epithelial cell injury and alveolar-capillary permeability in berylliosis. Am J Respir Crit Care Med 156(1):109-115.

Inoue Y, Cornebise M, Daniloff E, et al. 1996. Mast cell-associated basic fibroblast growth factor in the fibrotic response to environmental toxins. The beryllium model. Chest 109(Suppl. 3):43S-44S.

IRIS. 2001. Beryllium and compounds. Integrated Risk Information System. http://www.epa.gov/iris/subst/0014.htm. September 05, 2001.

*IRIS. 2002. Beryllium and compounds. Integrated Risk Information System. http://www.epa.gov/iris/subst/0014.htm. March 11, 2002.

*Iwan GR. 1987. Drinking water quality concerns of New York City, past and present. Ann N Y Acad Sci 502:183-204.

*Jacobson SA. 1933. Bone lesions in rats produced by the substitution of beryllium for calcium in the diet. Arch Pathol 15:18-26.

*Jagoe CH, Matey VE, Haines TA, et al. 1993. Effect of beryllium on fish in acid water is analogous to aluminum toxicity. Aquat Toxicol 24:241-256.

*James DG, Williams WJ. 1985. Sarcoidosis and other granulomatous disorders, Vol 24. In: Smith LH Jr., ed. Major problems in internal medicine. London, England: W.B. Saunders Company.

Jameson CW. 1996. Introduction to the conference on beryllium-related diseases. Environ Health Perspect 104(Suppl. 5):935-936.

*Johanson CE. 1980. Permeability and vascularity of the developing brain: Cerebellum vs cerebral cortex. Brain Res 190:3-16.

Johnson JS, Foote K, McClean M, et al. 2001. Beryllium exposure control program at the Cardiff atomic weapons establishment in the United Kingdom. Appl Occup Environ Hyg 16(5):619-630.

*Johnson NR. 1983. Beryllium disease among workers in a spacecraft-manufacturing plant - California. MMWR 32:419-425.

Joiner MC. 1989. A comparison of the effects of p(62)-Be and d(16)-Be neutrons in the mouse kidney. Radiother Oncol 13:211-224.

Joseph P, Muchnok T, Ong T-M. 2001. Gene expression profile in BALB/c-3T3 cells transformed with beryllium sulfate. Mol Carcinog 32:28-35.

*Joshi JG, Price DJ, Fleming J. 1984. Ferritin and metal toxicity. Protides Biological Fluids 31:183-186.

*Kalyoncu R. 1998. Coal Combustion Products. Mineral Yearbook: Volume I. Metals and Minerals. U.S. Geological Survey. S1-S5.

*Kanarek DJ, Wainer RA, Chamberlin RI, et al. 1973. Respiratory illness in a population exposed to beryllium. Am Rev Respir Dis 108:1295-1302.

*Kanematsu N, Hara M, Kada T. 1980. REC assay and mutagenicity study on metal compounds. Mutat Res 77:109-116.

*Kansas Dept of Health and Environ. 1999. Kansas Department of Health and Environment. Kansas Administrative Regulations.

*Kaplan DI, Sajwan KS, Adriano DC, et al. 1990. Phytoavailability and toxicity of beryllium and vanadium. Water Air Soil Pollut 53:203-212.

*Kay HD, Skill DL. 1934. Beryllium rickets: II. Prevention and cure of beryllium rickets. Biochem J 28:1222-1229.

*Kelleher PC, Martyny JW, Mroz MM, et al. 2001. Beryllium particulate exposure and disease relations in a beryllium machining plant. J Occup Environ Med 43(3):238-249.

*Kenaga E. 1980. Predicted bioconcentration factors and soil sorption coefficients of pesticides and other chemicals. Ecotoxicol Environ Safety 4:26-38.

Kent MS, Robins TG, Madl AK. 2001. Is total mass or mass of alveolar-deposited airborne particles of beryllium a better predictor of the prevalence of disease. A preliminary study of a beryllium processing facility. Appl Occup Environ Hyg 16(5):539-558.

*Kimmerle G. 1966. Beryllium. Vol 21. Handbook of experimental pharmacology. Springer-Verlag, Berlin.

Kolanz ME. 2001. Introduction to beryllium: Uses, regulatory history, and disease. Appl Occup Environ Hyg 16(5):559-567.

Kolanz ME, Madl AK, Kelsh MA, et al. 2001. A comparison and critique of historical and current exposure assessment methods for beryllium: implications for evaluating risk of chronic beryllium disease. Appl Occup Environ Hyg 16(5):593-614.

*Komori M, Nishio K, Kitada M, et al. 1990. Fetus-specific expression of a form of cytochrome P-450 in human livers. Biochemistry 29:4430-4433.

*Kotin P. 1994. Editorial. Re: The epidemiological evidence on the carcinogenicity of beryllium, by MacMahon. JOEM 35(1):25-26.

*Kotloff RM, Richman PS, Greenacre JK, et al. 1993. Chronic beryllium disease in a dental laboratory technician. Am Rev Respir Dis 147(1):205-207.

9. REFERENCES

*Krachler M, Rossipal E, Micetic-Turk D. 1999a. Trace of element transfer from the mother to the newborn--investigations on triplets of colostrum, maternal and umbilical cord sera. Eur J Clin Nutr 53(6):484-494.

*Krachler M, Rossipal E, Micetic-Turk D. 1999b. Concentrations of trace elements in arterial and venous umbilical cord sera. Trace Elem Electrolytes 16(1):46-52.

*Kram P, Tiruska J, Driscoll CT. 1998. Beryllium chemistry in the Lysina Catchment Czech Republic. Water Air Soil Pollut 105:409-415.

*Kreiss K, Mroz MM, Newman LS, et al. 1996. Machining risk of beryllium disease and sensitization with median exposures below µg/m3. Am J Ind Med 30(1):16-25.

*Kreiss K, Mroz MM, Zhen B, et al. 1993a. Epidemiology of beryllium sensitization and disease in nuclear workers. Am Rev Respir Dis 148(4 Pt 1):985-991.

*Kreiss K, Mroz MM, Zhen B, et al. 1997. Risks of beryllium disease related to work processes at a metal, alloy, and oxide production plant. Occup Environ Med 54(8):605-612.

*Kreiss K, Newman LS, Mroz MM, et al. 1989. Screening blood test identifies subclinical beryllium disease. J Occup Med 31:603-608.

Kreiss K, Wasserman S, Mroz MM, et al. 1993b. Beryllium disease screening in the ceramics industry. Blood lymphocyte test performance and exposure-disease relations. J Occup Med 35(3):267-274.

*Kriebel D, Sprince NL, Eisen EA, et al. 1988a. Beryllium exposure and pulmonary function: A cross sectional study of beryllium workers. Br J Ind Med 45:167-173.

*Kriebel D, Sprince NL, Eisen EA, et al. 1988b. Pulmonary function in beryllium workers: Assessment of exposure. Br J Ind Med 45:83-92.

*Krishnan K, Andersen ME. 1994. Physiologically based pharmacokinetic modeling in toxicology. In: Hayes AW, ed. Principles and methods of toxicology. 3rd ed. New York, NY: Raven Press, Ltd., 149-188.

*Krishnan K, Andersen ME, Clewell HJ III, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures: Case studies, mechanisms, and novel approaches. San Diego, CA: Academic Press, 399-437.

Kushner DJ. 1993. Effects of speciation of toxic metals on their biological activity. Water Pollut Res J Can 28(1):111-128.

*Lanchow University Department of Biology. 1978. Lan-chou Ta Hsueh Hsueh Pao, Tzu Jan K'o Hsueh Pao 1978 116-21. Chem Abstr 93:180539.

*Langner GC, Creek KL, Castro RG. 1997. Control of Beryllium Power at a DOE Facility. Los Alamos National Laboratory. LA-UR-3039.

*Larramendy ML, Popescu NC, DiPaolo JA. 1981. Induction by inorganic metal salts of sister chromatid exchanges and chromosome aberrations in human and syrian hamster cell strains. Environ Mutagen 3:597-606.

Lee JY, Atochina O, King B, et al. 2000. Beryllium, an adjuvant that promotes gamma interferon production. Infect Immun 68(7):4032-4039.

*Leeder JS, Kearns GL. 1997. Pharmcogenetics in pediatrics: Implications for practice. Pediatr Clin North Am 44(1):55-77.

*LeFevre ME, Joel DD. 1986. Distribution of label after intragastric administration of 7Be-labeled carbon to weanling and aged mice. Proc Soc Exp Biol Med 182:112-119.

Legator MS, Bueding E, Batzinger R, et al. 1982. An evaluation of the host-mediated assay and body fluid analysis: A report of the U.S. Environmental Protection Agency Gene-Tox program. Mutat Res 93:319-374.

Lehnert NM, Gary RK, Marrone BL, et al. 2001. Inhibition of normal human lung fibroblast growth by beryllium. Toxicology 160:119-127.

Leifer Z, Kada T, Mandel M, et al. 1981. An evaluation of tests using DNA repair-deficient bacteria for predicting genotoxicity and carcinogenicity: A report of the U.S. EPA's Gene-Tox program. Mutat Res 87:211-297.

Leonard A. 1988. Mechanisms in metal genotoxicity: the significance of in vitro approaches. Mutat Res 198:321-326.

Leonard A, Bernard A. 1993. Biomonitoring exposure to metal compounds with carcinogenic properties. Environ Health Perspect 101(Suppl. 3):127-133.

Leonard A, Lauwerys R. 1987. Mutagenicity, carcinogenicity and teratogenicity of beryllium. Mutat Res 186:35-42.

*Leung H-W. 1993. Physiologically-based pharmacokinetic modeling. In: Ballentine B, Marro T, Turner P, eds. General and applied toxicology. Vol. 1. New York, NY: Stockton Press, 153-164.

*Levy PS, Powers TE, Roth HD. (n.d.) Beryllium and lung cancer: A review and meta-analysis of the NIOSH Cohort Mortality Study.

*Lieben J, Metzner,F. 1959. Epidemiological findings associated with beryllium extraction. Am Ind Hyg Assoc J 20(6):152.

*Lieben J, Williams RR. 1969. Respiratory disease associated with beryllium refining and alloy fabrication. 1968 follow-up. J Occup Med 11:480-485.

*Lieben J, Dattoli JA, Israel HL. 1964. Probable berylliosis from beryllium alloys. Arch Environ Health 9:473-477.

*Lindenschmidt RC, Sendelbach LE, Witschi HP, et al. 1986. Ferritin and in vivo beryllium toxicity. Toxicol Appl Pharmacol 82:344-350.

Lisk DJ. 1988. Environmental implication of incineration of municipal solid waste and ash disposal. Sci Total Environ 74:39-66.

*Livingston, AL. 1978. Forage plant estrogens. J Toxicol Environ Health 4:301-324.

9. REFERENCES

*Llobet JM, Granero S, Schuhmacher M, et al. 1998. Biological monitoring of environmental pollution and human exposure to metals in Tarragona, Spain IV Estimation of dietary intake. Trace Elem Electrolytes 15(3):136-141.

*Lo FB, Arai DK. 1989. Biological monitoring of toxic metals in urine by simultaneous inductively coupled plasma-atomic emission spectrometry. Am Ind Hyg Assoc J 50:245-251.

*Lombardi G, Germain C, UrenkJ, et al. 2001. HLA-DP allele-specific T cell responses to beryllium account for DP-associated susceptibility to chronic beryllium disease. J Immunol 166:3549-3555.

*Lum KR, Gammon KL. 1985. Geochemical availability of some trace and major elements in surficial sediments of the Detroit River and western Lake Erie. J Great Lakes Res 11:328-338.

*MacMahon B. 1994. The epidemiological evidence on the carcinogenicity of beryllium in humans. J Occup Med 36(1):15-24.

*Maier LA. 2001. Beryllium health effects in the era of the beryllium lymphocyte proliferation test. Appl Occup Environ Hyg 16(5):514-520.

*Maier LA, Reynolds MV, Young DA, et al. 1999. Angiotensin-1 converting enzyme polymorphisms in chronic beryllium disease. Am J Respir Crit Care Med 159(4 Pt 1):1342-1350.

Maier LA, Tinkle SS, Kittie LA, et al. 2001. IL-4 fails to regulat*e in vitro* beryllium-induced cytokines in berylliosis. Eur Resp J 17:403-415.

Maliarik MJ, Chen KM, Major ML, et al. 1998. Analysis of HLA-DPB1 polymorphisms in African-Americans with sarcoidosis. Am J Respir Crit Care Med 158(1):111-114.

*Mancuso TF. 1970. Relation of duration of employment and prior respiratory illness to respiratory cancer among beryllium workers. Environ Res 3:251-275.

*Mancuso TF. 1979. Occupational lung cancer among beryllium workers. In: Proceedings of the conference on occupational exposure to fibrous and particulate dust and their extension into the environment. In: Lemen R, Dement J, eds. Dust and Disease. Park Forest South, IL: Pathotox Publishers, Inc., 463-482.

*Mancuso TF. 1980. Mortality study of beryllium industry workers' occupational lung cancer. Environ Res 21:48-55.

*Mancuso TF, El-Attar AA. 1969. Epidemiological study of the beryllium industry. Cohort methodology and mortality studies. J Occup Med 11:422-434.

Mandervelt C, Clottens FL, Demedts M, et al. 1997. Assessment of the sensitization potential of five metal salts in the murine local node assay. Toxicology 120(1):65-73.

Markert B, Thornton I. 1990. Multi-element analysis of an English peat bog soil. Water Air Soil Pollut 49:113-124.

Markham TN. 1996. Screening for chronic beryllium disease using beryllium specific lymphocyte proliferation testing. Int Arch Occup Environ Health 68:405-407.

Marshall E. 1999. Beryllium screening raises ethical issues. Science 285(5425):178-179.

*Martinsen I, Thomassen Y. 1986. Multielemental characterization of human lung tissues by ICP-AES. Acta Pharmacol Toxicol 59:620-623.

Martyny JW, Hoover MD, Mroz MM, et al. 2000. Aerosols generated during beryllium machining. J Occup Environ Med 42(1):8-18.

*Marx JJ, Burrell R. 1973. Delayed hypersensitivity to beryllium compounds. J Immunol 111:590-598.

Mason B. 1966. Principles of geochemistry. New York, NY: John Wiley and Sons, 45.

*Mason B, Moore CB. 1982. Principles of Geochemistry. New York, NY: John Wiley and Sons.

*Mathur S. 1994. Role of Liv-52 in protection against beryllium intoxication. Biol Trace Elem Res 41(3):201-215.

*Mathur S, Flora SJ, Mathur R, et al. 1993. Mobilization and distribution of beryllium over the course of chelation therapy with some polyaminocarboxylic acids in the rat. Hum Exp Toxicol 12(1):19-24.

Mathur S, Flora JS, Mathur R, et al. 1994a. Beryllium-induced biochemical alterations and their prevention following co-administration of meso-2,3-dimercaptosuccinic acid or 2,3-dimercaptopropane sulphonate in rats. J Appl Toxicol 14(4):263-267.

*Mathur S, Mathur R, Prakash AO. 1994b. Protective action of a herbal preparation Liv-52 against beryllium toxicity in rats. Biomed Environ Sci 7(2):180-197.

*Mathur R, Sharmi S, Mathur S, et al. 1987. Effect of beryllium nitrate on early and late pregnancy in rats. Bull Environ Contam Toxicol 38:73-77.

*Matsumoto A, Hisada Y, Yoshimura Y. 1991. Calcium and phosphate concentrations and alkaline and acid phosphatase activities in serum of the rat fed with low calcium and beryllium diets. Oral Ther Pharmacol 10:253-259.

*Mayr U, Butsch A, Schneider S. 1992. Validation of two in vitro test systems for estrogenic activities with zearalenone, phytoestrogens and cereal extracts. Toxicology 74:135-149.

McCawley MA, Kent MS, Berakis MT. 2001. Ultrafine beryllium number concentration as a possible metric for chronic beryllium disease risk. Appl Occup Environ Hyg 16(5):631-638.

*McConnochie K, Williams WR, Kilpatrick GS, et al. 1988. Chronic beryllium disease in identical twins. Br J Dis Chest 82:431-435.

McGarvan PD, Rood AS, Till JE. 1999. Chronic beryllium disease and cancer risk estimates with uncertainty for beryllium released to the air from the Rocky Flats plant. Environ Health Perspect 107(9):731-744.

McMahon B. 1991. Assessment of human carcinogenicity. In: Rossman MD, Preuss OP, Powers MB, eds. Beryllium - biomedical and environmental aspects. Baltimore, MD: Williams and Wilkins, 97-100.

9. REFERENCES

*Measures CI, Edmond JM. 1986. Determination of beryllium in natural waters in real time using electron capture detection gas chromatography. Anal Chem 58:2065-2069.

*Meehan WR, Smythe LE. 1967. Occurrence of beryllium as a trace element in environmental materials. Environ Sci Technol 1:839-844.

*Meneses M, Llobet JM, Granero S, et al. 1999. Monitoring metals in the vicinity of a municipal waste incinerator: temporal variation in soils and vegetation. Sci Total Environ 226:157-164.

*Merrill JR, Lyden EFX, Honda M, et al. 1960. Sedimentary geochemistry of the beryllium isotopes. Geochimica Cosmochimica Acta 18:108-129.

Middleton DC. 1998. Chronic beryllium disease: Uncommon disease, less common diagnosis. Environ Health Perspect 106(12):765-767.

Milford JB, Davidson CI. 1985. The sizes of particulate trace elements in the atmosphere- A review. J Air Pollut Control Assoc 35(12):1249-1260.

*Miyaki M, Akamatsu N, Ono T, et al. 1979. Mutagenicity of metal cations in cultured cells from Chinese hamster. Mutat Res 68:259-263.

Monts DL, Singh JP, Abhilasha YS, et al. 1998. Toward development of a laser-based continuous emission monitor system for toxic metals in off-gases. Combust Sci Technol 134:103-126.

*Morgareidge K, Cox GE, Bailey DE. 1975. Chronic feeding studies with beryllium sulfate in rats: Evaluation of carcinogenic potential. Pittsburgh, PA: Food and Drug Research Laboratories, Inc. Final Report to the Aluminum Company of America.

*Morgareidge K, Cox GE, Gallo MA. 1976. Chronic feeding studies with beryllium in dogs. Food and Drug Research Laboratories, Inc. Submitted to the Aluminum Company of America. Alcan Research and Development, Ltd., Kawecki-Berylco Industries, Inc., and Brush-Wellman, Inc.

*Morselli PL, Franco-Morselli R, Bossi L. 1980. Clinical pharmacokinetics in newborn and infants: Age-related differences and therapeutic implications. Clin Pharmacokin 5:484-527.

*Mroz MM, Kreiss K, Lezotte DC, et al. 1991. Reexamination of the blood lymphocyte transformation test in the diagnosis of chronic beryllium disease. J Allergy Clin Immunology 88:54-60.

Muller J, Ruppert H, Muramatsu Y, et al. 2000. Resevoir sediments- a witness of mining and industrial development (Malter Resevoir, eastern Erzebirge, Germany). Environ Geol 39(12):1341-1351.

*Muto H, Abe T, Takizawa Y, et al. 1994. Simultaneous multielemental analysis of daily food samples by inductively coupled plasma mass spectrometry. Sci Total Environ 144(1-3):231-239.

Nabekura T, Minami T, Hirunuma R, et al. 2001. Comparative uptake behavior of trace elements in adult and suckling rat lens. Toxicology 163:101-105.

*Namiesnik J, Zygmunt B. 1999. Role of reference materials in analysis of environmental pollutants. Sci Total Environ. 228:243-257.

NAS/NRC. 1989. Report of the oversight committee. In: Biologic markers in reproductive toxicology. Washington, DC: National Academy of Sciences, National Research Council, National Academy Press.

NATICH. 1992. National Air Toxics Information Clearinghouse. Office of Air Quality Planning and Standards, U.S. EPA, Research Triangle Park. May 21, 1992.

*Neal C, Jeffrey H, Conway T, et al. 1992. Beryllium concentrations in rainfall, stemflow, throughfall, mist and stream waters for an upland acidified area of mid-Wales. J Hydrol 136:33049.

Newman LS. 1993. To Be^{2+} or not to Be^{2+}: Immunogenetics and occupational exposure. Science 262(5131):197-198.

Newman LS. 1996a. Significance of the blood beryllium lymphocyte proliferation test. Environ Health Perspect 104(Suppl. 5):953-956.

Newman LS. 1996b. Immunology, genetics, and epidemiology of beryllium disease. Chest 109(Suppl. 3):40S-43S.

Newman LS, Campbell PA. 1987. Mitogenic effect of beryllium sulfate on mouse B lymphocytes but not T lymphocytes in vitro. Int Arch Allergy Appl Immunol 8:223-227.

Newman LS, Kreiss K. 1992. Nonoccupational beryllium disease masquerading as sarcoidosis: Identification by blood lymphocyte proliferative response to beryllium. Am Rev Respir Dis 145(5):1212-1214.

Newman LS, Bobka C, Schumacher B, et al. 1994a. Compartmentalized immune response reflects clinical severity of beryllium disease. Am J Respir Crit Care Med 150(1):135-142.

Newman LS, Buschman DL, Newell JD, et al. 1994b. Beryllium disease: Assessment with CT. Radiology 190(3):835-840.

*Newman LS, Kreiss K, King TE Jr, et al. 1989. Pathologic and immunological alterations in early stages of beryllium disease. Am Rev Respir Dis 139:1479-1486.

Newman LS, Llody J, Daniloff E. 1996. The natural history of beryllium sensitization with chronic beryllium disease. Environ Health Perspect 104(Suppl. 5):937-943.

*Newman LS, Mroz MM, Maier LA, et al. 2001. Efficacy of serial medical surveillance for chronic beryllium disease in a beryllium machining plant. JOEM 43(3):231-237.

Newman LS, Orton R, Kreiss K. 1992. Serum angiotensin converting enzyme activity in chronic beryllium disease. Am Rev Respir Dis 146(1):39-42.

*Nickell-Brady C, Hahn FF, Finch GL, et al. 1994. Analysis of K-ras, p53 and c-raf-1 mutations in beryllium-induced rat lung tumors. Carcinogenesis 15(2):257-262.

*Nicola RM, Branchflower R, Pierce D. 1987. Chemical contaminants in bottomfish. J Environ Health 49:342-347.

*Nikula KJ, Swafford DS, Hoover MD, et al. 1997. Chronic granulomatous pneumonia and lymphocytic responses induced by inhaled beryllium metal in A/J and C3H/HeJ mice. Toxicol Pathol 25(1):2-12.

9. REFERENCES

*NIOSH. 1989a. National Occupational Exposure Survey (NOES). Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health. March 29, 1989.

*NIOSH. 1989b. NIOSH manual of analytical method. 3rd ed. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, 7102-1 to 7102-3.

*NIOSH. 1992. NIOSH recommendations for occupational safety and Health: Compendium of policy documents and statements. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health.

*NIOSH. 1995. Report to Congress on Workers' Home Contamination Study Conducted Under The Workers' Family Protection Act (29 U.S.C. 671a). Department of Health and Human Services, Center for Disease Control and Prevention, National Institute for Occupational Safety and Health. NIOSH Pub No. 95-123.

NIOSH. 2000. Beryllium and beryllium compounds. Pocket guide to chemical hazards (NPG), HTML version. Department of Health and Human Services, Center for Disease Control and Prevention, National Institute for Occupational Safety and Health. wysiwyg://85/http://www.cdc.gov/niosh/homepage.html

*NIOSH. 2001. Beryllium and beryllium compounds. NIOSH pocket guide to chemical hazards. National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/npg/npgd0054.html. December 18, 2001.

*NJ Dept Environ Prot. 1995. New Jersey Department of Environmental Protection. DEP Units & Program Areas. Division of Water Quality. Rules and Regulations. NJAC 7:9-6- New Jersey Ground Water Quality Standards..

Nordlind K. 1986. Further studies on the ability of different metal salts to influence the DNA synthesis of human lymphoid cells. Int Arch Allergy Appl Immunol 79:83-85.

*NRC. 1993. National Research Council. Pesticides in the diets of infants and children. Washington, DC: National Academy Press.

NRC. 1999a. Criticality accident requirements. U.S. Nuclear Regulatory Commission. Code of Federal Regulations. 10 CFR 70.24.

NRC. 1999b. Fundamental nuclear material controls. U.S. National Regulatory Commission. Code of Federal Regulations. 10 CFR 70.58.

NRC. 1999c. General license: Fissile material, limited quantity per package. U.S. Nuclear Regulatory Commission. Code of Federal Regulations. 10 CFR 71.18.

*NTP. 2002. Tenth report on carcinogens. U.S. Department of Health and Human Services, National Toxicology Program, Research Triangle Park, NC. http://ntp-server.niehs.nih.gov/NewHomeROC/RAHC_list.html. July 12, 2002.

NTP. 1999. Report on Carcinogens Background Document for Beryllium and Beryllium Compounds. Meeting of the NTP Board of Scientific Counselors, Report on Carcinogens Subcommittee. U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program, Research Triangle Park, NC.

OAQPC. 2000. EMC - CFR promulgated test methods. Emission Measurement Center, Office of Air Quality Planning & Standards, U.S. Environmental Protection Agency. Method 104.

O'Brien AAJ, Moore DP, Keogh JAB. 1987. Pulmonary berylliosis on corticosteroid therapy, with cavitating lung lesions and aspergillomata - report on a fatal case. Postgrad Med J 63:797-799.

*OHM-TADS. 1990. Oil and Hazardous Material Technical Assistance Data Systems. July 12, 1990.

Ojo-Amaize EA, Agopian MS, Markham TN, et al. 1992. Primary sensitization and re-stimulation of human lymphocytes with beryllium in-vitro. J Allergy Clin Immunol 89(1 Pt 2):203.

OSHA. 1989. U.S. Department of Labor. Occupational Safety and Health Administration. Air contaminants; final rule. Federal Register 54:2332-2960.

OSHA. 1999a. Gases, vapors, fumes, dusts and mists. U.S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.55.

OSHA. 1999b. Air contaminants. U.S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1915.1000.

OSHA. 1999c. Air contaminants. U.S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000

*OSHA. 2001a. Air contaminants. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000. Table Z-1 and Z-2. http://frewebgate.access.gpo.gov/cgi-bin/get-cfr?TITLE=29&PART=1910&SECTION=1000&YEAR=2001&TYPE=TEXT. Decenber 18, 2001.

*OSHA. 2001b. Air contaminants—shipyards. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1915.1000. http://www.sha-slc.gov/OshStd_data/1915_1000.html. September 17, 2001.

*OSHA. 2001c. Gases, vapors, fumes, dusts, and mists. Construction industry. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.55. http://frwebgate.access.gpo.gov/cgi-bin/get-cfr.cgi?TITLE=29&PART=1926&SECTION=55&YEAR=2001&TYPE=TEXT. September 18, 2001.

*OSHA. 2001d. Gases, vapors, fumes, dusts, and mists. Construction industry. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.252(c)(8). http://frwebgate.access.gpo.gov/cgi-bin/...ART=1910&SECTION=252&YEAR=2001&TYPE=TEXT. December 18, 2001.

*OSW 2000. SW-846 On-line test methods for evaluating solid waste physical/chemical methods. Office of Solid Waste, U.S. Environmental Protection Agency. Methods 0060, 3031.

*OTA. 1990. Neurotoxicity: Identifying and controlling poisons of the nervous system. Washington, DC: Office of Technology Assessment. OTA-BA-438.

9. REFERENCES

*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.

Paatero J, Hatakka J. 2000. Source areas of airborne ^{7}Be and ^{210}Pb measured in Northern Finland. Health Phys 79(6):691-696.

Pacyna JM. 1985. Atmospheric trace elements from natural and anthropogenic sources. In: Nriagu JO, Davidson CI, eds. Toxic metals in the environment. New York: John Wiley & Sons, 33-52.

*Pappas GP, Newman LS. 1993. Early pulmonary physiologic abnormalities in beryllium disease. Am Rev Respir Dis 148(3):661-666.

*Paschal DC, Bailey GG. 1986. Determination of beryllium in urine with electrothermal atomic absorption using the L'vov platform and matrix modification. Atomic Spectroscopy 7:1-3.

*Paschal DC, DiPietro ES, Phillips DL, et al. 1989. Age dependence of metals in hair in a selected U.S. population. Environ Res 48:17-28.

*Paschal DC, Ting BG, Morrow JC, et al. 1998. Trace mescals in urine of United States residents: reference range concentrations. Environ Res 76(1):53-59.

Pasupathy K. 1999. Use of yeast respiratory adaptation test system to detect chemical mutagens/ carcinogens in mammals. Indian J Exp Biol 37(7):725-728.

*Paudyn A, Templeton DM, Baines AD. 1989. Use of inductively coupled plasma-mass spectrometry ICP-MS for assessing trace element contamination in blood sampling devices. In: Symposium on recent advances in biological trace element analysis, Ottawa, Ontario, Canada, August 7-10, 1988. Sci Total Environ 89:343-352.

Paustenbach DJ, Madl AK, Greene JF. 2001. Identifying an appropriate occupational exposure limit (OEL) for beryllium: Data gaps and current research initiatives. Appl Occup Environ Hyg 16(5):527-538.

*Petzow G, Zorn H. 1974. [Toxicology of beryllium-containing substances]. Chem Ztg 98:236-241. (German)

Pfeifer S, Bartlett R, Strausz J, et al. 1994. Beryllium-induced disturbances of the murine immune system reflect some phenomena observed in sarcoidosis. Int Arch Allergy Immunol 104(4):332-339.

Pirrone N, Keeler GJ, Warner PO. 1995. Trends of ambient concentrations and deposition fluxes of particulate trace metals in Detroit from 1982 to 1992. Sci Total Environ. 162:43-61.

*Policard A. 1950. Histological studies of the effects of beryllium oxide (glucine) on animal tissues. Br J Ind Med 7:117-121.

*Pougnet MA, Orren, MJ, Haraldsen L. 1985. Determination of beryllium and lithium in coal ash by inductively coupled plasma atomic emission spectroscopy. Int J Environ Anal Chem 21:213-228.

Pratt GC, Palmer K, Wu CY, et al. 2000. An assessment of air toxics in Minnesota. Environ Health Perspect 108(9):815-825.

*Price RJ, Skilleter DN. 1985. Stimulatory and cytotoxic effects of beryllium on proliferation of mouse spleen lymphocytes in vitro. Arch Toxicol 56:207-211.

*Price RJ, Skilleter DN. 1986. Mitogenic effects of beryllium and zirconium salts on mouse splenocytes in vitro. Toxicol Lett 30:89-95.

*Raven KP, Leoppert RH. 1997. Heavy metals in the environment. J Environ Qual 26:551-557.

*Reeves AL. 1965. The absorp`tion of beryllium from the gastrointestinal tract. Arch Environ Health 11:209-214.

Reeves AL. 1986. Beryllium. In: Friberg L, Nordberg GF, Vouk VB, eds. Handbook on the toxicology of metals. Second edition. Volume II: Specific metals. New York, NY: Elsevier Science Publishers, 95-116.

*Reeves AL, Deitch D, Vorwald AJ. 1967. Beryllium carcinogenesis. I. Inhalation exposure of rats to beryllium sulfate aerosol. Cancer Res 27:439-445.

*Reeves AL, Preuss OP. 1985. The immunotoxicity of beryllium. In: Dean J, et al., eds. Immunotoxicology and immunopharmacology. New York, NY: Raven Press, 441-455.

*Reeves AL, Vorwald AJ. 1967. Beryllium carcinogenesis. II. Pulmonary deposition and clearance of inhaled beryllium sulfate in the rat. Cancer Res 27:446-451.

*Resnick H, Roche M, Morgan KC. 1970. Immunoglobulin concentrations in berylliosis. Am Rev Respir Dis 101:504-510.

*Rhoads K, Sanders CL. 1985. Lung clearance, translocation, and acute toxicity of arsenic, beryllium, cadmium, cobalt, lead, selenium, vanadium, and ytterbium oxides following deposition in rat lung. Environ Res 36:359-378.

*Richeldi L, Kreiss K, Mroz MM, et al. 1997. Interaction of genetic and exposure factors in the prevalence of berylliosis. Am J Ind Med 32(4):337-340.

*Richeldi L, Sorrentino R, Saltini C. 1993. HLA-DPB1 glutamate 69: a genetic marker of beryllium disease. Science 262(5131):242-244.

*Robinson FR, Schaffner F, Trachtenberg E. 1968. Ultrastructure of the lungs of dogs exposed to beryllium-containing dusts. Arch Environ Health 17:193-203.

Rom WN, Lockey JE, Bang KI, et al. 1983. Reversible beryllium sensitization in a prospective study of beryllium workers. Arch Environ Health 38:302-307.

*Romney EM, Childress JD. 1965. Effects of beryllium in plants and soil. Soil Sci 100(3):210-217.

Rosenkranz HS, Leifer Z. 1980. Determining the DNA-modifying activity of chemicals using DNA polymerase-deficient Escherichia coli. In: de Serres FJ, Hollaender A, eds. Chemical mutagens: Principles and methods for their detection. New York, NY: Plenum Press, 109-147.

*Rosenkranz HS, Poirier LA. 1979. Evaluation of the mutagenicity and DNA-modifying activity of carcinogens and noncarcinogens in microbial systems. J Natl Cancer Inst 62:873-892.

Rossman MD. 1996. Chronic beryllium disease: Diagnosis and management. Environ Health Perspect 104(Suppl. 5):945-947.

Rossman MD. 2001. Chronic beryllium disease: A hypersensitivity disorder. Appl Occup Environ Hyg 16(5):615-618.

*Rossman MD, Kern JA, Elias JA, et al. 1988. Proliferative response of bronchoalveolar lymphocytes to beryllium. Ann Intern Med 108:687-693.

*Rossman R, Barres J. 1988. Trace element concentrations in near-surface waters of the great lakes and methods of collection storage and analysis. J Great Lakes Res 14:188-204.

Rubin ES. 1999. Toxic Releases from Power Plants. Environ Sci Technol 33(18):062-3067.

Saber WS, Ozkan M, Lee J-C, et al. 2000. Pulmonary function testing in patients with chronic beryllium disease. Chest 118(4):253S.

Sajwan KS, Ornes WH, Youngblood TV. 1996. Beryllium phytotoxicity in soybeans. Water Air Soil Pollut 86:117-124.

Sakaguchi S, Sakaguchi T, Nakamura I, et al. 1987. Cell-mediated immunity caused by beryllium compounds. Pharmacol Toxicol 61:325-329.

Sakaguchi T, Sakaguchi S, Nakamura I, et al. 1993. Distribution of radioisotopic beryllium in mice after administration by various routes of injection. J Toxicol Environ Health 39(4):517-526.

Sakaguchi S, Sakaguchi T, Nakamura I, et al. 1996. Effect of beryllium on delta-aminolevulinic acid dehydratase and porphobilinogen deaminase in pregnant mice. Pharmacol Toxicol 79(4):214-216.

Sakaguchi S, Sakaguchi T, Nakamura I, et al. 1997. Effect of beryllium chloride on porphyrin metabolism in pregnant mice administered by subcutaneous injection. J Toxicol Environ Health 50(5):507-517.

Saleh MA, Wilson BL. 1999. Analysis of metal pollutants in the Houston Ship Channel by inductively coupled plasma/mass spectrometry. Ecotoxicol Environ Saf 44:113-117.

*Salo JE, Harrison D, Archibald EM. 1986. Removing contaminants by groundwater recharge basins. Am Water Works Assoc J 78:76-86.

Saltini C, Amicosante M. 2001. Beryllium Disease. Am J Med Sci 321(1):89-98.

Saltini C, Amicosante M, Franchi A, et al. 1998. Immunogenetic basis of environmental lung disease: lessons from the berylliosis model. Eur Resp J 12(6):1463-1475.

*Saltini C, Kirby M, Trapnell BC, et al. 1990. Biased accumulation of T lymphocytes with "memory"-type CD45 leukocyte common antigen gene expression on the epithelial surface of the human lung. J Exp Med 171:1123-1140.

*Saltini C, Winestock K, Kirby M, et al. 1989. Maintenance of alveolitis in patients with chronic beryllium disease by beryllium-specific helper T cells. N Engl J Med 320:1103-1109.

*Sanders CL, Cannon WC, Powers GJ, et al. 1975. Toxicology of high-fired beryllium oxide inhaled by rodents. Arch Environ Health 30:546-551.

*Sanderson WT, Henneberger PK, Martyny J, et al. 1999. Beryllium contamination inside vehicles of machine shop workers. Am J Ind Med (Suppl. 1):72-74.

*Sanderson WT, Petersen MR, Ward EM. 2001a. Estimating historical exposures of workers in a beryllium manufacturing plant. Am J Ind Med 39:145-157.

*Sanderson WT, Ward EM, Steenland K, et al. 2001b. Lung cancer case-control study of beryllium workers. Am J Ind Med 39:133-144.

*Sanderson WT, Ward EM, Steenland K, et al. 2001c. Re: Lung cancer case-control study of beryllium workers. Am J Ind Med 40:284-285.

*Sarosiek J, Kosiba P. 1993. The effects of water and hydrosol chemistry on the accumulation of beryllium and germanium in selected species of macrohydrophytes. Water Air Soil Pollut 69:405-411.

Sato N, Kato T, Suzuki N. 1977. Multielement determination in tobacco leaves by photon activation analysis. J Radioanal Chem 36:221-238.

Sawyer RT, Doherty DE, Schumacher BA, et al. 1999. Beryllium-stimulated in vitro migration of peripheral blood lymphocytes. Toxicology 138:155-163.

Sawyer RT, Fadok VA, Kittle LA, et al. 2000a. Beryllium-stimulated apoptosis in macrophage cell lines. Toxicology 149:129-142.

Sawyer RT, Kittle LA, Hamada H, et al. 2000b. Beryllium-stimulated production of tumor necrosis factor-α by a mouse hybrid macrophage cell line. Toxicology 143:233-247.

*Schepers GWH. 1964. Biological action of beryllium: Reaction of the monkey to inhaled aerosols. Ind Med Surg 33:1-16.

*Schepers GWH, Durkan TM, Delahant AB, et al. 1957. The biological action of inhaled beryllium sulfate: a preliminary chronic toxicity study on rats. Arch Ind Health 15:32-38.

Schmidt M, Bauer A, Schmidbaur H. 1997. Beryllium chelation by dicarboxylic acids in aqueous solution. Inorganic Chemistry 36:2040-2043.

*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.

Schuhmacher M, Meneses M, Granero S, et al. 1997. Trace element pollution of soils collected near a municipal solid waste incinerator: Human health risk. Bull Environ Contam Toxicol. 59:861-867.

*Scott DR, Loseke WA, Holboke LE, et al. 1976. Analysis of atmospheric particulates for trace elements by optical emission spectrometry. Applied Spectroscopy 30:392-405.

SD Dept Environment and Natural Resources. 1998. Beryllium. Drinking water regulations. Drinking water standards. http://www.state.sd.us/state/executive/denr/denr.html.

Sedman RM, Polisini JM, Esparza JR. 1994. The evaluation of stack metal emissions from hazardous waste incinerators: Assessing human exposure through noninhalation pathways. Environ Health Perspect 102(Suppl. 2):105-112.

*Seiler DH, Rice C, Herrick RF, et al. 1996. A study of beryllium exposure measurements, Part 1: Estimation and categorization of average exposures from daily weighted average data in the beryllium industry. Appl Occup Environ Hyg 11(2):89-97.

Seko Y, Koyama T, Ichiki A, et al. 1982. The relative toxicity of metal salts to immune hemolysis in a mixture of antibody-secreting spleen cells, sheep red blood cells and complement. Res Commun Chem Pathol Pharmacol 36:205-213.

*Selivanova LN, Savinova TB. 1986. [Effects of beryllium chloride and oxide on the sexual function of female rats and development of their progeny.] Gig Sanit 8:44-46. (Russian)

*Sendelbach LE, Witschi HP. 1987a. Protection by parenteral iron administration against the inhalation toxicity of beryllium sulfate. Toxicol Lett 35:321-325.

*Sendelbach LE, Witschi HP. 1987b. Bronchoalveolar lavage in rats and mice following beryllium sulfate inhalation. Toxicol Appl Pharmacol 90:322-329.

*Sendelbach LE, Tryka AF, Witschi H. 1989. Progressive lung injury over a one-year period after a single inhalation exposure to beryllium sulfate. Am Rev Respir Dis 139:1003-1009.

*Sendelbach LE, Witschi HP, Tryka AF. 1986. Acute pulmonary toxicity of beryllium sulfate inhalation in rats and mice: Cell kinetics and histopathology. Toxicol Appl Pharmacol 85:248-256.

*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 Concentration in Soils and Other Materials of the Conterminous United States. U.S. Geological Survey Professional Paper 1270.

*Shan X, Yian Z, Ni Z. 1989. Determination of beryllium in urine by graphite-furnace atomic absorption spectrometry. Anal Chim Acta 217:271-280.

Sharma P, Johri s, Shukla S. 2000. Beryllium-induced toxicity and its prevention by treatment with chelating agents. J Appl Toxicol 20(4):313-318.

Shaw MJ, Hill SJ, Jones P, et al. 2000. Determination of beryllium in a stream sediment by high-performance chelation ion chromatography. J Chromatogr 876:127-133.

*Shukula S, Sharma P, Johri S, et al. 1998. Influence of chelating agents on the toxicity and distribution of beryllium in rats. J Appl Toxicol 18(5):331-335.

*Simmon VF. 1979a. In vitro mutagenicity assays of chemical carcinogens and related compounds with salmonella typhimurium. J Natl Cancer Inst 62:893-899.

*Simmon VF. 1979b. In vitro assays for recombinogenic activity of chemical carcinogens and related compounds with saccharomyces cerevisiae D3. J Natl Cancer Inst 62:901-909.

Simmon VF, Rosenkranz HS, Zeigler E, et al. 1979. Mutagenic activity of chemical carcinogens and related compounds in the intraperitoneal host-mediated assay. J Natl Cancer Inst 62:911-918.

Skerfving S, Benchko V, Vahter M, et al. 1999. Environmental health in the Baltic region-toxic metals. Scand J Work Environ Health 25(3):40-64.

Skilleter DN, Legg RF. 1989. Inhibition of epidermal growth factor-stimulated hepatocyte proliferation by the metallocarcinogen beryllium. Biochem Soc Trans 17:1040-1041.

*Skilleter DN, Price RJ. 1984. Lymphocyte beryllium binding: Relationship to development of delayed beryllium hypersensitivity. Int Arch Allergy Appl Immunol 73:181-183.

Skilleter DN, Price RJ. 1988. Effects of beryllium ions on tyrosine phosphorylation. Biochem Soc Trans 16:1047-1048.

Skilleter DN, Mattocks AR, Neal GE. 1988. Sensitivity of different phases of the cell cycle to selected hepatotoxins in cultured liver-derived (BL9L) cells. Xenobiotica 18:699-705.

*Smith CJ, Livingston SD, Doolittle DJ. 1997. An international literature survey of "IARC Group I Carcinogens" reported in mainstream cigarette smoke.

*Sparling DW, Lowe TP. 1996. Metal concentrations of tadpoles in experimental ponds. Environmental Pollution. 91(2):149-159.

Spencer HC, McCollister SB, Kociba RJ, et al. 1972. Toxicological studies on a beryllium containing exhaust product. In: Proceedings of the Third Annual Conference on Environmental Toxicology, October, Fairborn, OH. Wright-Patterson AFB, OH: Aerospace Medical Research Laboratory. AMRL-TR-72-130, 303-317.

*Sprince NL, Kanarek DJ, Weber AL, etal. 1978. Reversible respiratory disease in beryllium workers. Am Rev Resp Dis 117:236-242.

*Stadnichenko TM, Zubovic P, Sheffey NB. 1961. Beryllium content of American Coals. U.S. Geological Survey Bulletin 1084-K:253-295.

*Stange AW, Furman FJ, Hilmas DE. 1996a. Rocky Flats beryllium health surveillance. Environ Health Perspect 104(Suppl. 5):981-986.

Stange A, Furman J, Hilmas D. 2000. The utility of the beryllium lymphocyte proliferation test in chronic beryllium disease case finding. Am J Epidemiol 151(11):581.

*Stange AW, Hilmas DE, Furman FJ. 1996b. Possible health risks from low level exposure to beryllium. Toxicology 111(1-2):213-224.

*Stange AW, Hilmas DE, Furman FJ, et al. 2001. Beryllium sensitization and chronic beryllium disease at a former nuclear weapons facility. Appl Occup Environ Hyg 16(3):405-417.

*Steenland K, Ward E. 1992. Lung cancer incidence among patients with beryllium disease: a cohort mortality study. J Natl Cancer Inst 83:1380-1385.

*Steinmaus C, Balmes JR. 2000. Government laboratory worker with lung cancer: Comparing risks from beryllium, asbestos, and tobacco smoke. Environ Health Perspect 108(10):1003-1006.

*Sterner JH, Eisenbud M. 1951. Epidemiology of beryllium intoxication. Arch Ind Hyg Occup Med 4;123-151.

*Stiefel T, Schulze K, Zorn H, et al. 1980. Toxicokinetic and toxicodynamic studies of beryllium. Arch Toxicol 45:81-92.

*Stoeckle JD, Hardy HL, Weber AL. 1969. Chronic beryllium disease. Am J Med 46:545-561.

*Stokes RF, Rossman MD. 1991. Blood cell proliferation response to beryllium: analysis by receiver-operating characteristics. J Occup Med 33:23-28.

Stokinger HE. 1981. In: Clayton G, Clayton D, eds. Patty's industrial hygiene and toxicology, Vol. IIA, 3rd ed. New York, NY: John Wiley and Sons, Inc., 1537-1558.

*Stokinger HE, Sprague GF, Hall RH, et al. 1950. Acute inhalation toxicity of beryllium. I. Four definitive studies of beryllium sulfate at exposure concentrations of 100, 50, 10 and 1 mg per cubic meter. Arch Ind Hyg Occup Med 1:379-397.

*Stubbs J, Argyris E, Lee CW, et al. 1996. Genetic markers in beryllium hypersensitivity. Chest 109(Suppl. 3):45S.

*Tai Y, DeLong R, Goodkind RJ, et al. 1992. Leaching of nickel, chromium, and beryllium ions from base metal alloy in an artificial oral environment. J Prosthet Dent 68(4):692-697.

*Tapp,E, Path, MC. 1969. Changes in rabbit tibia due to direct implantation of beryllium salts. Arch Path 88:140-148.

Tarlo SM, Rhee K, Powell E, et al. 2001. Marked tachypnea in siblings with chronic beryllium disease due to copper-beryllium alloy. Chest 119(2):647-650.

*Taylor ML, Arnold EL. 1971. Ultratrace determination of metals in biological specimens quantitative determination of beryllium by gas chromatography. Anal Chem 42:1328-1332.

Taylor JS. 2001. Chronic beryllium disease of the skin and lungs. J Allergy Clin Immunol 107(2):S126.

*Teixeira CFP, Yasaka WJ, Silva LF, et al. 1990. Inhibitory effects of beryllium chloride on rat liver microsomal enzymes. Toxicology 61:293-301.

*Tepper LB. 1972. Beryllium. CRC Crit Rev Toxicol, 235-259.

Thorat DD, Mahadevan TN, Ghosh DK, et al. 2001. Beryllium concentrations in ambient air and its source identification. Environ Monit Assess 69:49-61.

Tinkle SS, Newman LS. 1997. Beryllium-stimulated release of tumor necrosis factor-alpha, interleukin-6, and their soluble receptors in chronic beryllium disease. Am J Respir Crit Care Med 156(6):1884-1891.

Tinkle SS, Kittle LA, Newman LS. 1999. Partial IL-10 inhibition of the cell-mediated immune response in chronic beryllium disease. J Immunol 163(5):2747-2753.

Tinkle SS, Kittle LA, Schumacher BA, et al. 1997. Beryllium induces IL-2 and IFN-gamma in berylliosis. Immunology 158(1):518-526.

Tinkle SS, Kittle L, Schwitters PW, et al. 1996a. Beryllium stimulates release of T helper 1 cytokines interleuken-2 and interferon gamma from BAL cells in chronic beryllium disease. Chest 109(3):5S-6S.

Tinkle SS, Schwitters PW, Newman LS. 1996b. Cytokine production by bronchoalveolar lavage cells in chronic beryllium disease. Environ Health Perspect 104(Suppl. 5):969-971.

Todorovic D, Popovic D, Djuric G. 1999. Concentration measurements of 7BE and 137Cs in ground level air in the Belgrade city area. Environ Int 25(1):59-66.

Togna G, Togna AR, Russo P, et al. 1997. Toxicological effects of beryllium on platelets and vascular endothelium. Toxicol Appl Pharmacol 144(2):262-267.

*Tolle DA, Arthur MF, VanVoris P. 1983. Microsm/field comparison of trace element uptake in crops grown in fly ash-amended soil. Sci Total Environ 31(3):243-261.

TRI88 1990. Toxics Release Inventory. Office of Toxics Substances, U.S. Environmental Protection Agency, Washington, DC.

TRI98 2000. Toxic Release Inventory. Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, D.C. http://www.epa.gov/egi-bin/broker?view...&_program=xp_tri.sasmacr.tristart.macro.

*TRI99 2002. Toxic Chemical Release Inventory. National Library of Medicine, National Toxicology Information Program, Bethesda, MD. TRI on-site and off-site releases (in pounds), all facilities (of 8) for releasing Beryllium, all industries. http://www.epa.gov/triexplorer/chemical.htm.

*Trichopoulos D. 2000. Written communication (comments) on: The alleged human carcinogenicity of beryllium. Submitted to the National Toxicology Program.

*Tsalev DL, Zaprianov ZK, eds. 1984. Atomic absorption spectrometry in occupational and environmental health practice. Boca Raton, FL: CRC Press, 96-100; 27-29.

*Tsujii H, Hoshishima K. 1979. [The effect of the administration of trace amounts of metals to pregnant mice upon the behavior and learning of their offspring.] Shinshu Daigaku Nogakubu Kiyo 16:13-27. (Japanese)

*Ulitzur S, Barak M. 1988. Detection of genotoxicity of metallic compounds by the bacterial bioluminescence test. J Biolumin Chemilumin 2:95-99.

USC. 1998. Hazardous air pollutants. US Code: Title 42, Section 7412. http://www4.law.cornell.edu/uscode/42/7412.text.html

9. REFERENCES

*USC. 2001. Hazardous air pollutants. United States Code. 42 USC 7412. http://www4.law.cornell.edu/uscode/42/7412.text.html. November 29, 2001.

USDI. 1990. Minerals yearbook: Beryllium. U.S. Department of Interior, Bureau of Mines, Washington, DC.

*UNSCEAR. 2000. Sources and effects of ionizing radiations. United Nations Scientific Committee on the Effects of Atomic Radiation, United Nations, 89, 114.

*Vacher J, Stoner HB. 1968. The transfer of beryllium in rat blood. Biochem J Pharmacol 17:93-107.

*Vaessen H, Szteke B. 2000. Beryllium in food and drinking water- a summary of available knowledge. Food Additives and Contaminants. 17(2):149-159.

*Valberg PA, Drivas PJ, McCarthy S, et al. 1996. Evaluating the health impacts of incinerator emissions. J Hazard Mater 47(1-3):205-227.

*VanOrdstrand HS, Hughes R, DeNardi JM, et al. 1945. Beryllium poisoning. J Am Med Assoc 129:1084-1090.

*Venugopal B, Luckey TD. 1977. Metal toxicity in mammals.2: Chemical toxicity of metals and metalloids. New York, NY: Plenum Press.

*Viera I, Sonnier M, Cresteil T. 1996. Developmental expression of CYP2E1 in the human liver: Hypermethylation control of gene expression during the neonatal period. Eur J Biochem 238:476-483.

*Viet SM, Torma-Krajewski J, Rogers J. 2000. chronic beryllium disease and beryllium sensitization at Rocky Flats: A case-control study. Am Ind Hyg Assoc J 61:244-254.

Vilaplana J, Romaguera C, Grimalt F. 1992. Occupational and non-occupational allergic contact dermatitis from beryllium. Contact Dermatitis 26(5):295-298.

*Vorwald AJ. 1968. Biologic manifestations of toxic inhalants in monkeys. In: Vagrborg H, ed. Use of Nonhuman primates in drug evaluation: A symposium. Southwest Foundation for Research and Education. Austin, Texas: University of Texas Press, 222-228.

*Vorwald AJ, Reeves AL. 1959. Pathologic changes induced by beryllium compounds. Arch Ind Health 19:190-199.

*VT Agency. 1998. Vermont Agency of Natural Resources. Vermont Air Toxics Web Page. http://www.anr.state.vt.us/dec/air/airtoxics/index.htm.

*WA Dept of Ecology. 1998. Washington State Department of Ecology. Air Quality Regulations. wysiwyg://240/http://www.wa.gov/ecology/.

*Wagner WD, Groth DH, Holtz JL, et al. 1969. Comparative chronic inhalation toxicity of beryllium ores, bertrandite and beryl, with production of pulmonary tumors by beryl. Toxicol Appl Pharmacol 15:10-29.

*Wagoner JK, Infante PF, Bayliss DL. 1980. Beryllium: An etiologic agent in the induction of lung cancer, nonneoplastic respiratory disease, and heart disease among industrially exposed workers. Environ Res 21:15-34.

*Waldichuk M, Jamieson WD, Berman SS. 1987. Reference materials as assurance of quality of seawater marine sediments and biological and biological tissues. Marine Pollution Bulletin. 18:477-481.

Wallbrink PJ, Murray AS. 1996. Distribution and variability of 7Be in soils under different surface cover conditions and its potential for describing soil redistribution processes. Water Resource Res 32(2):467-476.

Walsh K, Rees GH. 1978. Beryllium compounds. In: Grayson M, Eckroth D, eds. Kirk-Othmer encyclopedia of chemical technology, Vol. 3, 3rd ed. New York: John Wiley & Sons, Inc., 824-829.

Wambach PF, Tuggle RM. 2000. Development of an eight-hour occupational exposure limit for beryllium. Appl Occup Environ Hyg 15(7):581-587.

*Wang Z, Garris GM, Newman LS, et al. 2001. Beryllium sensitivity is linked to HLA-DP genotype. Toxicology 163:27-38.

Wang Z, White PS, Petrovic M, et al. 1999. Differential susceptibilities to chronic beryllium disease contributed by different Glu69 HLA-DPB1 and -DPA1 alleles. J Immunol 163(3):1647-1653.

*Ward E, Aachen A, Ruder A, et al. 1992. A mortality study of workers at seven beryllium processing plants. Am J Ind Med 22(6):885-904.

*Watanabe K, Shia S, Taccaceae S, et al. 1985. [Biotoxicity and beryllium distribution in organs by oral administration of beryllium compounds for long periods. II. Experimental study on oral administration of beryllium compounds.] Rodo Kagaku (J Science of Labor) 61:235-246. (Japanese)

Weast RC, ed. 1985. CRC Handbook of chemistry and physics. 66th ed. Boca Raton, FL: CRC Press, Inc., B-9, B-10, B-77, B-234, D-215.

Wegner R, Heinrich-Ramm R, Nowak D, et al. 2000. Lung function, biological monitoring, and biological effect monitoring of gemstone cutters exposed to beryls. Occup Environ Med 57(2):133-139.

*West JR, Smith HW, Chasis H. 1948. Glomerular filtration rate, effective renal blood flow, and maximal tubular excretory capacity in infancy. J Pediatr 32:10-18.

*White MR, Finkel AJ, Schubert J. 1951. Protection against experimental beryllium poisoning by aurin tricarboxylic acid. J Pharm Exp Ther 102:88-93.

WHO. 1990. Environmental Health Criteria 106: Beryllium. World Health Organization, Geneva.

*WI Dept of Natural Resources. 1997. Wisconsin Department of Natural Resources. Berylliium. Air pollution control. Control of hazardous pollutants. Chapter NR 455.

*Widdowson EM, Dickerson JWT. 1964. 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.

9. REFERENCES

*Williams GM, Mori H, McQueen CA. 1989. Structure-activity relationships in the rat hepatocyte DNA-repair test for 300 chemicals. Mutat Res 221:263-286.

*Williams WJ. 1996. United Kingdom beryllium registry: Mortality and autopsy study. Environ Health Perspect 104(Suppl. 5):949-951.

*Williams WJ, Kelland D. 1986. New aid for diagnosing chronic beryllium disease (CBD): laser ion mass analysis (LIMA). J Clin Pathol 39:900-901.

*Williams WJ, Williams WR. 1983. Value of beryllium lymphocyte transformation tests in chronic beryllium disease and in potentially exposed workers. Thorax 38:41-44.

*Williams WJ, Williams WR, Kelland D, et al. 1987. Beryllium skin disease. In: Proceedings from the 11th World Conference on Sarcoidosis, Milan 1987. Elsevier Press.

*Williams WR, Williams WJ. 1982. Comparison of lymphocyte transformation and macrophage migration inhibition tests in the detection of beryllium hypersensitivity. J Clin Pathol 35:684-687.

Windholz, M. 1983. The Merck index. 10th ed. Rahway, NJ: Merck & Co., Inc., 166-167.

Witschi H. 1968. Inhibition of deoxyribonucleic acid synthesis in regenerating rat liver by beryllium. Lab Invest 19(1):67-70.

*Witschi HP. 1970. Effects of beryllium on deoxyribonucleic acid-synthesizing enzymes in regenerating rat liver. Biochem J 120:623-634.

*Witschi HP, Aldridge WN. 1986. Uptake, distribution and binding of beryllium to organelles of the rat liver cell. Biochem J 106:811-820.

Woldichuk M, Jamieson WD, Berman SS. 1987. Reference materials as assurance of quality in analysis of seawater, marine sediments, and biological tissues. Mar Pollut Bull 18(9):477-481.

*Wolnik, KA, Fricks FL, CM Gaston. 1984. Quality assurance in the elemental analysis of foods by inductively coupled plasma spectroscopy. Spectrochimica Acta, Part B 398:649-655.

Xie Y, Miyamoto H, Kondo M, et al. 2001. Element concentrations in urine of patients suffering from chronic arsenic poisoning. Tahoka J Exp Med 193:229-235.

Yoshida T, Shia S, Nagoaka K, et al. 1997. A study on the beryllium lymphocyte transformation test and the beryllium levels in working environment. Ind Health 353:374-379.

*You C-F, Lee T, Li Y-H. 1989. The partition of Be between soil and water. Chem Geol 77:105-118.

*Zakour RA, Glickman BW. 1984. Metal-induced mutagenesis in the lacI gene of escherichia coli. Mutat Res 126:9-18.

*Zdrojewski A, DuBois L, Quickert N. 1976. Reference method for the determination of beryllium in airborne particulates. Sci Total Environ 6:165- 1731.

Zheng M, Fang M. 2000. Correlations between organic and inorganic species in atmospheric aerosols. Environ Sci Technol 34:2721-2726.

9. REFERENCES

*Ziegler EE, Edwards BB, Jensen RL, et al. 1978. Absorption and retention of lead by infants. Pediatr Res 12:29-34.

*Zissu D, Binet S, Cavelier C. 1996. Patch testing with beryllium alloy samples in guinea pigs. Contact Dermatitis 34(3):196-200.

Zorn H, Diem H. 1974. Die Bedeuting des Berullium und seiner Verbindungen fur den Arbeitsmedizimer. Zentralblatt Arbeitsmedizni 24:3-8.

*Zorn H, Stiefel T, Diem H. 1977. [The significance of beryllium and its compounds in industrial medicine.] Zbl Arbeitsmed 27:83-88. (German).

*Zorn H, Stiefel T, Porcher H. 1986. Clinical and analytical follow-up of 25 persons exposed accidentally to beryllium. Toxicol Environ Chem 2:163-171.

10. GLOSSARY

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

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

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

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

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

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

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

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

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Immunological Effects—Functional changes in the immune response.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

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

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

Lethal Dose$_{(LO)}$ (LD_{LO})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically-based dose-response model which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly

describe the biological effect (response) produced by the system following exposure to an exogenous substance.

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

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

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

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

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

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL-from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

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

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

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

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

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

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

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

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

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

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

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

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

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

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

APPENDIX A

ATSDR MINIMAL RISK LEVEL AND WORKSHEETS

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

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

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

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

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

APPENDIX A

MRL WORKSHEET

Chemical Name: Beryllium and Compounds
CAS Number:
Date: May 16, 2002
Profile Status: Third Post Public Comment Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to Figure: 11
Species: Dogs

Minimal Risk Level: 0.002 [X] mg beryllium/kg/day [ ] ppm

Reference: Morgareidge K, Cox GE, Gallo MA. 1976. Chronic feeding studies with beryllium in dogs. Food and Drug Research Laboratories, Inc. Submitted to the Aluminum Company of America. Alcan Research and Development, Ltd., Kawecki-Berylco Industries, Inc., and Brush-Wellman, Inc.

Experimental design: (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Groups of five male and five female Beagle dogs were fed a diet containing 0, 5, 50 or 500 ppm beryllium as beryllium sulfate tetrahydrate (0, 0.1, 1, and 12 mg beryllium/kg/day for males and 0, 0.2, 1, and 17 mg beryllium/kg/day for females) for 172 weeks. The basal diet was a commercial dog chow (Purina®) moistened with warm water; the dogs were given access to the food for 1 hour/day. After 33 weeks, a group of five male and five female dogs was added to the study and fed a diet containing 1 ppm (0.02 and 0.03 mg beryllium/kg/day for males and females, respectively); duration of exposure for this group was 143 weeks. The following parameters were used to assess toxicity: daily observations, food consumption, body weight, hematology and serum clinical chemistry (blood samples collected after 1, 3, 6, 16, 18, 24, 30, and 36 months of exposure), urinalysis (samples collected after 1, 3, 6, 18, 24, 30, and 36 months of exposure), organ weights (heart, liver, kidney, brain, spleen, pituitary, thyroids, adrenals, and gonads), and histopathology of the spleen, thymus, pancreas, lungs, gonads, stomach, small and large intestines, urinary bladder, heart, aorta, muscle, adrenals, thyroids, lymph nodes, salivary glands, gallbladder, liver, kidneys, pituitary, brain, spinal cord, skin, mammary gland, bone marrow, and eyes.

Effects noted in study and corresponding doses: Two moribund animals in the 500 ppm group were sacrificed during week 26; the remainder of the animals in the 500 ppm group were killed during week 33. Overt signs of toxicity in the 500 ppm group included lassitude, weight loss, anorexia, and visibly bloody feces. A slight anemia (slight decreases in erythrocyte, hemoglobin, and hematocrit; statistical analysis not reported), more apparent in the females than in the males, was observed after 3 and 6 months of exposure; however, there were no alterations in the bone marrow and none of the animals was seriously affected. The study authors noted that the anemia may have been related to the gastrointestinal tract hemorrhages rather than a direct effect of beryllium on the hematological system. All animals in the 500 ppm group showed fairly extensive erosive (ulcerative) and inflammatory lesions in the gastrointestinal tract. These occurred predominantly in the small intestine, and to a lesser extent in the stomach and large intestine, and were regarded by the authors as treatment-related. All of the animals with stomach or large intestinal lesions also had lesions in the small intestine, except for one animal with stomach lesions only. This animal had stomach lesions that were very localized and not very severe. Erythroid hypoplasia of the bone marrow, bile stasis and vasculitis in the liver, and acute inflammation in the lymph nodes were also observed in the 500 ppm group; these effects are likely to be secondary to the gastrointestinal hemorrhages and a likely systemic bacterial invasion through the damaged intestinal mucosa.

One dog in the 50 ppm group died after 70 weeks. Ulcerative gastrointestinal lesions were observed in this animal. No beryllium-related hematological, serum chemistry, urinalysis, organ weight, or body weight alterations were observed in the groups exposed to <500 ppm beryllium.

Dose and end point used for MRL derivation: THE CHRONIC-DURATION ORAL MRL FOR BERYLLIUM W CALCULATED USING A BENCHMARK DOSE METHOD THAT INVOLVES FITTING MATHEMAT RESPONSE DATA FOR ULCERATIVE LESIONS OF THE SMALL INTESTINE OF DOGS EXPOSED DIET (MORGAREIDGE ET AL. 1976). BECAUSE THERE WERE NO APPARENT SEX-RELATED DIF OF THESE LESIONS, THE INCIDENCE DATA FOR THE MALE AND FEMALE DOGS WERE COM DOSES FOR THE MALES AND FEMALES WERE AVERAGED. THE DOSE-RESPONSE DATA ARE P

DIETARY CONCENTRATION (PPM)	DOSE (MG BERYLLIUM/KG/DAY)	INCIDENCE
0	0	0/10
1	0.025	0/10
5	0.15	0/10
50	1	1/10
500	14.5	9/10

FOR THIS ANALYSIS, THE BENCHMARK DOSE (BMD) WAS DEFINED AS THE DOSE CORRESP THE INCIDENCE OF SMALL INTESTINE LESIONS COMPARED TO CONTROLS; THE BMDL IS LIMIT ON THE BMD. EPA'S BENCHMARK DOSE SOFTWARE (VERSION 1.3) WAS USED TO FIT MODELS (GAMMA, LOGISTIC, LOG-LOGISTIC, MULTISTAGE, PROBIT, LOG-PROBIT, QUANTA QUANTAL-QUADRATIC, AND WEIBULL) TO THE INCIDENCE DATA. MODEL FIT WAS JUDGE ASSOCIATED WITH THE CHI-SQUARE GOODNESS-OF-FIT STATISTIC GENERATED BY THE M INSPECTION OF THE PLOT OF OBSERVED AND PREDICTED VALUES. THE PROBIT MODEL I THE INCIDENCE DATA; THE OBSERVED AND PREDICTED INCIDENCES ARE ILLUSTRATED B FITS THE DATA USING THE MAXIMUM LIKELIHOOD METHOD AND THE FOLLOWING EQU BACKGROUND (1-BACKGROUND) X CUMNORM(INTERCEPT SLOPE X LOG(DOSE)), WHER CUMULATIVE NORMAL DISTRIBUTION FUNCTION. A BMDL OF 0.56 MG BERYLLIUM/KG/D MODEL.

[ ] NOAEL [ ] LOAEL [X] BENCHMARK DOSE (BMDL)

APPENDIX A

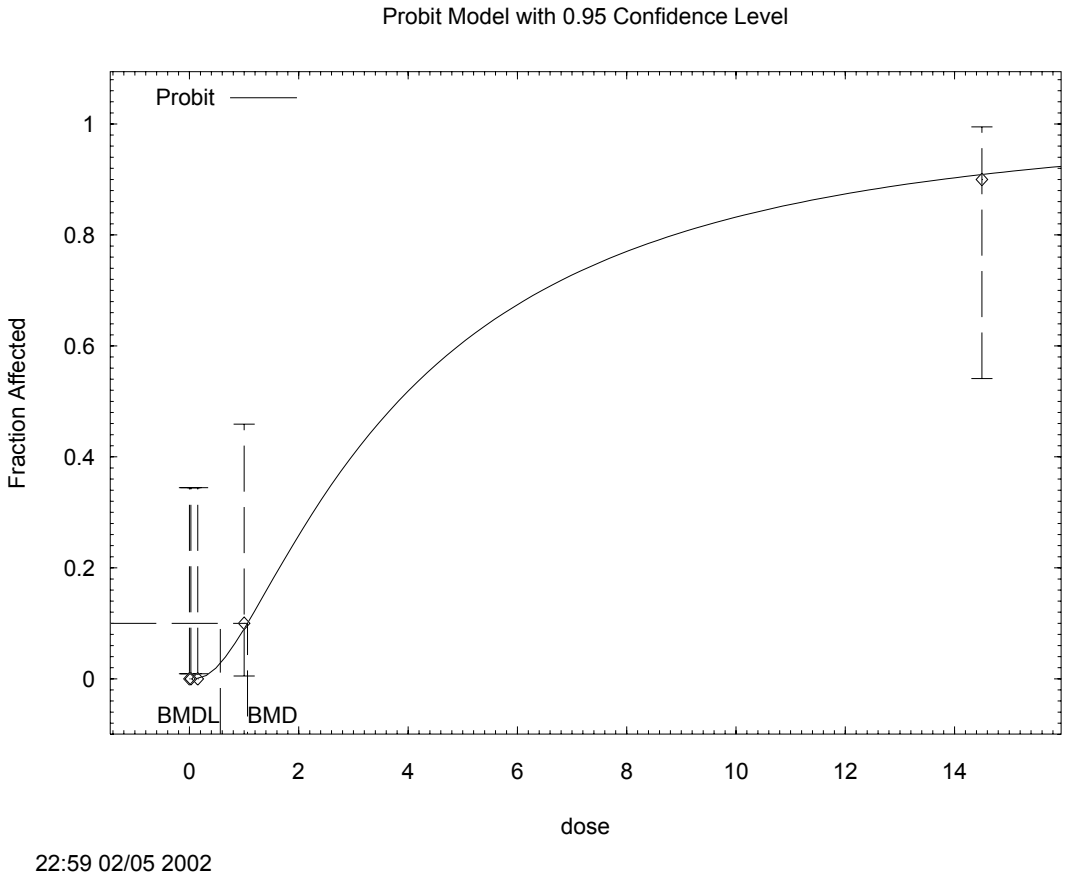


Figure 1. Observed and Predicted (by Probit Model) Incidences of Intestinal Lesions in Dogs exposed to Beryllium in the Diet.

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a extrapolation from animals to humans
[X] 10 for human variability
[X] 3 modifying factor to account for the lack of a study that supports the gastrointestinal effects found in the Morgareidge et al. [1976] dog study and the uncertainty as to whether the benchmark dose level is the NOAEL.

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

Yes. Daily doses were estimated using the estimated TWA body weights of 13.0, 12.7, 13.8, and 12.3 kg for males in the 1, 5, 50, and 500 ppm groups, respectively, and 10.2, 10.3, 11.2, and 8.6 kg for females, respectively and the reported average food intake of 300 g/day.

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

NA

Was a conversion used from intermittent to continuous exposure?

No

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

Gastrointestinal effects have not been reported in rats (Morgareidge et al. 1975; Schroeder and Mitchener 1976a) or mice (Schroeder and Mitchener 1976b) chronically exposed to dietary beryllium.

Agency Contact (Chemical Manager): Cassandra Smith, M.S.

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

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

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

The chapter covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter. If data are located in the scientific literature, a table of genotoxicity information is included.

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

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

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

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

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (3-1, 3-2, and 3-3) and figures (3-1 and 3-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 3-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

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

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 3-1).

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

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

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

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

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

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

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

LEGEND

See Figure 3-1

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

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

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

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

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

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

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

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

SAMPLE

1 6

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

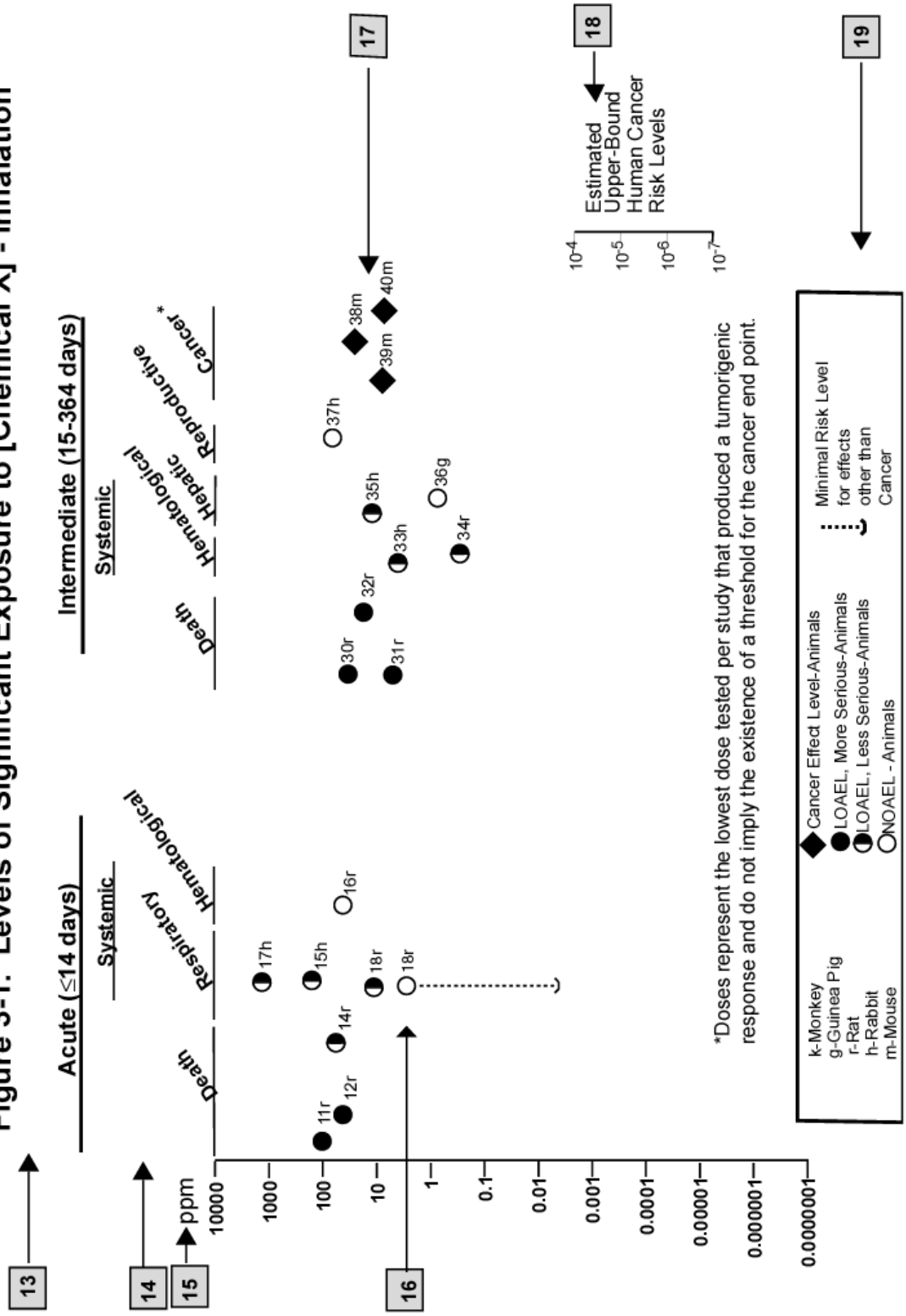
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 6 INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 6 Systemic	9	9	9	9	9		9
4 6 18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC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

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

12 6 [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

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



APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACOEM	American College of Occupational and Environmental Medicine
ACGIH	American Conference of Governmental Industrial Hygienists
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AOEC	Association of Occupational and Environmental Clinics
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotranferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	*Federal Register*
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LDH	lactic dehydrogenase
LH	luteinizing hormone
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

MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
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
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic

PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
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
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
$	greater than or equal to
=	equal to
<	less than

#	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
µm	micrometer
µg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

APPENDIX D

INDEX