BERYLLIUM

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UPDATE STATEMENT

A Toxicological Profile for beryllium was released on December 1988. This edition supersedes any previously released draft or final profile.

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

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FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987, on October 20, 1988, on October 26, 1989, on October 17, 1990, and on October 17, 1991. A revised list of 275 substances was published on October 28, 1992.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the lists. Each profile must include the following:

(A) The examination, summary, and interpretation of available toxicological information and epidemiological evaluations on a hazardous substance in order 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.

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

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and 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 is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented but 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.

Each toxicological profile begins with a public health statement, which 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 will be identified by ATSDR and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

Foreword

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 our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control and Prevention (CDC), and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

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

2. 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 endpoints.

3. 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.

4. Quality Assurance Review. The Quality Assurance Branch assures that consistency across profiles is maintained, identifies any significant problems in format or content, and establishes that Guidance has been followed.

1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about beryllium and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,300 sites on its National Priorities List (NPL). Beryllium has been found in at least 349 of these sites including 5 in Puerto Rico. However, we do not know how many of the 1,300 NPL sites have been evaluated for beryllium. As EPA evaluates more sites, the number of sites at which beryllium is found may change. This information is important for you to know because beryllium may cause harmful health effects and because these sites are potential or actual sources of human exposure to beryllium.

When a chemical 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 as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical or from skin contact with it.

If you are exposed to a hazardous chemical such as beryllium, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life style, and state of health.

1.1 WHAT IS BERYLLIUM?

Beryllium is a hard, grayish element that does not occur naturally. The element does occur as a chemical component of certain 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 also present in a variety of compounds. They do not have any particular smell. There are two types of beryllium compounds, those that dissolve in water and those that do 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. Pure beryllium metal has applications in nuclear weapons and reactors, aircraft and space vehicle structures and 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, and production and use is found in Chapters 3 and 4.

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 air. Beryllium enters waterways from the wearing away of rocks and soil. Most of the man-made beryllium that enters waterways comes when industry dumps waste water and when beryllium dust in the air from industrial activities settles over water. Beryllium, as a chemical component, occurs naturally in soil; however, disposal of coal ash, incinerator ash, and industrial wastes may increase the concentration of beryllium in soil. In air, beryllium compounds are present mostly as fine dust particles. The dust eventually settles over land and water. Rain and snow aid in the removal of beryllium from air. Sufficiently small beryllium particles may remain airborne for about 10 days. Most of the beryllium in water settles in the material on the bottom. Beryllium compounds remain in ocean water for a few hundred years before settling to the bottom of the ocean. Fish do not accumulate beryllium from water into their bodies to any great extent. A major portion of beryllium in soil does not dissolve in water but remains bound to soil, so it is not very 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 water-insoluble forms. More information about the fate and movement of beryllium in the environment is found in Chapter 5.

1.3 HOW MIGHT I BE EXPOSED TO BERYLLIUM?

You can be exposed to low 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/m^3 of air. Cities have higher levels of beryllium in the air because beryllium is released from burning coal and fuel oil. Beryllium was not found in 5% of 1,577 drinking water samples obtained throughout the United States. Of these samples, the average beryllium concentration was only 190 ng in a liter (L) of water. Beryllium, as a chemical component, is naturally found in some food. The concentration of beryllium in both raw carrots and field corn grown in the United States is less than 25 micrograms (ug) (1 ug = 1 millionth of a gram) in a kilogram (kg) of the fresh vegetables. The intake of beryllium for most people will be very small.

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, and converted into metal, alloys, and other chemicals. Workers engaged in machining metals containing beryllium, in recycling beryllium from scrap alloys, or in using beryllium products may also be exposed to higher levels of beryllium. An estimated 18,000 workers may be exposed to beryllium and beryllium oxide in the workplace.

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 tobaccos and can be inhaled from cigarette smoke. People who smoke may breathe considerably more 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. More information about beryllium exposure can be found in Chapter 5.

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 of time. 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 or is swallowed. For more information, please read Chapter 2.

1.5 HOW CAN BERYLLIUM AFFECT MY HEALTH?

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, the lung damage resembles pneumonia with reddening and swelling of the lungs. This condition is called acute beryllium disease. In this case, if you stop breathing air with beryllium in it, the lung damage may heal. Some people can become sensitive to beryllium. This is known as hypersensitivity or allergy. If you become sensitive (allergic) to beryllium, you will develop an immune or inflammatory reaction to 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. This disease can occur long after exposure to small amounts of either the soluble or the insoluble forms of beryllium. If you have this disease you may feel weak, tired, and have difficulty breathing.

Although the soluble and insoluble forms of beryllium can cause chronic beryllium disease, workers breathing air containing beryllium at less than 0.002 milligrams (mg) (1 mg = 1 thousandth of a gram of beryllium) in a cubic meter (mg/m^3) (a level that government rules permit in the workplace) will probably not develop lung damage as a result of exposure. Both the short-term, pneumonia-like disease and the chronic beryllium disease can be fatal. Long periods of exposure to beryllium have

been reported to cause cancer in laboratory animals, but some of these studies are not reliable. Some studies of workers reported an increased risk of lung cancer, but these studies are not conclusive, and new studies are being performed. The Department of Health and Human Services has determined that beryllium and certain beryllium compounds may reasonably be anticipated to be carcinogens. The International Agency for Research on Cancer has determined that beryllium and beryllium compounds are probably carcinogenic to humans. The EPA has determined that beryllium is a probable human carcinogen. We have no evidence that 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 and intestines into the bloodstream. Beryllium contact with skin that has been scraped or cut can 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 2.

1.6 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, normal levels of beryllium do not necessarily mean that you were not exposed to an excessive amount. There is also a test that uses blood cells or cells washed out of the lung. If these cells start growing in the presence of beryllium, the possibility is strong that you have become sensitive to beryllium and have chronic beryllium disease. For more information, please read Chapters 2 and 6.

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

The National Institute for Occupational Safety and Health (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 a concern that beryllium may cause cancer. The Occupational Safety and Health Administration (OSHA) has set a limit of 2 μg beryllium/m^3 of workroom air for an 8- hour work shift. The Environmental Protection Agency restricts the amount of beryllium emitted into the environment by industries that process beryllium ores, metal, oxide, alloys, or waste to 10 grams (g) in a 24-hour period, or to an amount that would result in atmospheric levels of 0.01 μg beryllium/m^3 of air, averaged over a 30-day period. For more information, please read Chapter 7.

1.8 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, E-29
Atlanta, Georgia 30333

This agency can also provide you with information on the location of the nearest occupational and environmental health clinic. These clinics specialize in the recognition, evaluation, and treatment of illnesses resulting from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of beryllium and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for beryllium based on toxicological studies and epidemiological investigations.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals 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, developmental, reproductive, 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. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine 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 tables and figures may differ depending on the user’s perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious" effects. Public

health officials and project managers 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 (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with the carcinogenic effects of beryllium are indicated in Figures 2-1 and 2-2. Because cancer effects could occur at lower exposure levels, the figures also show 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.

Estimated of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability and extrapolation of data from laboratory animals to humans.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1989a), 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.

Beryllium is a lightweight, corrosion-resistant 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, which contain beryllium oxide and beryllium hydroxide. 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.

2.2.1 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. 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, but improvements in industrial hygiene over the last 30-40 years have effectively reduced workroom beryllium levels to below the OSHA standard of 0.002 mg/m^3

2.2.1.1 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 noneoplastic respiratory disease was higher among employees who remained in the industry for <5 years after initial exposure and were exposed prior to 1950. 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). The results suggest that with regard to occupational exposure, women may be more sensitive than men to beryllium. 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 2.2.1.2 under Respiratory Effects, exposure to beryllium can result in two types of nonneoplastic respiratory disease, acute pneumonitis 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 1968). 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. LC_{50} values in rats were 0.15 mg beryllium/m^3 as beryllium sulfate and 0.86 mg beryllium/m^3 (4 hours) as beryllium phosphate (Venugopal and Luckey 1977). 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. A 4-hour LC^{50} value in guinea pigs was 4.02 mg beryllium/m^3 as beryllium phosphate (Venugopal and Luckey 1977). This concentration was also reported as a 4-hour LC_{100} in cats. Three of 10 guinea pigs and 2 of 10 hamsters died when exposed to 4.3 mg beryllium/m^3 as beryllium sulfate tetrahydrate 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/m3 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. The lethality of beryllium fluoride may be related more to the deleterious effects of fluoride than beryllium: beryllium fluoride in the lungs may dissociate into hydrofluoric acid. Based on limited comparisions 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 tetrahydrate 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/^{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 2-1 and plotted in Figure 2-1.

2.2.1.2 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/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 values for each systemic effect in each species and duration category are recorded in Table 2-1 and plotted in Figure 2- 1.

Respiratory Effects. In humans, the respiratory tract has been identified as one of the major target systems following inhalation exposure to beryllium. Following an accidental leakage of beryllium dust, 25 laboratory workers were exposed to an undertermined concentration of beryllium chloride over a period of 10-20 hours (Zorn et al. 1986). Exposure resulted in elevated serum beryllium levels 3.5 times greater than background levels. No exposure- related respiratory effects were observed following sprometry and X-ray of the thorax.

TABLE 2-1- Levels of Significant Exposure to Beryllium - Inhalation

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL ($mgBe/m^3$)	LOAEL (effect) Less serious ($mg\ Be/m^3$)	LOAEL (effect) Serious ($mg\ Be/m^3$)	Reference	Form
1	Rat	10 d 5 d/wk 6 hr/d				31 (2/20 died)	Hall et al. 1950	BeO
2	Rat	1 d 4 hr/d				0.15 (LC_{50})	Venugopal and Luckey 1977	$BeSO_4$
3	Rat	1 d 4 hr/d				0.86 (LC_{50})	Venugopal and Luckey 1977	$Be3(PO_4)_2$
4	Rat	14 d 2 hr/d				2.59 (20/20 died)	Sendelbach and witschi 1987	$BeSO_4$
5	Rat	14 d 5 d/wk 6 hr/d				4.3 (10/10 died)	Stokinger et al. 1950	$BeSO_4$
6	Rat	50 min				0.8 (20/74)	Haley et al 1990	Be
7	Gn pig	1 d 4 hr/d				4.02 (LC_{50})	Venugopal and Luckey 1977	$Be3(PO_4)_2$
8	Gn pig	14 d 5 d/wk				4.3 (3/10 died)	Stokinger et al.	$BeSO_4$

		6 hr/d				1950	
9	Hamster	14 d 5 d/wk 6 hr/d			4.3 (2/10 died)	Stokinger et al. 1950	$BeSO_4$
10	Cat	1 d 4 hr/d			4.02 (LC_{100})	Venugopal and Luckey 1977	$Be3(PO_4)_2$
11	Monkey	7-17 d 6 hr/d			0.184 (2/4 died)	Schepers 1964	BeF_2
12	Monkey	8-10 d 6 hr/d			13 (4/4 died)	Schepers 1964	$BeHPO_4$
13	Monkey	7 d 6 hr/d			0.198 (1/4 died)	Schepers 1964	$BeSO_4$
Systemic							
14	Rat	50 min	Resp		0.8 (acute pneumonitis progressing to chronic inflammation necrosis)	Haley et al. 1990	Be
15	Rat	1 hr	Resp		13 (pneumonitis)	Sendelbach et al. 1986	$BeSO_4$
16	Rat	1 hr	Resp	7.0 (increased Lactic dehydrogenase and alkaline phosphatase in bronchoalveolar lavage fluid)		Sendelbach and Witchi 1987	$BeSO_4$

17	Rat	1 hr				4.05(pneumonitis)	Sendelbach et al. 1989	$BeSO_4$
18	Rat	1 hr	Resp		0.447 (lung inflammation)		Hart et. al. 1989	$BeSO_4$
		4-8 hr/d						
19	Rat	10 d	Resp	31			Hall et al. 1950	BeO
		5 d/wk	Hemato	31				
		6 hr/d	Hepatic	31				
			Renal	31				
			Other (body weight)	31				
20	Rabbit	10 d	Resp	31			Hall et al. 1950	BeO
		5 d/wk	Hemato		31 (decreased erythrocyte count)			
		6 hr/d	Hepatic	31				
			Renal	31				
			Other (body weight)	31				
21	Gn pig	10 d	Resp	31			Hall et al. 1950	BeO
		5 d/wk	Hemato	31				
		6 hr/d	Renal	31				
			Other (body weight)	31				
22	Mouse	1 hr	Resp		13 (Lung inflammation)		Sendelb-ach et al. 1986	$BeSO_4$

23	Mouse	14 d 5 d/wk 6 hr/d	Other		4.3 (13% body weight loss)		Stokinger et al. 1950	$BeSO_4$
24	Mouse	1 hr	Resp		7.2 (increased lactic dehydrogenase and alkaline phosphatase in bronchoalveolar lavage fluid)		Sendelbach and Witschi 1987	$BeSO_4$
25	Dog	1 d	Resp			10 (granulomas in lung)	Haley et al. 1989	BeO
26	Dog	20 min	Resp			115 (granulomas foci, inflmmation of the lung)	Robinson et al. 1968	BeF_2, BeO, $BeCl_2$
			Other		115 (transient anorexia, weight loss)			
						13 (emphysema)	Schepers 1964	$BeHPO_4$
27	Monkey	8-10 6 hr/d	Resp		13 (enlarged heart)			
			Cardio		13 (hepatocyte degeneration)			
			Hepatic					
			Renal	13	97 (degeneration of the nephrons)			

			Other		13 (severe weight weight loss 8-34%)		
			Other	13 (hypoplasia of the adrenal gland)			
28	Monkey	7-18 d	Resp		0.184 (emphysema)	Schepers 1964	BeF_2
		6 hr/d	Cardio	0.184 (enlarged (heart)			
			Hepatic	0.184 (hepatocellular degenration)			
			Renal	0.184 (degeneration of the nephrons)			
			Other	0.184 (adrenal hypotrophy)			
			Other		0.184 (19-23% weight loss)		
29	Monkey	7 d	Resp		0.198 (emphysema)	Schepers 1964	$BeSO_4$
		6 hr/d	Cardio	0.198 (enlarged heart)			
			Renal	0.198			

				(glomerular degeneration)			
			Other		0.198 (24% average weight loss)		
Immunological							
30	Rat	1-6 d 4-8 hr/d	0.035			Schepers et al. 1957	$BeSO_4$
31	Dog	1 d		10 (Lymph node hyperplasia, lymphocyte stimulation)		Haley et al. 1989	BeO
32	Monkey	7-18 d 6 hr/d		0.184 (hyperplasia of Lymph nodes)		Schepers 1964	BeF_2
33	Monkey	7 d 6 hr/d		0.198 hyrperplasia of lymph nodes)		Schepers 1964	$BeSO_4$
34	Monkey	8-10 d 6 hr/d		13 (hypoplasia of lymph nodes)		Schepers 1964	$BeHPO_4$
INTERMEDIATE EXPOSURE							
Death							
35	Rat	6 mo 5 d/wk 6 hr/d			0.210 (increased mortality)	Wagner et al. 1969	BeO
36	Rat	15 d 5 d/wk 6 hr/d			30 (6/13 males, 9/10 famales	Hall et al. 1950	BeO

		6 hr/d	famales died)	1950	
37	Rat	51-100 d 5 d/wk 6 hr/d	0.43 (23/47 died)	Stokinger et al. 1950	$BeSO_4$
38	Gn pig	51-100 d 5 d/wk 6 hr/d	0.43 (2/34 died)	Stokinger et al. 1950	$BeSO_4$
39	Mouse	51 d 5 d/wk 6 hr/d	2.0 (4/38 died)	Stokinger et al. 1950	$BeSO_4$
40	Dog	51 d 5 d/wk 6 hr/d	2.0 (4/5 died)	Stokinger et al. 1950	$BeSO_4$
41	Hams-ter	6 mo 5 d/wk 6 hr/d	0.210 (increased mortality)	Wagner et al. 1969	BeO
42	Hams-ter	51 d 5 d/wk 6 hr/d	2.0 (5/10 died)	Stokinger et al. 1950	$BeSO_4$
43	Hams-ter	6 mo 5 d/wk 6 hr/d	0.620 (increased mortality)	Wagner et al. 1969	BeO
44	Cat	51-100 d 5 d/wk 6 hr/d	0.43 (1/5 died)	Stokinger et al. 1950	$BeSO_4$
45	Monkey	30 d 6 hr/d	0.198 (1/4 died)	Schepers 1964	$BeHPO_4$
46	Monkey	51-100 d 5 d/wk 6 hr/d	2.0 (1/1 died)	Stokinger et al. 1950	$BeSO_4$
47	Monkey	6 mo	0.210	Wagner	BeO

		5 d/wk 6 hr/d				(increased mortality)	et al. 1969	
Systemic								
48	Rat	15 d 5 d/wk 6 hr/d	Resp			30 (respiratory distress, increased rates)	Hall et al. 1950	BeO
			Other			30 (steady weight loss)		
49	Rat	6 mo 5 d/wk 6 hr/d	Resp			0.210 (granuloma in lung)	Wagner et al. 1969 1969	BeO
50	Rat	6 mo 5 d/wk 6 hr/d	Hemato Hepatic Renal	0.620 0.620 0.620			Wgner et al. 1969	BeO
51	Rat	180 d 5-6 d/wk 4-8 hr/d	Resp			0.035 (metaplasia, granulomas)	Schepers et al. 1957	$BeSO_4$
52	Rat	10 wk 6 hr/d	Derm/oc		0.5 (inflammatory reaction on skin)		Stiefel et al. 1980	$Be(NO_3)_2$
53	Rat	51-100 d 5 d/wk 6 hr/d	Hemato	0.04	0.43 (macrocytic anemia; Leukocytosis)		Stokinger et al. 1950	$BeSO_4$
			Hepatic		2.0 (increased serum albumin globulin)			
			Renal	0.43	2.0 (proteinuria)			
54	Rabbit	51-100 d	Resp			0.04 (atelectasis)	Stokinger et al.	$BeSO_4$

							1950	
		5 d/wk 6 hr/d	Hemato	0.04	0.43 (macrocytic anemia; leukocytosis)			
55	Rabbit	60 d	Resp	30			Hall et al. 1950	BeO
		5 d/wk 6 hr/d	Hemato		30 (macrocytic anemia)			
56	Gn pig	10 wk 6 hr/d	Derm/oc		0.5 (inflammatory reaction on skin)		Stiefel et al. 1980	$Be(NO_3)_2$
57	Dog	17.5 d	Resp			31 (emphysema, atelectasis, inflammation)	Hall et al. 1950	BeO
		5 d/wk	Hepatic	31				
		6 hr/d	Renal	31				
58	Dog	51-100 d	Resp			0.04 (emphysema)	Stokinger et al. 1950	$BeSO_4$
		5 d/wk 6 hr/d	Cardio		0.04 (decreased arterial oxygen tension)			
			Hemato		0.04 (macrocytic anemia)			
			Hepatic		0.04 (increased serum albumin and globulin)			
			Renal	0.04	0.43 (proteinuria)			
			Other		0.04 (10% body weight loss)			
59	Dog	15 d	Cardio		30 (decrease		Hall et	BeO

		5 d/wk 6 hr/d			in arterial oxygen tension)		al. 1950	
			Hemato		30 (Leukocy-tosis)			
			Other		30 (7-14% body weight loss)			
60	Dog	40 d 5 d/wk 6 hr/d	Resp Cardio		3.6 (decrea-sed arterial oxygen tension)	3.6 (emphysema)	Hall et al. 1950	BeO
			Hemato		3.6 (macroc-ytic anemia)			
			Hepatic		3.6 (decre-ased serum protein)			
			Renal	3.6				
			Other			3.6 (anorexia and 25% weight loss)		
61	Hamster	6 mo 5 d/wk 6 hr/d	Hemato Hepatic Renal	0.620 0.620 0.620			Wagner et al. 1969	BeO
62	Hamster	6 mo 5 d/wk 6 hr/d	Resp			0.210 (granu-lomas of the lung)	Wagner et al. 1969	BeO
63	Cat	15 d	Resp	30.0			Hall et al. 1950	BeO
		5 d/wk	Other			30 (anorexia,		

		6 hr/d				severe weight loss emacia-tion)		
64	Cat	51-100 d 5 d/wk 6 hr/d	Resp Other			0.04 (emphysema) 0.04 (severe weight loss - 43%)	Stokinger et al. 1950	$BeSO_4$
65	Monkey	30 d 6 hr/d	Resp Hepatic Renal Other	0.198 0.198		0.198 (emphysema) 0.198 (15-39% weight loss)	Schepers 1964	$BeHOP_4$
66	Monkey	15 d 5 d/wk 6 hr/d	Resp Other	30.0		30 (marked weight loss)	Hall et al. 1950	BeO
67	Monkey	51-100 d 5 d/wk 6 hr/d	Resp Other			0.04 (emphy sema) 0.43 (31% weight loss)	Stokinger et al. 1950	$BeSO_4$
68	Monkey	6 mo 5 d/wk 6 hr/d	Resp		0.210 (Lung inflammation)		Wagner et al. 1969	BeO
69	Monkey	6 mo 5 d/wk 6 hr/d	Resp Hemato Hepatic Renal	0.620 0.620 0.620	0.620 (Lung inflammation)		Wagnere et al. 1969	BeO
70	Pig	51 d 5 d/wk	Other			2.0 (28% weight loss)	Stokinger et al.	$BeSO_4$

		6 hr/d				1950	
Immunlogical							
71	Rat	30 d 5-6 d/wk 4-8 hr/d	0.035			Schepers et al. 1957	BehOP4
72	Rat	6 mo 5 d/wk 6 hr/d	0.620			Wagner et al. 1969	BeO
73	Rat	10 wk 6 hr/d		0.5 (increased T-cell activity)		Stiefel et al. 1980	$Be(NO_3)_2$
74	Gn pig	10 wk 6 hr/d		0.5 (increased T-cell activity)		Stiefel et al. 1980	$Be(NO_3)_2$
75	Hamster	6 mo 5 d/wk 6 hr/d	0.620			Wagner et al. 1969	BeO
76	Monkey	6 mo 5 d/wk 6 hr/d	0.620			Wagner et al. 1969	BeO
77	Monkey	30 d 6 hr/d		0.197 (hypopl-asia of Lymph nodes)		Schepers 1964	$BeHOP_4$
Cancer							
78	Rat	180 d 5-6 d/wk 4-8 hr/d			0.035 (CEL - lung cancer)	Schepers et al. 1957	$BeSO_4$
CHRONIC EXPOSURE							
Death							
79	Rat	72 wk 5 d/wk			0.034 (increa sed mortality	Reeves et al.	$BeSO_4$

		7 hr/d				of females)	1967	
Systemic								
80	Human	12.6 yr average	Resp			0.0012 (breathing difficulties, scarring the lung	Cullen et al. 1987	mix
81	Human	occup 4-8 yr	Resp			0.0012 (inflmmation and granulomatous lesion of the lung)	Cullen et al. 1987	mix
82	Human	occup	Resp			0.0046 (chronic interstitial pneumonitis)	Johnson 1983	Be
			Hemato	0.0046				
83	Rat	12-17 mo 5 d/wk 6 hr/d	Resp			0.210 (granuloma in lung)	Wagner et al. 1969	BeO
84	Rat	72 wk 5 d/wk 7 hr/d	Resp		0.034 (inflammation and proliferation in lung)		Reeves et al. 1967	$BeSO_4$
			Other		0.034 (decrease in body weight)			
85	Rat	6-18 mo 5 d/wk 6 hr/d	Resp		0.0547 (inflammation and fibrosis of the lung		Vorwald and Reeves 1959	$BeSO_4$
86	Rat	12-17 mo	Resp		0.620 (conso-		Wagner	BeO

		5 d/wk			lidation of			et al.	
		6 hr/d	Hemato	0.620	lung)			1969	
			Hepatic	0.620					
			Renal	0.620					
			Other		0.620 (15% decreased body weight gain)				
87	Rat	6-18 mo	Resp		0.006 (inflam-			Vorwald	BeSO
		5 d/wk			mation and			and	
		6 hr/d			fibrosis of			Reeves	
					the and lung)			1959	
88	Hamster	12-17 mo	Resp			0.210 (granu-		Wagner	BeO
		5 d/wk				lomas in the		et al.	
		6 hr/d				lung)		1969	
89	Hamster	12-17 mo	Hemato	0.620				Wagner	BeO
		5 d/wk	Hepatic	0.620				et al.	
		6 hr/d	Renal	0.620				1969	
90	Monkey	12-23 mo	Resp		0.620 (lung			Wagner et	BeO
		5 d/wk	Hemato	0.620	inflammation)			al. 1969	
		6 hr/d	Hepatic	0.620					
			Renal	0.620					
91	Monkey	12-23 mo	Resp		0.210 (lung			Wagner et	BeO
		5 d/wk			inflammation)			al. 1969	
		6 hr/d							
92	Human	occup			0.0046 (granuloma of the lymph nodes)			Johnson 1983	Be
93	Human	occup			0.0012 (increased T-cell activity)			Cullen et al. 1987	mix
94	Rat	12-17 mo		0.620				Wagner et	BeO

		5 d/wk 6 hr/d			al. 1969	
95	Hamster	12-17 mo 5 d/wk	0.620		Wagner et al. 1969	BeO
96	Monkey	12-23 mo 5 d/wk 6 hr/d	0.620		Wagner et al. 1969	BeO
Cancer						
97	Rat	12-17 mo 5 d/wk 6 hr/d	0.620 (CEL-Lung cancer)		Wagner et al 1969	BeO
98	Rat	6-18 mo 5 d/wk 6 hr/d	0.0547 (CEL lung cancer)		Vorwald and Reeves 1969	BeSO4
99	Rat	72 wk 5 d/wk		0.034. (CEL-lung cancer	Reeves et 1967	BeSO4
100	Rat	6-18 mo 5 d/wk 6 hr/d		0.006 (CEL-lung cancer	Vorwald and Reeves 1959	BeO
101	Monkey	63 wk 5 d/wk 6 hr/d		0.035 (CEL-lung cancer)	Vorwald 1968	BeSO4

[a] The number corresponds to entries in Figure 2-1.
Be = beryllium; $BeCl_2$ = beryllium chloride; BeF_2 = beryllium fluoride; $BeHPO_4$ = beryllium hydrogen phosphate; $Be(NO_3)_2$ = beryllium nitrate; BeO = beryllium oxide; = beryllium phosphate; $BeSO_4$ = beryllium sulfate; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Derm/oc = dermal/ocular;Gn pig = guinea pig; Hemato = hematological; hr = hour(s);

LC^{50} = lethal concentration, 50% kill; LC^{100} = lethal concentration, 100% 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)

TABLE 2-1- Levels of Significant Exposure to Beryllium - Inhalation

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FIGURE 2-1. Levels of Significant Exposure to Beryllium - Inhalation

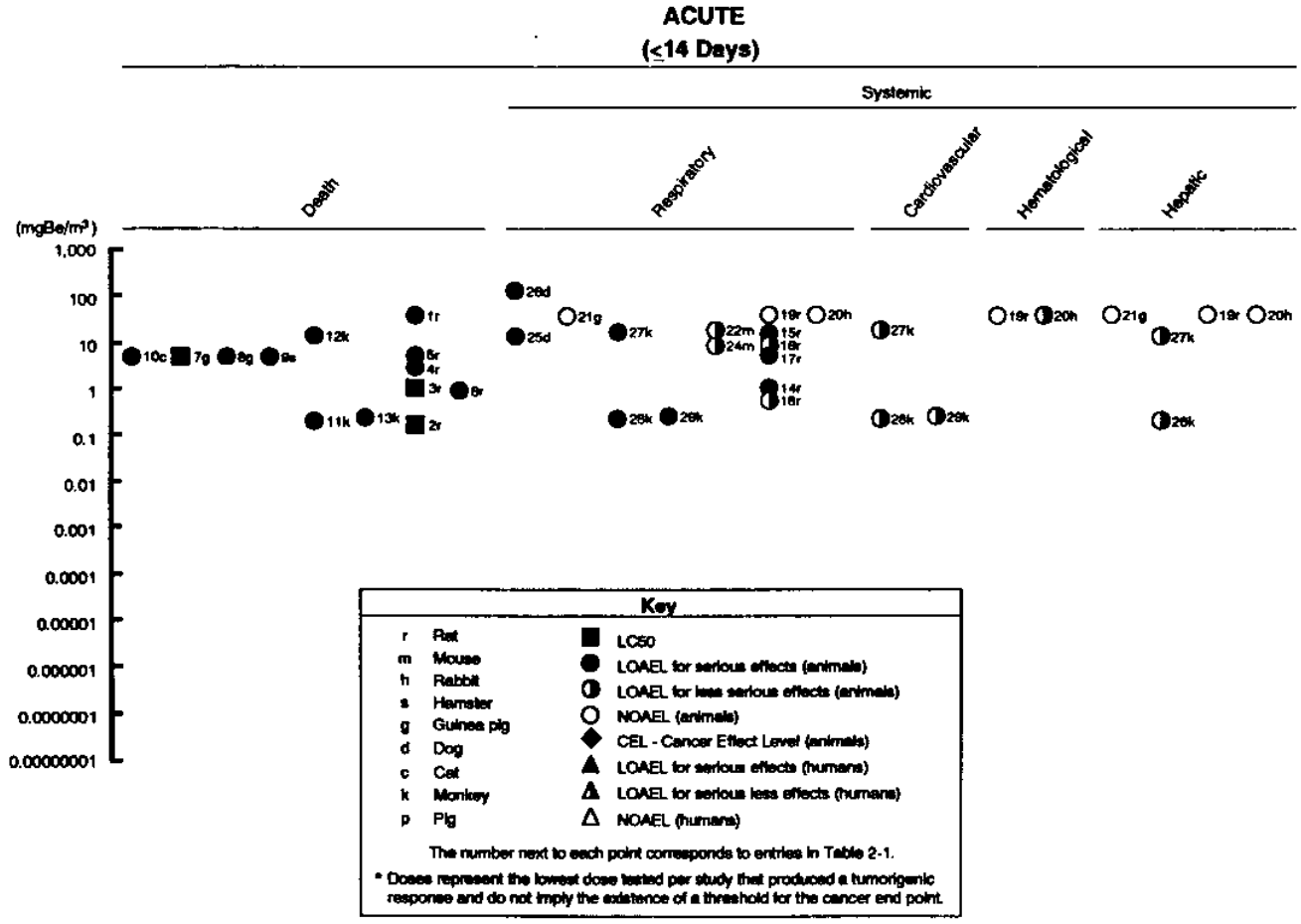


FIGURE 2-1. Levels of Significant Exposure to Beryllium - Inhalation

FIGURE 2-1 (Continued)

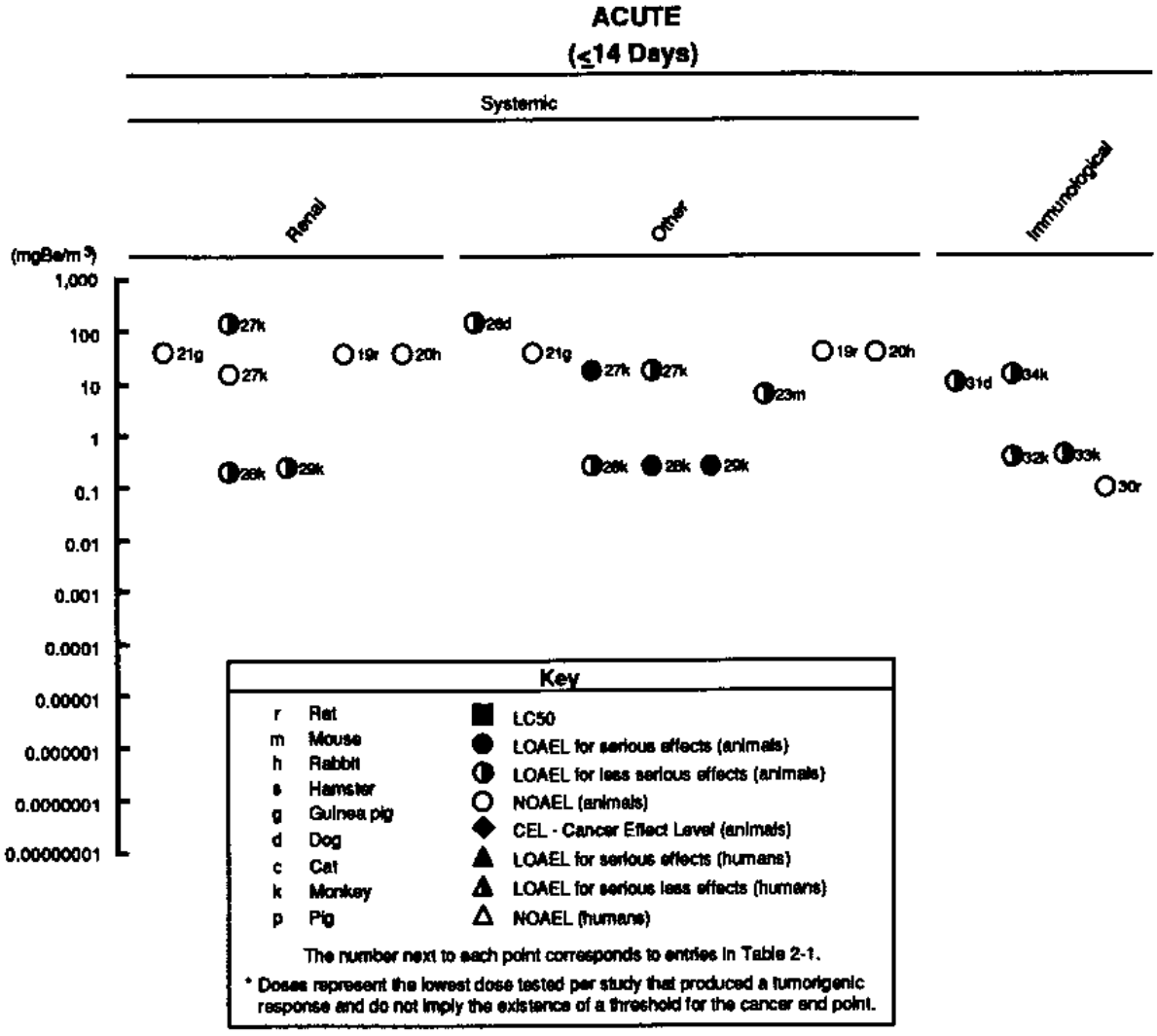


FIGURE 2-1. Levels of Significant Exposure to Beryllium - Inhalation -- continued

FIGURE 2-1 (Continued)

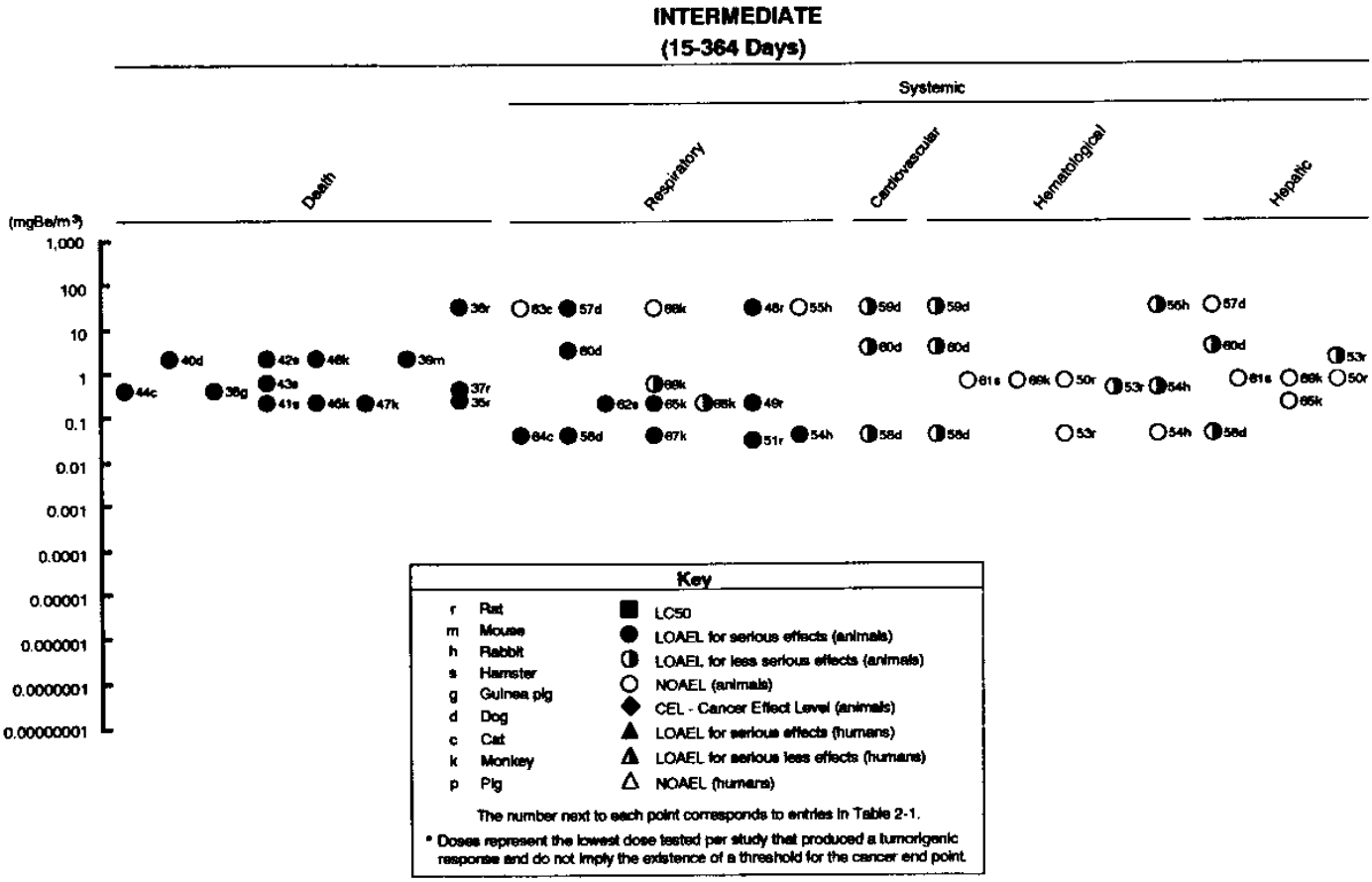


FIGURE 2-1. Levels of Significant Exposure to Beryllium - Inhalation -- continued

FIGURE 2-1 (Continued)

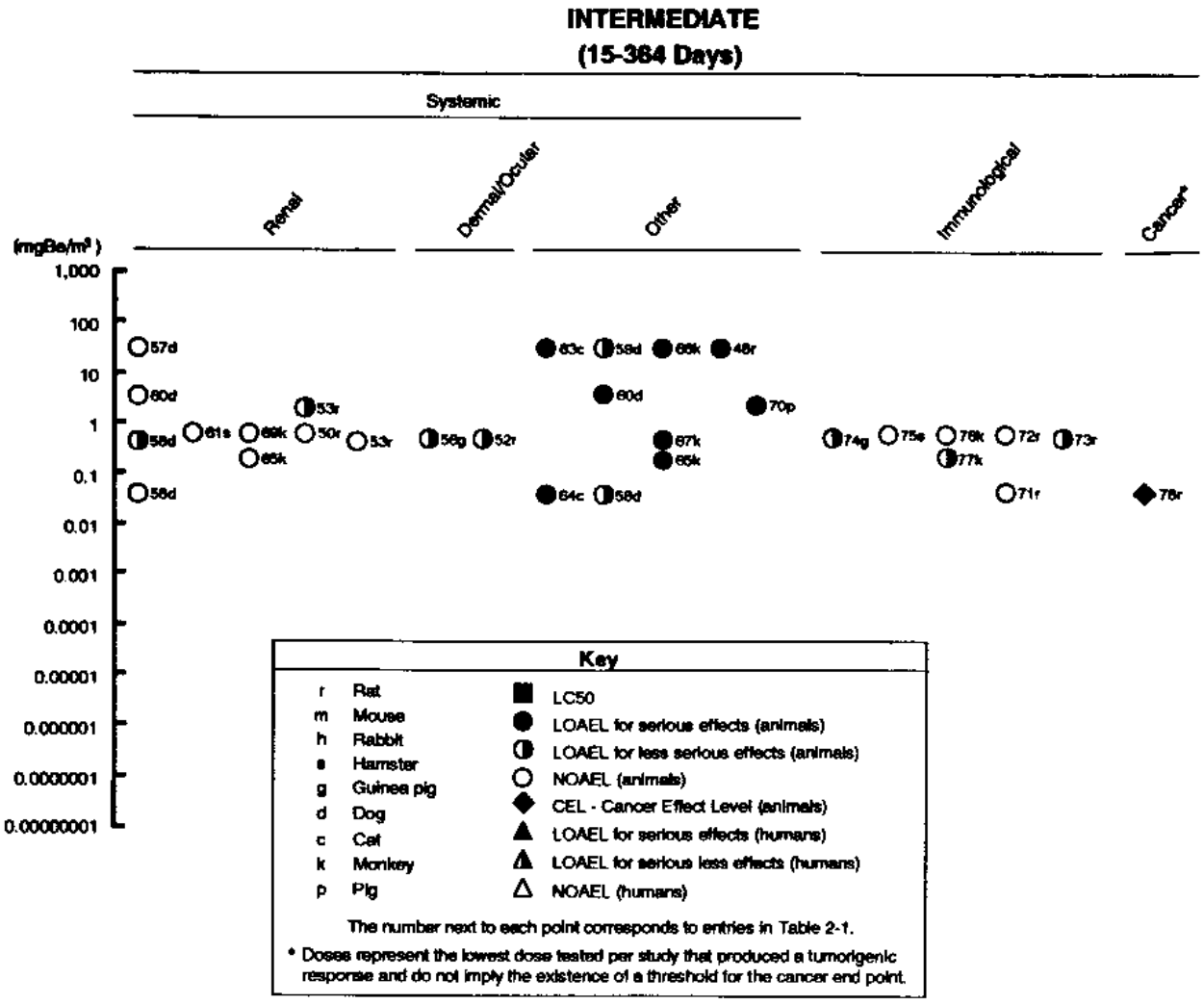


FIGURE 2-1. Levels of Significant Exposure to Beryllium - Inhalation -- continued

FIGURE 2-1 (Continued)

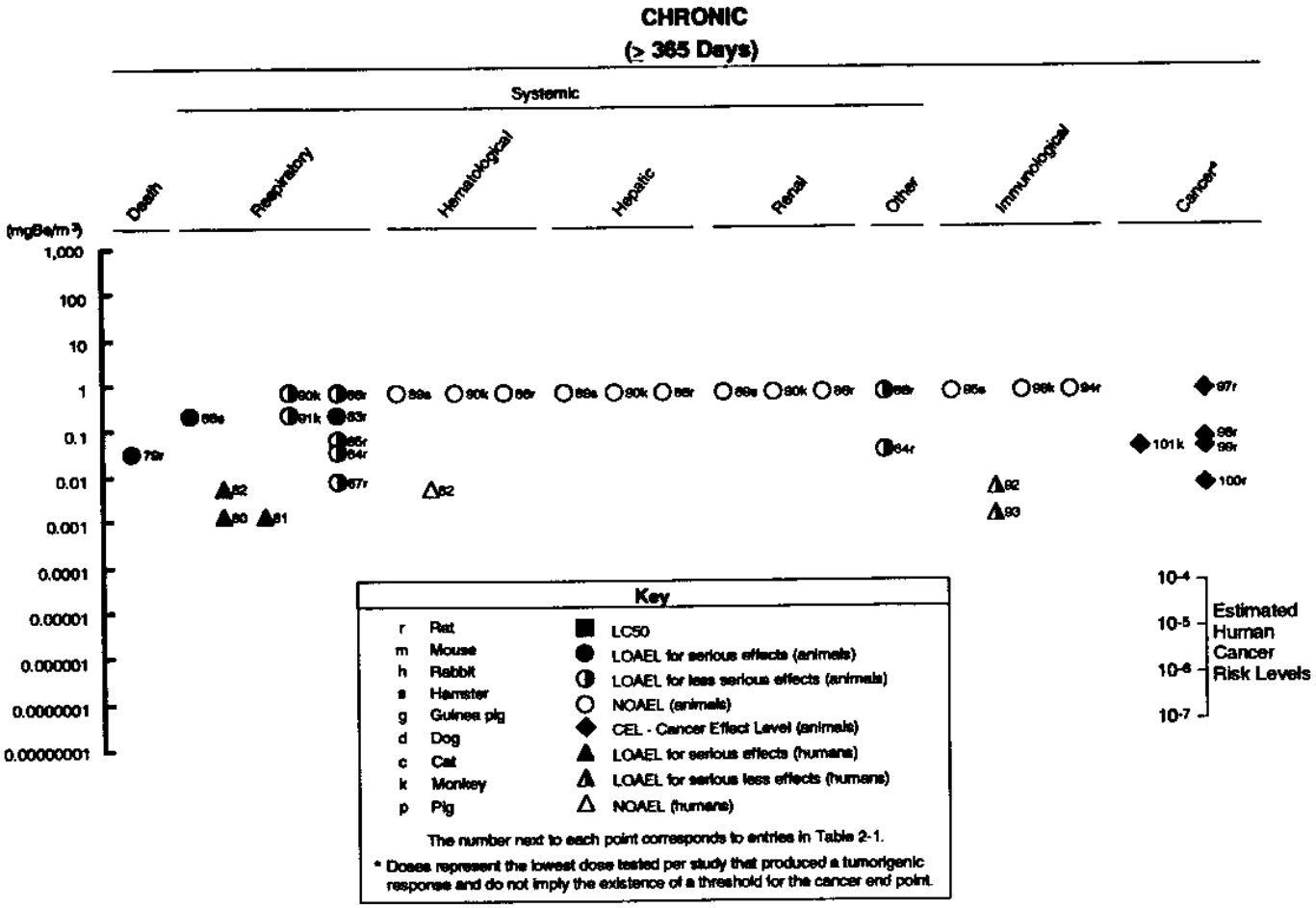


FIGURE 2-1. Levels of Significant Exposure to Beryllium - Inhalation -- continued

Most studies reporting respiratory effects in humans involve chronic, occupational exposure to beryllium. Inhalation of high concentrations of soluble beryllium compounds by exposed workers has been associated with the development of acute chemical pneumonitis. Exposure to less soluble forms of beryllium may also cause acute pneumonitis but are more often associated with chronic beryllium disease (berylliosis) in which granulomatous lesions develop in the lung. 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. 1948). The syndrome of acute beryllium pneumonitis has been virtually eliminated in workers first exposed to

beryllium after 1950, except in instances where accidental exposures have exceeded the OSHA standard of 0.002 mg/m^3 (Eisenbud and Lission 1983). Dose relationships for chronic beryllium disease are more difficult to establish because the exposure histories do not correlate with the incidence of the disease. However, the number of cases of chronic beryllium disease have dramatically decreased in workers first exposed after 1950, demonstrating the effectiveness of the 0.002 mg/m^3 OSHA standard in controlling chronic beryllium disease, as well as acute beryllium disease. Case histories of 170 workers exposed to beryllium (beryllium sulfate, beryllium fluoride, or beryllium oxyfluoride) reported that 128 workers had irritation of nasal and pharyngeal mucous membranes, sore nose and throat, weight loss, labored breathing, decreased vital capacity, anorexia, and increased fatigue (VanOrdstrand et al. 1945). Seventeen workers who were chronically exposed to beryllium in a fluorescent lamp plant developed anorexia, dyspnea, cough, easy fatigue, and weakness (Hardy and Tabershaw 1946). 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. In a cross-sectional study of 297 white male workers in a beryllium plant, pulmonary function tests revealed small decreases in forced vital capacity and forced expiratory volume in 1 second related to beryllium exposure (Kriebel et al. 1988). The significance of these changes is uncertain. Five workers employed at a precious metal refinery between 1972 and 1985 developed lung granulomas (Cullen et al. 1987). Measurements of the in vitro proliferative responses of lymphocytes obtained by bronchoalveolar lavage indicated that four of the five workers were hypersensitive to beryllium. Results of subsequent industrial hygiene monitoring of the plant showed that three of the four beryllium- sensitive individuals worked in the furnace area where beryllium fume concentrations may have been consistently $<$0.002 mg beryllium/m^3. Time-weighted-average personal air samples throughout the refinery ranged from 0.00022 to 0.043 mg beryllium/m^3, with 10% of the measured samples $>$0.002 mg beryllium/m^3 Radiographic or spirometric testing of 45 additional refinery workers did not reveal any evidence of sarcoidosis or chronic beryllium disease. Although the results of this study suggest that chronic beryllium disease may have resulted from occupational exposure to beryllium at levels $<$0.002 mg/M^3, the study had several limitations including underestimation of exposure levels by the standard filter methods of collection; measurement of levels only in 1983, although exposures occurred between 1964 and 1977; limited sampling, which was performed in two discrete 1-week periods, 3 months apart, may have missed high concentrations; the possibility that the workers in question were also exposed to high levels of beryllium that were measured outside the furnace area; and the presence of moderate concentrations of other metal contaminants (arsenic, cadmium, lead, and nickel) in the samples.

In another study of 41 individuals with chronic beryllium disease, reduced vital capacity and total lung capacity, increased alveolar-arterial oxygen tension difference, arterial hypoxemia, and decreased carbon monoxide diffusion capacity were consistently observed (Andrews et al. 1969). Three machinists who worked with beryllium metal from the late 1950s to the mid-1970s had similar decreases in pulmonary function (Johnson 1983). The exposure concentration of the workplace was determined to be 0.0046 mg beryllium/m^3 from an air sample taken in 1977. The pathological reports indicated that the men had chronic interstitial pneumonitis.

A study of twins exposed to beryllium oxide reported decreased lung function and X-ray detectable, nodular shadows in the mid and lower zones of the lung (McConnochie et al. 1988).

In another study of 14 individuals with chronic beryllium disease, each case had noncaseating granuloma diagnosed by either open lung biopsy or transbronchial biopsy (Rossman et al. 1988).

Chest X- rays were abnormal in every case with the most common finding being diffuse symmetrical fine nodular infiltrates. Mild to moderate hilar adenopathy was present in six individuals. The most significant abnormality on pulmonary function testing, conducted in 13 of the patients, was a reduced diffusing capacity (mean = 58.4% of predicted). A restrictive pattern was present in 9 of 13 patients, but no significant airway obstruction was present. The in vitro proliferative response of blood lymphocytes were positive in 6 of 14 of the patients, but all 14 patients had significant proliferative responses of their lung cells to beryllium.

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°C) for 30-180 minutes had initial alveolar deposition of 1-63 ug 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 with a moderate infiltration of lymphocytes also developed in the lungs of rats exposed to beryllium oxide. Hamsters, similarly exposed until an initial lung burden of 16-17 ug beryllium was achieved, developed only a few small areas of granuloma and degeneration of macrophages. Pulmonary lavage fluid from rats exposed to 0.447 mg beryllium/m^3 as beryllium oxide (calcined at 560°C) for 1 hour was examined at various intervals for ≥21 days after exposure for cell populations, enzyme levels of acid and alkaline phosphatase, 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 barrier. 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 treated lungs indicated damage to the cellular populations; the increase in protein indicated alveolar damage. These studies demonstrate the ability of soluble beryllium to damage the lung long after exposure ceases. Dogs exposed to 10 mg beryllium/m^3 as beryllium oxide calcined at 500°C or 1000°C developed granulomas in the lung (Haley et al. 1989). Histopathology also revealed intense alveolar septal fibrosis and epithelial hyperplasia. Beryllium oxide calcined at 500°C 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 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 laded macrophages and a few lymphocytes (Wagner et al. 1969). However, when the rats were exposed to 0.620 mg beryllium/m3 as beryl ore, the lungs were largely unaffected except for a few small areas of atypical proliferation. Monkeys exposed to 0.210 or 0.620 mg beryllium/m3 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/m3 as beryllium oxide for 17.5 days (Halls et al. 1950). While rats exposed to 0.035 mg beryllium/m^3 as beryllium sulfate for 30 days had no morphological changes in the lung, rats exposed to the same concentration for 6 months had epithelialization of the alveoli, focal metaplasia, granulomas, and neoplasms (Schepers et al. 1957). Exposure of rabbits, dogs, cats, and monkeys to 0.04 mg beryllium/m^3 as beryllium sulfate tetrahydrate 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 health effects in animals similar to 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. 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. Rates exposed to 0.034 mg berlylium/m^3 as beryllium sulfate tetrahydrate for 72 weeks had inflamed lungs, emphysema, arteriolar wall thickening, granulomas, fibrosis, and proliferative responses within the alveoli (Reeves et al. 1976). 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. 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).

Heart elnargement was observed in monkeys after acute inhalation exposure to $\geq$13 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 tetrahydrate for 100 days (Stokinger et al. 1950). The effects of beryllium compounds on the cardiovascular system probably

represent compensatory increases in cardiac musculture due to fibrosis or emphysema 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 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 30 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 tetrahydrate for 100 days (Stockinger et al. 1950). Exposure to 2.0 and 0.43 mg beryllium/m^3 as beryllium sulfate tetrahydrate in rats, rabbits, and dogs caused transient leukocytosis; exposure to 2.0 mg beryllium/m^3 caused mild thrombocytosis. With progressive exposure, dogs exposed to 0.04 mg beryllium/m^3 as beryllium sulfate tetrahydrate 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 caused 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 revelaed 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 the 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 tetrahydrate, 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 tetrahydrate 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).

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 tetrahydrate 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 tetrahydrate, 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 tetrahydrate.

Intermediate-duration exposure 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 examinations 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 tetrahydrate (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).

Dermal/Ocular Effects. According to a case history, twins occupationally exposed to beryllium had reduced tear secretions (McConnochie et al. 1988). Skin biopsies revealed granulomas containing beryllium. 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).

Other Systemic 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 to deliver alveolar depositions of 138 and 16 μg beryllium, respectively, had increased adrenal weight (Sanders et al. 1975). The exact exposure concentrations were not specified.

Effects on body weight have been observed in humans after inhalation exposure to beryllium or its compounds. Weight loss was common among 128 of 170 workers with berylliosis (VanOrdstrand et al. 1945). Weight loss was also reported in case histories taken from 17 workers at a fluorescent lamp manufacturing plant (Hardy and Tabershaw 1946).

Weight loss, severe at times, has been observed in animals after inhalation exposure to beryllium compounds. Due to impaired food consumption and metabolic changes, monkeys exposed for acute durations to $\geq$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% of their original body weight (Schepers 1964). Mice exposed to 4.3 mg beryllium/m^3 as beryllium sulfate had a 13% decrease in body weight. 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).

the first 7 days after exposure (Robinson et al. 1968).

Dogs exposed to 3.6 mg beryllium/m^3 as beryllium oxide for 40 days or 30 mg beryllium/m^3 as beryllium oxide for 15 days had decreased body weight. Prolonged exposure resulted in a weight loss of 25% (Hall et al. 1950). Decreased body weight also was observed in dogs exposed to 0.04 mg beryllium/m^3 as beryllium sulfate for ≤100 days (Stokinger et al. 1950). Cats exposed to 30 mg beryllium/m^3 as beryllium oxide for 15 days (Hall et al. 1950) or 0.04 mg beryllium/m^3 as beryllium sulfate for up to 100 days (Stokinger et al. 1950) had severe weight loss. Severe weight loss was also observed in monkeys exposed to 30 mg beryllium/m^3 as beryllium oxide for 15 days (Hall et al. 1950), 0.198 mg beryllium/m^3 as beryllium hydrogen phosphate for 30 days (Schepers 1964), or 0.43 mg beryllium/m^3 as beryllium sulfate for ≤95 days (Stokinger et al. 1950). Rats exposed to 30 mg beryllium/m^3 as beryllium oxide for 15 days had a steady rate of weight loss during exposure (Hall 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).

2.2.1.3 Immunological 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. Alterations of the immune system were not observed in laboratory workers exposed after an accidental leakage of beryllium dust (Zorn et al. 1986).

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°C than at 1000°C, due to the greater solubility of the 500°C calcined beryllium oxide (Haley et al. 1989). The dogs exposed to beryllium oxide calcined at 500°C 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 0.197 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).

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 2-1 and plotted in Figure 2-1.

2.2.1.4 Neurological Effects

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

2.2.1.5 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to beryllium or its compounds. Developmental effects were observed in rat fetuses following intratracheal exposure of pregnant rats to beryllium chloride or beryllium oxide (Selivanona and Savinova 1981). Further details are provided in Section 2.4.

2.2.1.6 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals after inhalation

exposure to beryllium or its compounds. No effects on reproductive parameters were observed after male and female rats were treated intratracheally with beryllium oxide and allowed to mate (Clary et al. 1975). Further details are provided in Section 2.4.

2.2.1.7 Genotoxic Effects

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

Genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

There are a number of retrospective studies on occupational exposure to beryllium or its compounds. A retrospective mortality study of 6,818 former male beryllium workers, who had been employed in the industry for various times during the period from 1942 to 1967, found no statistically significant increased risk of death from any cause or any type of cancer, using the United States death rates as the basis for comparison (Bayliss et al. 1971). An early retrospective cohort study examined cancer incidence among workers in two beryllium plants and workers in the rubber industry (Mancuso and El-Attar 1969). The results were confounded by exposure to other chemicals in the rubber industry and improper reporting of health effects. A similar study suggested that lung cancer occurred more frequently among workers employed for a short period of time in the beryllium plants, and that cancer rates increased in males who had sustained prior occupational respiratory illness (Mancuso 1970). However, the lack of proper statistical analysis and controls made the findings questionable. A retrospective cohort study of 3,266 workers in two beryllium production facilities reported an increased cancer incidence (Mancuso 1979). The comparisons were conducted between the cohorts and the general population. When the latent period was $\geq$15 years, the total observed deaths due to cancer were 22 compared to 9.86 expected for one of the plants and 36 observed compared to 22.02 expected for the other. These comparisons were reported to be statistically significant. The workers from the previous cohorts were again studied, and a cohort from the rayon industry was used for comparison (Mancuso 1980). The total observed cancer deaths in the cohorts (80) compared to the total cancer deaths of rayon workers (57.06) was statistically significant ($p<0.01$). The incidence of lung cancer was significant when comparing workers exposed for $\geq$49 months ($p<0.01$). A similar study was conducted involving a cohort of 3,055 white males from a beryllium extraction, processing, and fabrication facility (Wagoner et al. 1980). The cohort was employed between January 1, 1942 and September 1968 and kept track of until January 1, 1976. The overall number of cancer deaths observed and expected were 47 and 34.29, respectively. In the group of workers with a latent period $\geq$25 years, the lung cancer rate was 20 observed compared to 10.79 expected ($p<0.01$). When the data were corrected to eliminate an 11% understimate of expected deaths and to account for the smoking contribution, none of the comparisons of observed versus expected were statistically significant (EPA 1987). In a retrospective study, a cohort of 421 white male workers included in the Beryllium Case Registry was compared to the general white male population for statistical analysis (Infante et al. 1980). Seven deaths were observed compared to 2.81 expected for lung cancer. When the lung cancer rate was determined from workers with previously diagnosed respiratory problems, the number of observed deaths was 6 versus 1.91 expected ($p<0.05$). The results of the study indicate a greater tendency for cancer to develop in beryllium workers who have a history of beryllium-induced

respiratory illness.

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. There were 70 deaths from all types of cancer, 28 of which were due to lung cancer (SMR = 200, 95% CI 1.33-2.89). Of these, 22 lung cancer deaths occurred in men (SMR = 176, 95% CI 1.02-2.67), and 6 occurred in women (SMR = 404, 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 than those with chronic beryllium disease. 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. Therefore, the lung cancer excess was probably not due to smoking, and the 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 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. Although the human data regarding the carcinogenicity of beryllium and its compounds are limited or flawed, some beryllium compounds are carcinogenic in animals after inhalation exposure as discussed below. An upper-bound estimate of cancer risk was derived by EPA (1987). This estimate is based on human data from the Wagoner et al. (1980) study, instead of animal data, because of the uncertainty inherent in the use of animal data. Information provided by NIOSH (1972) and Eisenbud and Lisson (1983) regarding typical beryllium levels in production plants, for the time period covered by the Wagoner et al. (1980) study, indicates that the narrowest range for median exposure was 100-1,000 ug/m^3. Using the range of exposure levels, the upper-bound estimate of cancer risk was calculated to be 2.4×10^3 $(\mu g/)^{3-1}$ (EPA 1987; IRIS 1992). The exposures associated with individual lifetime upper-bound risks of 10^{-4} to 10^{-7} are 4×10^{-5} to 4×10^{-8} mg/m^3. These exposure levels and the associated risk levels are plotted in Figure 2-1.

Some beryllium compounds are carcinogenic in animals exposed via inhalation. 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 Cancer Effect Levels (CELs) in each species are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.2 Oral Exposure

2.2.2.1 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 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) and 9.8 mg beryllium/kg (Venugopal and Luckey 1977). The LD_{50} values for beryllium fluoride were 18-20 mg beryllium/kg in mice (Kimmerle 1966; Lanchow 1978) and 18.8 mg beryllium/kg/day in rats (Venugopal and Luckey 1977). 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.

In chronic studies, no effect on survival was observed in rats exposed to $\leq$31 mg beryllium/kg/day as beryllium sulfate in the diet (Morgareidge et al. 1975) or in rats and mice exposed to 0.7 or 0.95 mg beryllium/kg/day, respectively, as beryllium sulfate in drinking water (Schroeder and Mitchener 1975a, 1975b).

The LD_{50} value in rats and mice are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, or dermal/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.

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

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 3.9 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.

TABLE 2-2. Levels of Significant Exposure to Beryllium - Oral

Key to figure[a]	species	Route	Exposure duration/ frequency	System	NOAEL (mg Be/kg/day)	LOAEL (Effect) Less Serious (mg Be/kg/day)	LOAEL (Effect) Serious (mg Be/kg/day)	Reference	Form
ACUTE EXPOSURE									
Death									
1	Rat	(NR)	1 d			120 (LD_{50})		Lanchow 1978	$BeSO_4$
2	Rat	(NR)	1 d			200 (LD_{50})		Kimmerle 1966	$BeCl_2$
3	Rat	(G)	1 d			18.8 (LD_{50})		Venugopal and Luckey 1977	BeF_2
4	Rat	(G)	1 d			18.3 (LD_{50})		Venugopal and Luckey 1977	BeO, BeF_2
5	Mouse	(GW)	1 d			140 (LD_{50})		Ashby et al. 1990	$BeSO_4$
6	Mouse	(G)	1 d			19.1 (LD_{50})		Venugopal and Luckey 1977	BeF_2
7	Mouse	(NR)	1 d			18-20 (LD_{50})		Lanchow 1978	BeF_2
8	Mouse	(NR)	1 d			18-20 (LD_{50})		Kimmerle 1966	BeF_2
INTERMEDIATE EXPOSURE									
Systemic									
9	Rat	(F)	24-28 d	Musc/skel		10 (rickets)		Guyatt et al. 1933	$BeCo_3$. $Be(OH)_2$
10	Rat	(F)	13-42 d	Musc/skel		121 (rickets)		Jacobson 1933	$BeCo_3$.

									$Be(OH)_2$
2									
CHRONIC EXPOSURE									
Systemic									
11	Rat	(F)	2 yr	Resp	31.0			Morgareidge et al. 1975	$BeSO_4$
				Cardio	31.0				
				Gastro	31.0				
				Hemato	31.0				
				Musc/Skel	31.0				
				Hepatic	31.0				
				Renal	31.0				
				Derm/oc	31.0				
12	Rat	(W)	3.2 yr	Resp	0.7			Schroeder and Mitchener 1975a	$BeSO_4$
				Cardio	0.7				
				Hemato	0.7				
				Hepatic	0.7				
				Renal		0.7 (glucosuria)			
13	Mouse	(W)	898 d	Resp	0.95			Schroeder and Mitchener 1975b	$BeSO_4$
				Cardio	0.95				
				Hemato	0.95				
				Hepatic	0.95				
				Renal	0.95				

[a] The number corresponds to entries in Figure 2-2.
Be = beryllium; $BeCl_2$ = beryllium chloride; $BeCO_3.Be(OH)_2$ = beryllium carbonate (basic); BeF_2 = beryllium fluoride; BeO = beryllium oxide; BeF_2 = beryllium oxyfluoride; $BeSO_4$ = beryllium sulfate; Cardio = cardiovascular; d = day(s); Derm/oc = dermal/ocular; (F) = feed; (G) = gavage; Gastro = gastrointestinal; (GW) = gavage in water; Hemato = hematological; LD_{50} = Lethal dose, 50% kill; LOAEL = Lowest-observed-

adverse-effect level; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; (NR) = not reported; Resp = respiratory; (W) = drinking water; yr = year(s)

TABLE 2-2. Levels of Significant Exposure to Beryllium - Oral

TABLE 2-2. Levels of Significant Exposure to Beryllium - Oral

FIGURE 2-2. Levels of Significant Exposure to Beryllium - Oral

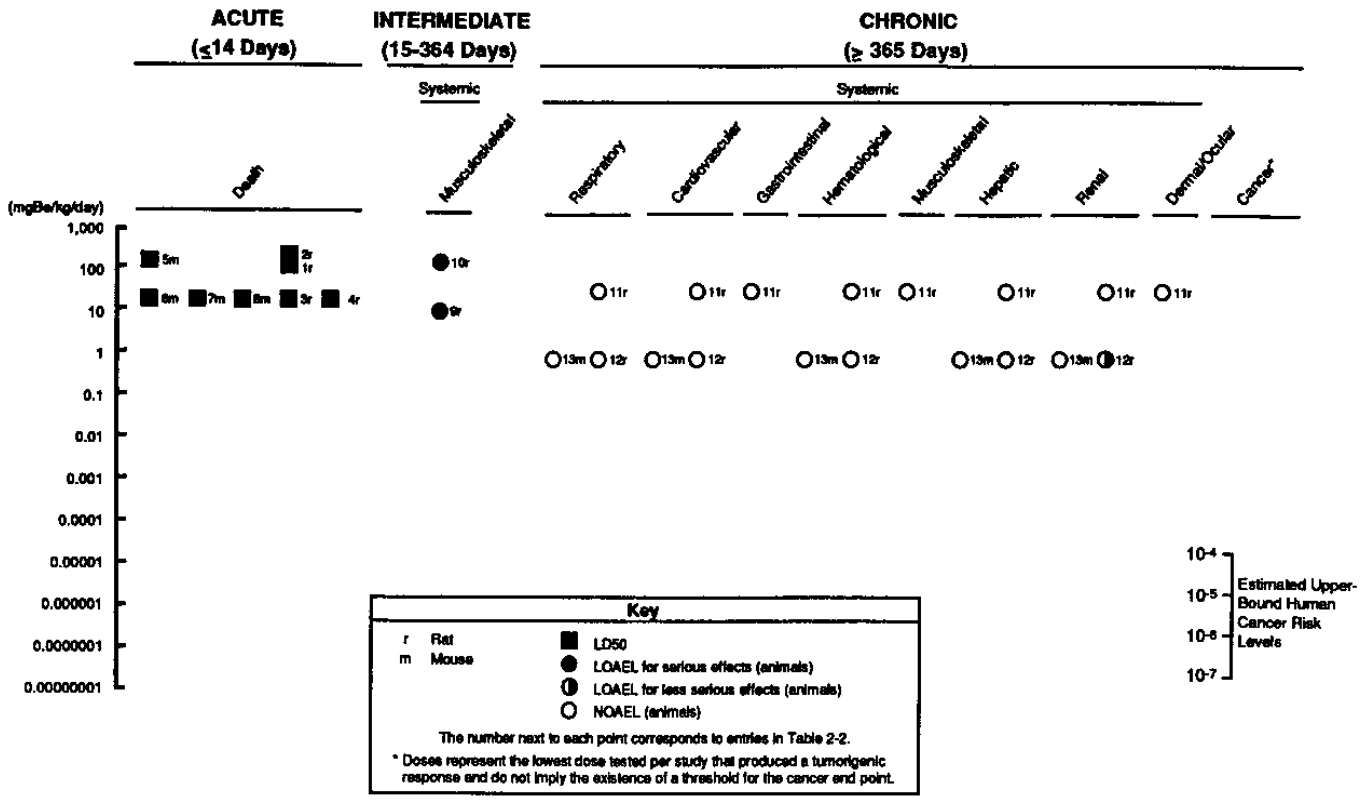


FIGURE 2-2. Levels of Significant Exposure to Beryllium - Oral

No microscopic lung abnormalities were observed 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 0.95 mg beryllium/kg/day as beryllium sulfate in the drinking water did not cause lung effects in rats and mice, respectively (Shroeder and Mitchener 1975a, 1975b).

Cardiovascular Effects. Data regarding cardiovascular effects in animals after oral exposure to beryllium or its compounds are limited. Rats exposed to ≤31 mg beryllium/kg/day as beryllium sulfate in the diet did not have microscopic abnormalities in the heart or aorta (Morgareidge et al. 1975). Histological examination revealed that chronic exposure to 0.7 or 0.95 mg beryllium/kg/day as beryllium sulfate in the drinking water did not cause cardiac effects in rats or mice, respectively (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. One study was located regarding gastrointestinal effects in animals after oral exposure to beryllium sulfate. Histological examination of rats exposed to ≤31 mg

beryllium/kg/day as beryllium sulfate in the diet for 2 years revealed no microscopic abnormalities of the stomach, small intestine, or large intestine (Morgareidge et al. 1975).

Hematological Effects. One study was located regarding hematological effects in animals after oral exposure to beryllium sulfate. Histological examination of rats exposed to ≤31 mg beryllium/kg/day as beryllium sulfate in the diet established no evidence of microscopic abnormalities of the spleen and bone marrow (Morgareidge et al. 1975). Other hematological indices were not measured.

Musculoskeletal Effects. Early studies indicate that rats fed large amounts of beryllium carbonate in the diet developed rickets. Rats fed a diet supplemented with 10, 20, 40, 80, 160, and 240 mg beryllium/kg/day as beryllium carbonate developed rickets even at the lowest dose (Guyatt et al. 1933). The severity in the fragility of the bones increased with increasing concentrations of beryllium. Young rats fed a diet providing 242 or 121 mg beryllium/kg/day as beryllium carbonate developed several weakened bones, an effect closely resembling rickets or osteoporosis (Jacobson 1933). When rats were fed a diet in which beryllium carbonate (concentrations not specified) was substituted for calcium carbonate, lesions developed, similar to those described above. Exposure to ≤31 mg beryllium/kg/day as beryllium sulfate for 2 years did not cause morphological abnormalities in the muscle tissue of rats (Morgareidge et al. 1975). Bones were not examined in this study.

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.

Rats fed ≤31 mg beryllium/kg/day as beryllium sulfate for 2 years did not develop morphological abnormalities of the liver or changes in liver weight (Morgareidge et al. 1975). 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 the kidney tissue; however, kidney weight increased slightly (Morgareidge et al. 1975). Morphological alternations of the kidney were not observed in either sex of rats or mice exposed to 0.7-0.95 mg beryllium/kg/day as beryllium sulfate, respectively (Schroeder and Mitchener 1975a, 1975b). Female rats, however, developed a transient glucosuria (Schroeder and Mitchener 1975a).

Dermal/Ocular Effects. Information regarding dermal/ocular effects in animals after oral exposure to beryllium or compounds is limited. Histological examination of the eyes and skin of rats exposed to ≤31 mg beryllium/kg/day as beryllium sulfate in the diet for 2 years did not indicate morphological changes (Morgareidge et al. 1975).

2.2.2.3 Immunological 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 or rats chronically exposed to ≤31 mg beryllium/kg/day as beryllium sulfate in the diet (Morgareidge et al. 1975). More sensitive tests of the immune function were not conducted.

2.2.2.4 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). This information is insufficient to conclude that beryllium does not cause neurological effects because more sensitive neurological or neurobebavioral tests were not performed.

2.2.2.5 Developmental Effects

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

2.2.2.6 Reproductive Effects

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

Only one study was located regarding reproductive effects in animals after oral exposure to beryllium. 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.

2.2.2.7 Genotoxic Effects

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

Only one study was located regarding the genotoxicity of beryllium in animals after oral exposure to beryllium. No increased incidence of micronuclei in polychromatic erythrocytes was observed in mice given 71 or 115 mg beryllium/kg beryllium sulfate tetrahydrate by gavage (Ashby et al. 1990).

Other genotoxicity studies are discussed in Section 2.4.

2.2.2.8 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. A carcinogenic response was suggested by a significantly increased incidence of reticulum cell sarcoma in the lungs of male rats exposed to 0.3 and 2.8 mg beryllium/kg/day as beryllium sulfate in the diet for 2 years (Morgareidge et al. 1975). However, no increased incidence was observed in the high dose male rats (31 mg beryllium/kg/day) or in female rats. The incidence of reticulum cell sarcomas in the lungs of the male rats was as follows: 10 of 49 in controls, 17 of 35 in the low dose group, 16 of 40 in the intermediate dose group, and 12 of 39 in the high dose group. No significantly increased incidence of tumors was observed in rats or mice exposed chronically to 0.7-0.95 mg beryllium/kg/day, respectively, as beryllium sulfate in the drinking water, although the incidence of total tumors in treated male rats (9 of 33) was slightly increased, compared to controls (4 of 26) (Schroeder and Mitchener 1975a, 1975b). Although these results do not provide evidence that beryllium is carcinogenic via oral exposure, beryllium is carcinogenic via inhalation exposure. An oral q_1^* of 4.3 $(mg/kg/day)^{-1}$ for beryllium was derived from the male rat data in the study by Schroeder and Mitchener (1975a) (IRIS 1990). The doses associated with individual lifetime upper-bound risks of 10^{-4} to 10^{-7} are $2.3x10^{-5}$ to $2.3x10^{-8}$ mg/kg/day and are plotted in Figure 2-2.

2.2.3 Dermal Exposure

2.2.3.1 Death

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

2.2.3.2 Systemic Effects

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

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

Guinea pigs were sensitized with 12 biweekly injections of 0.0005 mg beryllium sulfate tetrahydrate intradermally (Marx and Burrell 1973). Sensitization was confirmed by patch testing with beryllium sulfate, beryllium fluoride, or beryllium oxide. Histological examinations, after positive reactions to the patch test, established evidence of interstitial fibrosis of the alveolar walls, inflammation, necrosis, emphysema, and focal granulomata, which consisted of histocytes, plasma cells, and lymphocytes, within the alveolar spaces or around the vascular system. The LOAEL value for respiratory effects is recorded in Table 2-3.

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

Guinea pigs were sensitized with 12 biweekly injection of 0.0005 mg beryllium sulfate tetrahydrate

intradermally (Marx and Burrell 1973). Sensitization was confirmed by patch testing with beryllium sulfate, beryllium fluoride, or beryllium oxide. The guinea pigs developed a focal hematopoietic tissue hyperplasia and follicular hyperplasia, as indicated by histopathology. Small granulomata and deposits of hemosiderin were observed occasionally in the spleen. The LOAEL value for hematological effects is recorded in Table 2-3.

Dermal/Ocular Effects. Dermatological abnormalities due to beryllium exposure were reported in the case histories of 42 workers (VanOrdstrand et al. 1945). The dermatological manifestations were characterized as edematous, papulovesicular dermatitis. Ulceration occurred only after the skin was 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 2.2.3.3).

Guinea pigs sensitized with 12 biweekly injections of 0.0005 mg beryllium sulfate intradermally were exposed dermally to 0.00025 mg beryllium sulfate, 0.00048 beryllium fluoride, or 0.0018 beryllium oxide (Marx and Burrell 1973). The reaction consisted of a focal inflammatory infiltrate of foreign body giant cells, histocytes, plasma cells, eosinophils, and lymphocytes. The reaction began at =6-8 hours, peaked at 72 hours, and resolved by 3 weeks. The different compounds increased the severity of the reactions in the following order: beryllium fluoride > beryllium sulfate > beryllium oxide; the differences are based on the solubilities of the salts. Similar reactions were found in guinea pigs sensitized by dermal application of two drops of a 0.4 M solution of beryllium fluoride in methyl cellosolve/water/Tween 80 or by intracutaneous injection of 0.1 mL of a 0.01 M solution of beryllium fluoride in water (Belman 1969). The reactions were elicited by subsequent testing with beryllium fluoride or beryllium chloride. The LOAEL values for dermal/ocular effects in guinea pigs are recorded in Table 2-3.

2.2.3.3 Immunological 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.

TABLE 2-3. Levels of Significant Exposure to Beryllium - Dermal

Species	Exposure duration/ frequency	System	NOAEL	LOAEL (effect) Less serious	Serious	Reference	Form
ACUTE EXPOSURE							
Systemic							
Gn pig	1 d	Resp			0.25 µg (emphysema, inflammation necrosis)	Marx and Burrell 1973	$BeSO_4$
		Hemato	0.25 µg	(hyperplasia of hematopoietic tissue of spleen)			
		Derm/oc	0.25 µg	(skin delayed type hypersensitive reaction)			
Gn pig	1 x	Derm/oc	0.1 M	(delayed type hypersensitive reaction)		Belman 1969	$BeCl_2$
Gn pig	1 x	Derm/oc	0.02 M	(delayed type hypersensitive reaction)		Belman 1969	BeF_2
Immunological							
Human	48 hr		0.019 mg Be/mL	(allergic		Curtis 1951	BeF

			dermatitis)		
Human	48 hr	0.19 mg Be/mL	(allergic dermatitis)	Curtis 1951	$BeSO_4$
Human	48 hr	0.19 mg Be/mL	(allergic dermatitis)	Curtis 1951	$BeCl_2$
Human	48 hr	0.19 mg Be/mL	(allergic dermatitis)	Curtis 1951	$Be(No_3)_3$
Gn pig	1 x	0.02 M	(delayed type hypersensitive reaction)	Belman 1969	BeF_2
Gn pig	1 x	0.1 M	(delayed type hypersensitive reaction)	Belman 1969	$BeCl_2$
INTERMEDIATE EXPOSURE					
Immunological					
Gn pig	24 wk 1x/2wk	0.0005 mg	(increased T-cell activity)	Marx and Burrell 1973	$BeSO_4$

$BeCl_2$ = beryllium chloride; BeF_2 = Beryllium fluoride; $Be(NO_3)_3$ = beryllium nitrate; $BeSO_4$ = beryllium sulfate; d = day(s); Derm/oc = dermal/ocular; Gn pig = guinea pig; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-effect level; M = molar; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s); x = time

TABLE 2-3. Levels of Significant Exposure to Beryllium - Dermal

TABLE 2-3. Levels of Significant Exposure to Beryllium - Dermal

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). The LOAEL values for immunological effects in each species and duration category are recorded in Table 2-3.

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

2.2.3.4 Neurological Effects

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

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

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Beryllium compounds are absorbed primarily through the lungs, but sufficient information to determine the rate and extent of absorption were 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 from 2 to 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 four-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, steadystate concentrations in the blood were reached after 8-12 hours of exposure (Stiefel et al. 1980).

2.3.1.2 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. 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 $\leq$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 $\leq$0.9% in the 0.019 mg beryllium/kg/day group and $\leq$0.2% in the 0.190 mg beryllium/kg/day group. Rats exposed to $\leq$31 mg beryllium/kg/day as beryllium sulfate tetrahydrate 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).

2.3.1.3 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 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 poor dermal absorption.

2.3.2 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.

2.3.2.1 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 ç-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 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 a. 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 500°C had higher beryllium concentrations in the extrapulmonary tissue, principally the liver and skeleton, than dogs exposed to beryllium oxide calcined at 1000°C, due to the greater solubility of the 500°C 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 ç-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.

2.3.2.2 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 distribution 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 exposed to 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).

2.3.2.3 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 2.3.1.3).

2.3.3 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).

2.3.4 Excretion

2.3.4.1 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

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°C or 1,000°C 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°C 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-time of 54 days. The long- term component accounted for 41% of the initial lung burden and had a half-time 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°C was described by a single-component negative exponential function with a half-time 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- times were 64 days for 500°C calcined beryllium oxide and 240 days for 1,000°C calcined beryllium oxide. After exposure to beryllium oxide calcined at 500°C, cumulative excretion of beryllium (as % of initial lung burden) was 24% at 32 days, 19% at 64 days, and 42% at 180 days; excretion in the feces (as % total excreted) was 59% at 32 days, 45% at 64 days, and 47% at 180 days; and excretion in the urine (as % total excreted) was 41% at 32 days, 55% at 64 days, and 53% at 180 days. After exposure to beryllium oxide calcined at 1,000°C, cumulative excretion of beryllium was 18% at 32 days, 21% at 64 days, and 19% at 180 days; excretion in the feces was 68% at 32 days, 67% at 64 days, and 54% at 180 days; and excretion in the urine was 32% at 32 days, 33% at 64 days, and 46% at 180 days. Thus fecal excretion predominated at early times after exposure to either beryllium oxide aerosols, and at all times for 1,000°C calcined beryllium oxide. Dogs exposed to beryllium oxide calcined at 500°C 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°C was cleared more rapidly than beryllium oxide calcined at 1,000°C. 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 mechanical 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.

2.3.4.2 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).

2.3.4.3 Dermal Exposure

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

2.4 RELEVANCE TO PUBLIC HEALTH

Human exposure to beryllium and its compounds occurs primarily in the workplace. High concentration occupational exposure to soluble beryllium compounds can result in acute beryllium pneumonitis, while occupational exposure to soluble or insoluble beryllium compounds can result in chronic beryllium disease. The number of cases of these diseases has declined since 1950 when the OSHA time- weighted average permissible exposure limit of 0.002 mg/m^3 became effective. The general population can be exposed to beryllium through inhalation of air, consumption of food and water, and skin contact with water or soil that contains beryllium. The average concentration of beryllium in ambient air in the United States is 0.03 ng/m^3, but the median concentration in cities is 0.2 ng/m^3, due primarily to burning of coal and fuel oil (see Section 5.2). The average concentration of beryllium in drinking water samples that were found to contain it was 190 ng/L. The mean concentration in soil in the United States is 0.6 mg/kg. The concentration of beryllium in these media may be higher at or near hazardous waste sites. The inhalation route is of greatest concern for systemic effects because beryllium and its compounds are poorly absorbed after oral and dermal exposure. However, skin contact can cause allergic reactions.

The respiratory tract in humans and animals is the primary target of inhalation exposure to beryllium and its compounds. Inhalation exposure to beryllium has been associated with lung cancer in animals, and beryllium is a suspect carcinogen in humans. Inhalation of some forms of beryllium can cause obstructive and restrictive diseases of the lung, known as chronic beryllium disease (berylliosis); inhalation of high concentrations can causes chemical pneumonitis. The development of chronic beryllium disease appears to involve cell-mediated immune responses that are genetically regulated. The prevalence of nonneoplastic respiratory disease due to beryllium exposure in the general population is unknown. A prevalence of respiratory disease of 0.4-4.9% in exposed workers has been found. The heart is an indirect target organ for beryllium in humans, monkeys, and dogs, with effects probably secondary to the respiratory effects. Renal effects have been observed in animals inhaling low concentrations of beryllium oxide, as indicated by proteinuria.

been observed in animals inhaling low concentrations of beryllium oxide, as indicated by proteinuria. Lethal concentrations also caused kidney necrosis in monkeys. Hepatic effects were not observed in humans or animals, unless the concentrations were high enough to be lethal. Similarly, high dietary concentrations caused skeletal effects resembling rickets or osteoporosis in rats. Macrocytic anemia was also observed in rabbits and dogs exposed to beryllium oxide. Dermal exposure causes the formation of skin granulomas in the intact skin of sensitized individuals. The ability of the general population to become sensitized to beryllium and develop contact dermatitis and skin granulomas is unknown, although in one study 8 of 16 controls were able to become sensitized (Curtis 1951). The immune system is involved in the granulomatous reactions in the skin and lungs of sensitive individuals. Humans and animals exposed to beryllium or its compounds had increased T-cell activity and histological abnormalities of the lymph nodes and spleen.

Death. No studies were located regarding death in humans after oral or dermal exposure to beryllium or its compounds. Death has resulted from respiratory distress caused by occupational exposure to beryllium. Retrospective cohort studies report that workers exposed to beryllium have higher mortality rates, than the general population, due to nonneoplastic respiratory disease (Infante et al. 1980; Wagoner et al. 1980). Acute lethality data are available for a number of species and compounds. The lethality data in animals do not indicate much species variation. The lethality of beryllium compounds varies with the form and solubility of the compound and the route of exposure. Soluble compounds are better absorbed from the lung, which accounts for lower LC_{50} values for soluble beryllium compounds. Beryllium compounds are less toxic via oral exposure, due to the formation of beryllium phosphate precipitates which cannot penetrate the gastrointestinal tract. Beryllium fluoride is highly toxic, mainly due to the fluoride ion. The concentrations of beryllium likely to cause death in humans are not known. Humans are likely to be exposed to beryllium and its compounds since beryllium and its compounds can exist in the air as particulates, fumes, or mists. Oral and dermal exposure to beryllium and its compounds may occur in humans via the consumption or use of drinking water in which the soluble forms of beryllium seeped from a waste site into the groundwater. Moreover, these compounds may be present in the soil at hazardous waste sites.

Systemic Effects

Respiratory Effects. The lung appears to be the main target organ for beryllium toxicity in humans and animals. Acute exposure to high concentrations of the more soluble compounds of beryllium can cause chemical pneumonitis (VanOrdstrand et al. 1945), the symptoms of which include cough, substernal burning, shortness of breath, anorexia, and increasing fatigue. Exposure to lower concentrations of less soluble beryllium compounds causes chronic beryllium disease during which granulomas, fibrosis, and emphysema are present in the lung (Cullen et al. 1987; Hardy and Tabershaw 1946). Chronic beryllium disease in workers is associated with reductions of the vital lung capacity, total lung capacity, forced expiratory volume, and diffusion capacity of the lung (Freiman and Hardy 1970; Johnson 1983). Other effects associated with chronic beryllium disease include increased alveolar-arterial oxygen tension difference and arterial hypoxemia (Andrews et al. 1969). Chronic beryllium disease appears to be characterized by a marked proliferative response of bronchoalveolar cells to beryllium (Rossman et al. 1988). The prevalence of chronic beryllium disease in beryllium workers has been found to range from 0.4% to 4.9% (Eisenbud and Lisson 1983).

In animals, acute inhalation exposure to beryllium sulfate or low-fired beryllium oxide causes

proliferative changes in the lung, accompanied by cellular infiltrations consisting mainly of macrophages and polymorphonuclear leukocytes (Hart et al. 1984; Sendelbach et al. 1986). Acute chemical pneumonitis also has been observed in animals after acute inhalation exposure to soluble beryllium salts (Stokinger et al. 1950). Acute exposure to beryllium- containing dusts or low or high fired beryllium oxide may cause a chronic, toxic lung disease (Robinson et al. 1968; Sanders et al. 1975). Slight differences in response to low-fired versus high-fired beryllium oxide may be related to the differences in the solubility of the compound. Low-fired beryllium oxide is more soluble than high-fired beryllium oxide and causes effects similar to those caused by soluble beryllium salts. The acidity of the soluble beryllium salt aerosols contributes to their toxicity. Rats exposed to beryllium sulfate for 1 hour (Sendelbach et al. 1986) or to metallic beryllium for 50 minutes (Haley et al. 1990) developed lung lesions that became progressively worse with time, indicating that the effects of beryllium were latent. Overt effects were not observed until quite some time after exposure had ended. Rats exposed to beryllium sulfate for intermediate durations had severe lesions in the lung (Schepers et al. 1957). 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°C 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, 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 ($H\text{-}2^a$ haplotype) mice received intratracheal injections of beryllium sulfate or beryllium oxide calcined at 550°C or 1100°C (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).

In an oral study of intermediate duration, rats exposed to beryllium nitrate in the diet had thickening of the alveolar epithelium with areas of necrosis in the lung (Goel et al. 1980). However, it is possible that the lung effects were due to inhalation of beryllium nitrate particulates into the lungs during feeding. Respiratory effects due to oral exposure to beryllium are probably of little concern to humans, since humans generally do not aspirate food into the lungs while eating. No studies were located regarding respiratory effects in humans or animals after dermal exposure to beryllium or its compounds.

Beryllium may cause respiratory effects in humans exposed occupationally; however, the number of cases of acute and chronic beryllium disease has declined markedly over the past 40 plus years since the OSHA standard of 0.002 mg/m^3 has been in effect, with new cases being reported generally only in instances where the OSHA standard has been exceeded. 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) (see Chapter 5) are lower than occupational levels. It is unknown whether exposure levels near hazardous waste sites are high enough to cause respiratory disease.

Cardiovascular Effects. Exposure to beryllium in the workplace has resulted occasionally in right atrial and ventricular hypertrophy (Hardy and Tabershaw 1946). In monkeys, acute exposure to $\leq$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 caused heart enlargement (Schepers 1964). Inhalation exposure to beryllium oxide for longer durations caused decreased arterial oxygen tension in dogs (Stokinger et al. 1950). The cardiovascular effects of exposure to beryllium compounds may represent compensatory increases in cardiac musculature due to the fibrosis or emphysema that occurs when beryllium is inhaled. Enlargement of the heart occurs in order to compensate for the lack of oxygenated blood to the body, as noted by the decreased arterial oxygen tension in dogs. Chronic oral exposure to beryllium did not cause cardiac effects in rats or mice (Morgareidge et al. 1975; Schroeder and Mitchener 1975a, 1975b). While secondary cardiovascular effects may be of concern to people occupationally exposed in cases where the OSHA standard of 0.002 mg/m^3 has been exceeded, exposure levels in the environment are not likely to be high enough to cause these effects. Whether levels of beryllium in the air at or near hazardous waste sites are high enough to cause cardiovascular effects is not known. The risk can only be evaluated on a site- by site basis.

Hematological Effects. Case reports of humans exposed to beryllium did not indicate hematological alterations (Johnson 1983; VanOrdstrand et al. 1945). In rabbits exposed to beryllium oxide, erythrocyte counts decreased progressively as the duration of exposure increased, causing macrocytic anemia (Hall et al. 1950). Macrocytic anemia was also observed in dogs exposed to beryllium oxide for 40 days and in rats, rabbits, and dogs exposed to beryllium sulfate for 100 days

(Stokinger et al. 1950). Leukocytosis was also observed in animals exposed to beryllium compounds via inhalation. Whether hematological effects will occur in humans exposed under any exposure scenario cannot be predicted from the available information.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation, oral, or dermal exposure to beryllium or its compounds. However, animal data indicate that beryllium affects the skeletal system. Rats fed a diet in which beryllium carbonate was substituted for calcium carbonate developed rickets and osteoporosis (Guyatt et al. 1933; Jacobson 1933). Beryllium may substitute for calcium in the bone when the diet is calcium deficient, resulting in rickets or osteoporosis. Beryllium fed as a part of the regular diet to rats did not cause malformations of muscle tissue (Morgareidge et al. 1975). Whether skeletal or muscular effects will occur in humans exposed under any exposure scenario cannot be predicted from the available information.

Hepatic Effects. Information regarding hepatic effects in humans after exposure to beryllium or its compounds is limited to case histories of workers in a beryllium plant (Hardy and Tabershaw 1946). Autopsies revealed subacute, progressive focal and diffuse hepatic necrosis. One study was located regarding the accidental exposure of 25 persons to beryllium dust (Zorn et al. 1986). No hepatic effects were observed, as indicated by analysis of serum levels of SGOT (serum glutamic oxaloacetic transaminase) and SGPT (serum glutamic pyruvic transaminase).

Acute exposure to beryllium hydrogen phosphate and beryllium fluoride caused hepatocyte degeneration, sinusoid degeneration, and Kupffer cell mobilization in monkeys, as indicated by histopathology (Schepers 1964). Hepatotoxic effects were observed only in monkeys exposed to lethal concentrations of the most soluble beryllium compounds. Acute exposure to beryllium oxide via inhalation did not cause liver lesions in rats, rabbits, hamsters, or guinea pigs (Hall et al. 1950; Sanders et al. 1975). No hepatic effects were observed in rabbits exposed to beryllium sulfate via inhalation (Stokinger et al. 1950). Dogs exposed to beryllium oxide for intermediate durations had decreased serum protein levels, which may indicate altered hepatic metabolism (Hall et al. 1950). Conversely, dogs and rats exposed to beryllium sulfate had increased serum albumin and globulin levels (Stokinger et al. 1950). As indicated by histopathology and enzyme analysis, exposure to beryllium ores for 6-23 months did not cause liver effects in rats, hamsters, and monkeys (Wagner et al. 1969). Increased serum cholesterol levels in rats have been associated with chronic exposure to beryllium sulfate in drinking water (Shroeder and Mitchener 1975a). Hence, it appears that hepatic effects due to beryllium exposure occur only when exposure levels are lethal. Soluble forms of beryllium are more likely to cause hepatic effects in animals than insoluble forms are. Beryllium concentrations in the workplace or in air and water in the ambient environment or near or at hazardous waste sites are not likely to be high enough to cause hepatic effects in humans.

Renal Effects. Information regarding renal effects in humans after exposure to beryllium or its compounds is limited to case histories of workers in a beryllium plant. Autopsies revealed marked hyperemia of the kidney (Hardy and Tabershaw 1946). Kidney stones had been reported 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, but, although suggestive, cannot be absolutely attributed to beryllium disease (Stoeckle et al. 1969). Studies indicate that renal effects in animals exposed to beryllium or its compounds are rare, except at lethal concentrations. In monkeys, lethal

concentrations of beryllium hydrogen phosphate, beryllium sulfate, or beryllium fluoride caused glomerular damage, tubule degeneration, and slight focal nephron degeneration of the kidney, as indicated by histopathology (Schepers 1964). Acute exposure to beryllium oxide did not cause renal effects in rats, rabbits, hamsters, or guinea pigs (Hall et al. 1950; Sanders et al. 1975; Stokinger et al. 1950). Prolonged inhalation exposure to beryllium oxide or beryllium sulfate caused proteinuria in rats and dogs (Hall et al. 1950; Stokinger et al. 1950). Liver lesions were not observed in rats, hamsters, and monkeys exposed to beryllium oxide for 6-23 months (Wagner et al. 1969). Chronic exposure to beryllium sulfate in drinking water caused glucosuria in female rats (Schroeder and Mitchener 1975a). Current beryllium concentrations in the workplace or in the air or water in the ambient environment or at or near hazardous waste sites are probably not high enough to cause renal effects in humans.

Dermal/Ocular Effects. According to a case study, twins occupationally exposed to beryllium had reduced tear secretions and granulomas of the skin, probably from dermal and ocular contact with the compound (McConnochie et al. 1988). Examination of 42 individuals exposed dermally to beryllium revealed lesions of the skin, characterized as edematous, papulovesicular dermatitis (VanOrdstrand et al. 1945). Conjunctivitis occurred only after splash burn or contact dermatitis of the upper face. Ulcers occurred only after the skin was abraded. Similar lesions, resulting from cuts and abrasions sustained at work, were observed in 26 employees of the beryllium industry (Williams et al. 1987).

Guinea pigs sensitized to beryllium dermally or intradermally with beryllium sulfate and fluoride develop allergic reactions when challenged with beryllium compounds (Belman 1969; Marx and Burrell 1973).

Available studies indicate that dermal exposure to soluble beryllium compounds causes skin lesions in sensitized humans and animals. The lesions are generally severe if the skin was abraded before exposure. Dermal exposure to soluble beryllium compounds in the workplace or at hazardous waste sites may cause adverse dermatological effects in sensitized humans.

Other Systemic Effects. Effects of beryllium exposure on the adrenal gland have been observed in a human and in animals. Autopsy of a worker exposed to beryllium in a fluorescent lamp manufacturing plant revealed marked hyperemia and cellular vacuolization of the adrenal gland (Hardy and Tabershaw 1946).

Adrenal hypoplasia and hypotrophy in monkeys was caused by inhalation exposure to lethal concentrations of beryllium (Schepers 1964). Similarly, adrenal weight decreased in rats and hamsters exposed to 1-100 mg beryllium/m^3 as beryllium sulfate for 30-180 minutes (Schepers et al. 1957). The exact exposure levels and durations were not specified. Other tests for adrenal functions, such as glucocorticoid levels, are not reported in the available literature.

Exposure to beryllium under current occupational conditions or in the air or water in the ambient environment or at or near hazardous waste sites will probably not cause adrenal effects in humans.

Body weight changes have been observed in humans and animals exposed to beryllium. Data from 170 case histories of beryllium workers indicate that weight loss was common among individuals with a history of respiratory disease (VanOrdstrand et al. 1945).

Available studies report severe weight losses among animals exposed to beryllium via inhalation for

acute, intermediate, and chronic durations. Body weight decreased as much as 34% in monkeys exposed to beryllium fluoride, beryllium hydrogen phosphate, or beryllium sulfate (Schepers 1964). Decreased food consumption alone could not account for the weight loss. Inhalation exposure to beryllium oxide and beryllium sulfate for intermediate durations caused severely decreased body weight in cats, dogs, and monkeys (Hall et al. 1950; Stokinger et al. 1950). Body weight losses in these species reportedly were more severe than in rats, mice, or hamsters (Hall et al. 1950; Stokinger et al. 1950; Wagner et al. 1969). Body weight losses were greater in female rats exposed to 0.034 mg beryllium/m^3 as beryllium sulfate for 72 weeks, than in male rats (Reeves et al. 1967). It is not known whether beryllium concentrations in the air or water at or near hazardous waste sites are high enough to cause body weight changes in humans.

Immunological Effects. Acute exposure of humans to beryllium did not affect the immune system, as indicated by the measurement of immune cell secretions (Zorn et al. 1986). However, exposure to beryllium may cause granulomatous lesions in the lung (Cullen et al. 1987) and mediastinal lymph nodes (Johnson 1983) due to cell-mediated immune responses to beryllium (Rossman et al. 1988; Saltini et al. 1989). These granulomas are an accumulation and proliferation of mononuclear cells. The cells that proliferate in response to beryllium exposure have been shown to be CD4+ lymphocytes (Saltini et al. 1989). This response can be blocked by antibodies to HLA Class II molecules or by antibodies to the IL-2 receptor. The immune component of chronic beryllium disease has been examined via the lymphocyte proliferation test for sensitivity to beryllium and for the ratio of T-helper cells to T- suppressor cells (McConnochie et al. 1988) These tests suggested that proliferation of lymphocytes in vitro with beryllium and increased numbers of T-helper cells are closely related (Cullen et al. 1987). As discussed in the subsection on respiratory effects above, animal models of chronic beryllium disease have increased our understanding about the potential pathogenesis of chronic beryllium disease in humans. Studies in which guinea pigs (Barna et al. 1981, 1984) and mice (Huang et al. 1992) were injected intratracheally with beryllium oxide or beryllium sulfate have confirmed that beryllium-induced granulomatous lung disease involves cell-mediated immune responses, and suggested that the immune mechanisms are genetically controlled in these species. Genetic differences in immune responses may explain the low prevalence of chronic beryllium disease in humans.

Hypersensitivity to beryllium observed in humans and guinea pigs has been attributed to the formation of a beryllium-protein complex that is an antigen in vivo, provoking the cell-mediated immune response. Interaction of beryllium with the membrane of the lymphocyte has been observed in humans and guinea pigs (Skilleter and Price 1984). Mitogenic effects of beryllium salts have been observed in mouse spleen cells in vitro, and may result from the direct interaction of beryllium with the lymphocyte membrane (Price and Skilleter 1985, 1986).

Hyperplasia of the lymph nodes has been observed in dogs (Haley et al. 1989) and monkeys (Schepers 1964) after acute inhalation exposure to beryllium oxide, beryllium sulfate, or beryllium fluoride.

Beryllium exposure may also cause a delayed, hypersensitive reaction in skin. Skin granulomas biopsied from workers exposed to beryllium had the same mononuclear infiltrates as detected in the lung, with measurable quantities of beryllium in the tissue (Williams et al. 1987). Sensitized guinea pigs also developed granulomatous lesions and allergic reactions on the skin after dermal challenge with beryllium salts (Belman 1969; Marx and Burrell 1973).

Thus, chronic beryllium disease and beryllium-induced skin granuloma and allergy involves cell-mediated immune response mechanisms that appear to be genetically regulated in sensitive individuals. It is possible, therefore, that exposure to beryllium in the workplace, in the ambient environment, or at or near hazardous waste sites may cause sensitization in humans.

Neurological Effects. No studies were located regarding neurological effects in humans after inhalation, oral, or dermal exposure to beryllium or its compounds. Histological examination of the brain, nerve, and spinal cord did not reveal any lesions in rats exposed to ≤31 mg beryllium/kg/day as beryllium sulfate tetrahydrate in the diet for 2 years (Morgareidge et al. 1975). Since beryllium is poorly absorbed through the gastrointestinal tract and via dermal contact, it is unlikely that exposure to beryllium by these routes in any setting would cause neurological effects in humans. Since neurological effects have not been documented in humans exposed to beryllium occupationally, it is unlikely that inhalation exposure of humans in the workplace, in ambient air, or at or near hazardous waste sites would result in neurological effects.

Developmental Effects. No studies were located regarding developmental effects in humans or animals after inhalation, oral, or dermal exposure to beryllium or its compounds.

Intratracheal injection of rats with 50 mg beryllium/kg beryllium chloride or beryllium oxide on days 3, 5, 8, and 20 of gestation resulted in increased fetal mortality on day 5 with the beryllium chloride treatment and on days 3 and 5 with the beryllium oxide treatment (Selivanova and Savinova 1986). Fetal weight was decreased on day 3 after treatment with either compound. There was an increased percentage of pups with internal abnormalities in rats treated with beryllium chloride on days 3 and 5 and with beryllium oxide on days 3, 5, and 8. There were no differences in the number of live births per dam or in fetal length. Beryllium nitrate injected intravenously into rats on days 1, 11, 12, 13, and 15 of gestation produced increased fetal resorption on day 11 (Mathur et al. 1987). Pups delivered to rats given beryllium nitrate on gestation days 1, 12, 13, 15, and 17 died 2-3 days after delivery. Other studies in which beryllium salts were injected into pregnant mice indicate 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). The results of these intratracheal and injection studies raise a concern that beryllium causes fetotoxic and developmental effects, but whether developmental effects would occur in humans from exposure to beryllium at the workplace, in the environment, or at or near hazardous waste sites cannot be determined from the available information.

Reproductive Effects. No studies were located regarding reproductive effects in humans after inhalation, oral, or dermal 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. Rats given ≤31 mg beryllium/kg/day as beryllium sulfate tetrahydrate in the diet had no lesions of the prostate, seminal vesicles, epididymis, ovaries, uterus, or oviducts, as indicated by histopathology (Morgareidge et al. 1975). It is not known whether exposure to beryllium at the workplace, in the environment, or at or near hazardous waste sites may cause reproductive effects in humans; however, negative results in animal studies indicate that the effects are not likely to occur.

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 tetrahydrate corresponding to 80% and 50% of the LD_{50} values (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 2-4. 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. 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 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 2-4. Genotoxicity of Beryllium and Its Compounds In Vitro

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Compound
Prokaryotic organisms:					
Salmonella typhimurium	Gene mutation	-	-	Ashby et al. 1990; Simmon et al. 1979; Rosenkranz and Poirier 1979; Arlaukas et al. 1985; 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	Gene mutation	No data	+	Hsie et al. 1979	Beryllium sulfate
K1-BH4 cell					
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. 1979	Beryllium chloride
Human lymphocytes	Chromosomal aberration	No data	+	Larramondy et al. 1981	Beryllium sulfate
Rat hepatocyte	DNA-repair	No data	-	Williams et al. 1981	Beryllium sulfate
Syrian hamster cells	Chromosomal aberration	No data	+	Larramondy et al. 1981	Beryllium sulfate

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

TABLE 2-4. Genotoxicity of Beryllium and Its Compounds In Vitro

TABLE 2-4. Genotoxicity of Beryllium and Its Compounds In Vitro

Cancer. Epidemiology studies discussed in Section 2.2.1.8 suggest an increased risk of lung cancer due to occupational exposure to beryllium. Increased incidences of lung cancer were reported among workers at beryllium extraction, processing, and fabrication facilities. The extraction and processing of beryllium involves the production of several compounds reported to be carcinogenic in animals. No correlation between the incidence of lung cancer and exposure has been established because the data from the Beryllium Case Registry did not report exposure levels. Moreover, several of these studies have been criticized for improper calculation of expected deaths from lung cancer, inadequate evaluation of confounding factors such as smoking, and use of inappropriate controls (EPA 1987). A recent study that accounted for smoking and used appropriate controls and statistical methods has strengthened the evidence in humans (Steenland and Ward 1992). NTP (1991) 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. Based on sufficient evidence for carcinogenicity of beryllium and these beryllium compounds in animals and limited evidence for the carcinogenicity of beryllium in humans, IARC (1987) has classified beryllium and beryllium compounds in Group 2A, that is, probably carcinogenic to humans. Based on sufficient evidence for carcinogenicity of beryllium in animals and inadequate evidence in humans, the EPA classifies beryllium in Group B2, that is, a probable human carcinogen (IRIS 1992). These classifications are based in part on cancer studies conducted in animals by the intratracheal, intravenous, and intramedullary routes, as well as on the positive findings in inhalation studies in animals. The EPA has derived upper- bound estimates of cancer risk for both inhalation and oral exposure to beryllium (IRIS 1990). These estimates are 2.4×10^{-3} $(\mu g/m^3)^{-1}$ for inhalation exposure and 4.3 $(mg/kg/day)^{-1}$ for oral exposure. Although soluble beryllium compounds appear to be weakly genotoxic in some in vitro studies, the mechanism of genotoxicity has not. Beryllium has an affinity for the nucleus in in vitro studies and is capable of inhibiting cell division (Skilleter et al. 1988; Witschi and Aldridge 1968).

2.5 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).

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 biologic 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 2.5.1.

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 often not 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 2.5.2.

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, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "Populations That Are Unusually Susceptible."

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Beryllium

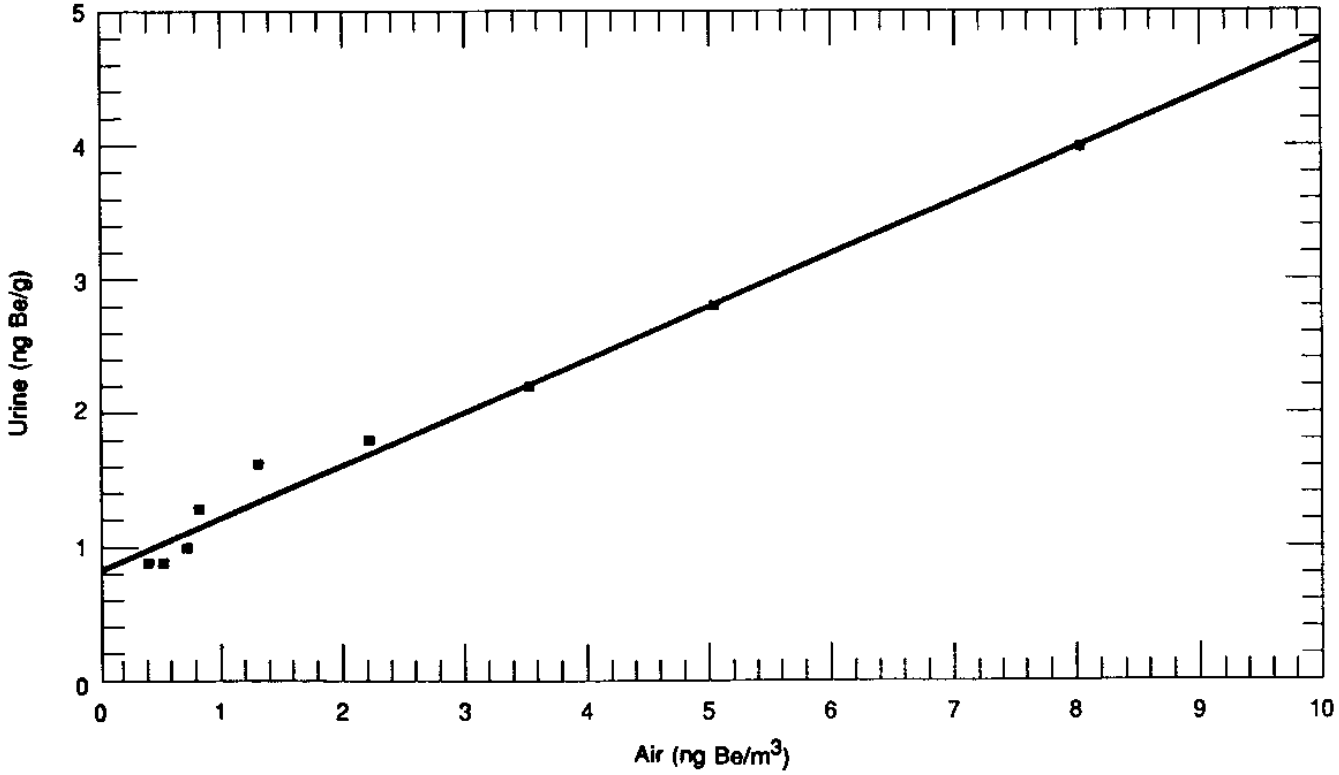
There are several tests for measuring beryllium in biological fluids and tissues (Frame and Ford 1974; Foreman et al. 1970; Hurlburt 1978; IARC 1980; Mortisen and Thomassen 1986; Paschal and Bailey 1986; Shan et al. 1989). These include measurement of beryllium levels in the urine and blood. Information 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 both blood (Stiefel et al. 1980; Zorn et al. 1986) and urine (Stiefel et al. 1980), and of 0.02 g 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). In addition, a lymphocyte proliferation test measures hypersensitivity to beryllium in previously exposed individuals (see Section 2.5.2).

Background urinary levels of beryllium were determined to be ~1.0 ng beryllium/g, 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 2-3 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. 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 2µg beryllium/m for an 8-hour day and 25 µg beryllium/m for a 30-minute 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 2.3.4.1). 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 2.3.1).

FIGURE 2-3. Relationship Between Urine Level of Beryllium and Air Concentration*



*Source: Stiefel et al. 1980

FIGURE 2-3. Relationship Between Urine Level of Beryllium and Air Concentration *

2.5.2 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. 1988). 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.

An antigen-specific lymphocyte proliferation test is useful for measuring hypersensitivity in individuals previously exposed to beryllium and has been used in the diagnosis of individuals with chronic beryllium disease (Rossmann et al. 1988; Williams and Williams 1982, 1983). The test was positive in all individuals with chronic beryllium disease, negative in subjects who were suspected of having chronic beryllium disease but found to be negative, and positive in only 2 of 117 healthy beryllium workers. The positive test in the two healthy workers indicated both exposure and sensitization (Williams and Williams 1983). The in vitro beryllium blood lymphocyte proliferation test is frequently positive in beryllium patients and negative in patients with sarcoidosis; thus, this test may distinguish chronic beryllium disease from sarcoidosis (James and Williams 1985; Stokes and Rossman 1991). However, the results of peripheral blood lymphocyte proliferation responses to beryllium have been variable in patients with chronic beryllium disease (Kriess et al. 1989; Newman et al. 1989; Saltini et al. 1989; Stokes and Rossman 1991; Williams and Williams 1983); therefore, the tests is not absolutely disgnostic of chronic beryllium disease. Bronchoalveolar lavage and testing of the lung lymphocytes for their proliferative response to beryllium appears to give positive results in all patients with chronic beryllium disease (Rossman et al. 1988; Saltini et al. 1989). Laser ion mass analysis of histological sections of lung or skin granulomas can distinguish chronic beryllium disease from other granulomatous disease such as sarcoidosis (Williams and Kelland 1986). This technique was used to detect beryllium at ppm levels in the granulomas (but not in the surrounding tissue) of persons with clearly defined, chronic beryllium disease.

2.6 INTERACTIONS WITH OTHER CHEMICALS

Mortality rates were lower if rats exposed to 2.59 mg beryllium/m^3 as beryllium sulfate tetrahydrate 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).

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

The inhibitory effects of beryllium on hepatic microsomal enzymes was demonstrated by injecting rats with beryllium (0.1 mmol beryllium/kg as beryllium chloride) 12-24 hours prior to the administration of pentobarbital or zoxazolamine (Teixeira et al. 1990). The effects of pentobarbital (sleeping time) and zoxazolamine (paralysis) increased 50% in the beryllium-pretreated rats, compared to controls. Beryllium chloride pretreatment of rats significantly decreased the clearance rates of pentobarbital and zoxazolamine from the plasma. The inability to metabolize and clear pentobarbital or zoxazolamine in the plasma, as indicated by prolonged activity in the rat, suggests that beryllium inhibits cytochrome P-450 in the liver, which may be due to an interference with hemoprotein synthesis.

The presence of beryllium oxide in the lungs of rats following acute inhalation exposure to beryllium oxide decreased the clearance rate of radioactive plutonium oxide from the lungs when the rats were exposed to an aerosol of radioactive plutonium oxide 30 or 60 days later (Sanders et al. 1975). The decreased clearance of plutonium oxide by beryllium oxide was believed to be due to beryllium oxide-induced damage to macrophages. Thus, beryllium oxide could prolong potential toxic effects of other chemicals that are cleared through the action of macrophages.

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.

2.7 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 include genetic make-up, developmental stage, health and nutritional status, and chemical exposure history. These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic and renal) or the pre-existing compromised function of target organs. For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, "Populations With Potentially High Exposure."

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°C) 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 ($H\text{-}2^a$ haplotype) mice, but not in BALB/c ($H\text{-}2^d$ haplotype) or C57BL/6 ($H\text{-}2^b$ haplotype) mice, after intratracheal injection of beryllium sulfate, suggesting that genetic differences at the H-2 major histocompatibility complex 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.

2.8 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.

2.8.1 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 1992). Chronic granulomas observed following dermal exposure are surgically removed (HSDB 1992). 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.

2.8.2 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 2.3.4.1). 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 2.3.1.2), that portion which is absorbed appears to preferentially accumulate in bone (Furchner et al. 1973; Morgareidge et al. 1975; Reeves 1965). Beryllium may substitute for calcium in bone, and result in rickets or osteoporosis (Guyatt et al. 1933; Jacobson 1933). 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).

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). Administering a high calcium diet might result in displacement of beryllium by calcium in the bone, thus preventing rickets or osteoporosis, but precautions against iatrogenically inducing hypercalcemia or nephrocalcinosis would need to be taken. 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.

2.8.3 Interfering with the Mechanism of Action for Toxic Effects

As discussed in Section 2.6, 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.

As discussed in Section 2.2.1.2, 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 the 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 Skileter 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 (see Section 2.4).

It has been established that beryllium inhibits DNA synthesis. 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 discused in Section 2.8.2.

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA 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 or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.9.1 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 2-4. 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

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 imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information (i.e., data gaps that must necessarily be filled).

Studies regarding adverse health effects in humans after exposure to beryllium or its compounds are limited (Figure 2-4). 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 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 were reported.

FIGURE 2-4. Existing Information on Health Effects of Beryllium

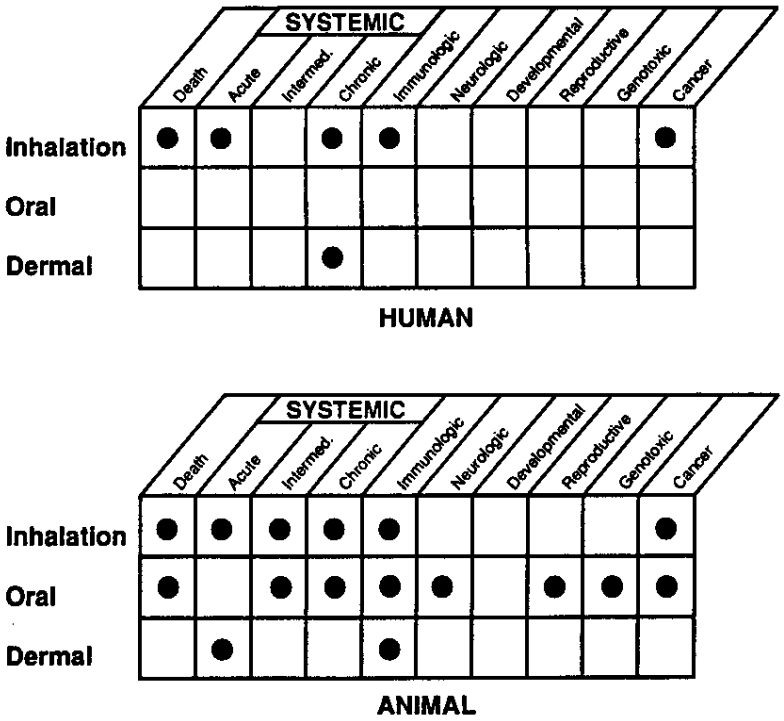


FIGURE 2-4. Existing Information on Health Effects of Beryllium

The data base 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.

2.9.2 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. 1948; 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 1987; 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. 1948; Rossman et al. 1988). An acute inhalation MRL has not been derived because of uncertainties regarding exposure levels in human studies and the lack of appropriate NOAEL values from the animal data. Furthermore, serious respiratory effects and death were observed at the lowest concentration tested in acute experiments. 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; Kimmerly 1966; Lanchow 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 Fevry 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. An acute inhalation study in animals at low exposure levels would be useful to determine the NOAEL for respiratory effects. 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. Since chronic beryllium disease can occur after acute and chronic exposure to beryllium compounds, it can also occur after intermediate- duration exposure. 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). Only one study reported pulmonary effects in rats exposed to beryllium nitrate in the diet (Goel et al. 1980). It is possible, however, that the rats inhaled beryllium nitrate particulates into the lungs, while eating. Derivation of an intermediate-duration inhalation MRL is precluded because the lowest concentrations tested in intermediate-duration experiments resulted in serious respiratory effects (emphysema) and increased mortality. Derivation of an intermediate-duration oral MRL is precluded because serious effects (rickets) were observed in rats in the only intermediate-duration oral studies (Guyatt et al. 1933; Jacobson 1933). 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). Hence, studies regarding inhalation, oral, and dermal exposure to low concentrations of beryllium for intermediate durations would be useful for determining the respective NOAELs for systemic effects, which may be useful for the development of intermediate-duration inhalation and oral MRLs. This information would be useful to the general population and to populations residing at or near hazardous waste sites.

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 Lission 1983; Hardy and Tabershaw 1946; Rossman et al. 1988) 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 (Cullen et al. 1987; Eisenbud and Lission 1983; Eisenbud et al. 1948). Acute lung inflammation was also observed after occupational exposure to soluble beryllium compounds (Eisenbud et al. 1948). 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. Hence, derivation of a chronic inhalation MRL is precluded. Data were not located regarding effects in humans after chronic oral exposure to beryllium. Target organs of beryllium sulfate toxicity are not identified in chronic feeding studies in rats (Morgareidge et al. 1975) or in drinking water studies in rats and mice (Schroeder and Mitchener 1975a, 1975b). However, beryllium is poorly absorbed from the gastrointestinal tract, which may explain this lack of data. The lack of identified target organs following chronic oral exposure to beryllium precludes the derivation of a chronic oral MRL. Data regarding the effects of chronic dermal exposure to beryllium were limited to findings of dermatities 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 2.9.3). 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; Steenland and Ward 1992; Wagoner et al. 1980). However, the integrity 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 (Wagner et al. 1969; Vorwald and Reeves 1959; Reeves et al. 1967; Vorwald 1968), 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 beryllium is considered an animal carcinogen and a probable carcinogen in humans (IARC 1978; IRIS 1992; NTP 1991). A well-conducted chronic inhalation study in rats and mice using several exposure levels would add confidence to the data base 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; Schroeder and Mitchener 1975a, 1975b). 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; Larramondy 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 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 or animals after inhalation, oral, or dermal exposure to beryllium or its compounds. 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 beyllium 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 exposed to beryllium sulfate in drinking water for 2 years did not reveal any abnormalities in nerve tissues (Morgareidge et al. 1975). 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; Mortisen 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. 1988). 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, lympth 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 mechanism of beryllium induced rickets and 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.

2.9.3 On-going Studies

Studies sponsored by the National Institute of Health, National Cancer Institute to assess the mechanism by which beryllium produces mutagenic effects in bacteria will be conducted by E.T. Snow of New York University Medical Center (CRISP 1990). The purpose of this study will be to examine site specific damage to the genome and the interactions with DNA polymerases. Another study sponsored by the National Institute of Health, National Institute of Environmental Health

study sponsored by the National Institute of Health, National Institute of Environmental Health Sciences conducted by L.S. Newman of the National Jewish Center for Immunological Research and Medicine will assess the effects of beryllium on humoral and cell-mediated immune systems in vitro and in vivo (CRISP 1990). The study will also involve the isolation and cloning of beryllium specific T-cells. A retrospective cohort study sponsored by NIOSH will be conducted by E.M. Ward in workers employed in beryllium plants between 1940 and 1969 (FEDRIP 1990). This study will assess the association between beryllium exposure and the increased risk of lung cancer and other respiratory/cardiovascular diseases. Scientists at the Lovelace Inhalation Toxicology Research Institute are conducting studies to determine the potential for interactions between inhaled beryllium metal and $^{239}PuO_2$ in rats to induce cancer and to define an appropriate animal model to investigate the specific cellular mechanisms involved in the induction of chronic beryllium disease (Finch 1992). A study sponsored by the National Institute of Health, National Institute of Environmental Sciences, conducted by H. Kreiss of the National Jewish Center for Immunological Research and Medicine, involving the use of the lymphocyte transformation test will be used to determine its appropriateness to screen for chronic beryllium disease (CRISP 1990). This study will include 750 beryllium exposed workers and 100 controls.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Data regarding the chemical identity of beryllium and compounds are reported in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of beryllium and compounds are listed in Table 3-2. Beryllium chloride, fluoride, nitrate, phosphate, and sulfate (tetrahydrate) are all water-soluble. The remaining compounds listed in Table 3- 2 are either insoluble or sparingly soluble.

Consistent with the high charge to the radius ratio, beryllium has a strong tendency to form compounds with covalent bonds. Beryllium also forms complex ions such as BeF_4^{-2}, $[Be(H_2O)]^{+2}$, and chelated compounds with acetylacetone and other ligands (Cotton and Wilkinson 1980). Although beryllium belongs to group 2A of the periodic table, it is different from other alkaline earth elements since its oxide is amphoteric. Beryllium compounds have many chemical properties similar to aluminum compounds (Reeves 1986).

TABLE 3-1. Chemical Identity of Beryllium and Compounds[a]

Characteristic	Beryllium	Beryllium chloride	Beryllium fluoride	Beryllium oxide	Beryllium hydroxide
Synonym(s)	Beryllium-9; Glucinium; Glucinum; beryllium metallic	Beryllium dichloride	Beryllium difluoride	Beryllia; monoxide	Beryllium hydrate;
Registered trade name(s)	No data	No data	No data	Thermalox 995	No data
Chemical formula	Be	$BeCl_2$	BeF_2	BeO	$Be(OH)_2$
Chemical structure	Be	$BeCl_2$	BeF_2	BeO	$Be(OH)_2$
Identification numbers:					
CAS registry	7440-41-7	7787-47-5	7787-49-7	1304-56-9	13327-32-7
NIOSH RTECS	DS1750000	DS2625000	DS2800000	DS4025000	DS3150000
EPA hazadrous waste	P015	No data	No data	No data	No data
OHM/TADS	7216604[b]	7217359[b]	7800049[b]	No data	No data
DOT/UN/NA/ IMCO shipping	UN1567/IMO6.1	NA1566/IMO6.1	NA1566/IMO6.1	UN1566/IMO6.1	UN 1566/IMO6.1

HSDB	512	357	355	1607	350
NCI	No data	No data	No data	No data	No data

Synonym(s)	Beryllium	Nitric acid,	Sulfuric acid,	Basic beryllium[d]
	orthophosphate[c]	Beryllium salt	Beryllium salt	Carbonate; bis [carbonate(2-)][d] dihydroxy triberyllium[d]
Registered trade name(s)	No data	No data	No data	No data
Chemical formula	$Be_3(PO_4)_2 \cdot 3H_2O$[c]	$Be(NO_3)_2$	$BeSO_4$	(BeCO3)2·Be(OH)2d
Chemical structure	$Be_3(PO_4)_2 \cdot 3H_2O$[c]	$Be(NO_3)_2$	$BeSO_4 \cdot Be(OH)2d$	BeCO3)2
Identification numbers:				
CAS registry	35089-00-0[c]	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[d]
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	721722[b] (anhydrous)	7217228[b] (anhydrous)	No data
DOT/UN/NA/IMCO shipping	No data	UN2464/IMO5.1	UN1566/IMO6.1	No data
HSDB	No data	1431	347	No data
NCI	No data	No data	No data	No data

[a]AII information obtained from HSDB 1990 except where noted
[b]OHM/TADS 1990
[c]Weast 1985
[d]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 3-1. Chemical Identity of Beryllium and Compounds a

TABLE 3-2. Physical and Chemical Properties of Beryllium and 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[b]	Glassy, hygroscopic mass[d]	Amorphous powder or crystalline solid[d]	Light, amorphous powder[d]	Powder
Melting point	1,287-1,292°C[e]	555°C[d]	Decomposes (loses water) when heated[f]	2,508-2,547°C[b]	No data
Boiling point	2,970°C[e]	1,175°C[b]	Not applicable	3,787°C[b]	No data
Density	1.846 g/cm^3 e	1.986 g/cm^3 (25°C)[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]	0.8×10^{-4} mol/L[g] (3.44 mg/L)	Very sparingly[g]	Insoluble (cold) decomposes (hot)
Organic 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, alikali
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°C)	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	h	h	h	h
Explosive limits	No data	No data	No data	No data	No data

Property	Beryllium chloride	Beryllium nitrate (tetrahydrate)	Beryllium phosphate ($3H_2O$)	Beryllium sulfate (anhydrous)	Beryllium sulfate ($4H_2O$)
Molecular weight	79.92	205.08[b]	271.03	105.07	177.13
Color	Colorless	White[b]	White[b]	Colorless[b]	Colorless[b]
Physical	Needles	Crystals[b]	Solid[b]	Tetragonal crystals	Tetragonal crystals
Melting point	405°C	60.5°C[b]	100°C (loses H_2O) (decomposses)[b]	550-600°C (decomposes)	100°C (loses $2H_2O$)
Boiling point	520°C	142°C (decomposes)[b]	No data	Not applicable	400°C (loses $4H_2O$)
Density	1.899 g/cm^3 (25°C)	1.557 g/cm^3 [b]	No data	2.443 g/cm^3	1.713 g/cm^3 (10.5°C)
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°C)[b] (1.66×10^6 mg/L)	Soluble	Insoluble	39.1 parts/ 100 parts H_2O (20°C)[b] (3.91×10^5 mg/L)
Organic 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
Flammability	No data	No data	No data	No data	No data

limits					
Conversion factors	h	h	h	h	h
Explosive limits	No data	No data	No data	No data	No data

[a]AII 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.

TABLE 3-2. Physical and Chemical Properties of Beryllium and Compounds a

TABLE 3-2. Physical and Chemical Properties of Beryllium and Compounds a

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Commercial production of beryllium and compounds begins with the processing of beryllium-containing ores. The only two ores used commercially in the United States are bertrandite ($4BeO\ 2SiO_2\ H_2$) and beryl ($3BeO\ Al_2O_3\ 6SiO_2$) (Ballance et al. 1978; USDI 1990; Weast 1985). Brush Wellman, Inc. is the only ore processor in the United States. Bertrandite ore is mined using open-pit methods from deposits near Spor Mountain, Utah, and transported to the Brush Wellman, Inc. mill near Delta, Utah, for processing. In addition to bertrandite treatment that is conducted at this plant, imported beryl and small quantities of domestically produced beryl are also processed here. The ore is leached with sulfuric acid to form a beryllium sulfate, which is converted to basic beryllium carbonate by reaction with aqueous ammonium carbonate. Subsequent heating yields beryllium hydroxide, which is processed into metal, alloys, and beryllium oxide. Beryllium hydroxide is also produced from beryl ore by a sulfate extraction process.

Beryllium metal is commercially produced from the hydroxide (Ballance et al. 1978). The hydroxide is initially reacted with ammonium bifluoride to form beryllium fluoride, which is then reduced with magnesium metal to yield beryllium metal and magnesium fluoride. A purer beryllium metal can be obtained by electrolysis of beryllium scrap, pebbles, or salts.

Copper-beryllium alloy is commercially the most important beryllium alloy. Copper-beryllium master alloy is manufactured commercially by an arc-furnace method in which beryllium oxide is reduced by carbon in the presence of molten copper at 1,800-2,000 °C. The resulting master alloy usually contains 4.0- 4.25 weight % beryllium. Copper-beryllium alloys can be produced by melting the two metals together. The master alloy produced by the arc-furnace method is then melted together with virgin copper or copper scrap and/or other metals to produce the desired alloy, which is customarily cast into billets. Production of copper-beryllium alloys by melting the metals together is not economical on a commercial scale because beryllium metal is expensive (Ballance et al. 1978).

Beryllium oxide, an important end product of beryllium processing, is manufactured from the technical-grade hydroxide by dissolving the hydroxide in sulfuric acid to form the sulfate ($BeSO_4\ 4H_2O$), which is calcined carefully at selected temperatures to yield the oxide (Walsh and Rees 1978).

The United States is the leading producer of beryllium ores and the leading producer and consumer of beryllium metal, alloys, and oxide (USDI 1990). In 1989, U.S. mine shipments of beryllium-containing ore were 184 metric tons of beryllium metal equivalent. Including imports of beryllium ore, stockpiling, and inventory uses, the U.S. consumption of beryllium in 1989 was 217 metric tons of metal equivalent.

The major U.S. manufacturers of beryllium alloys are Brush Wellman, Inc., in Elmore, Ohio, and NGK Metals Corp. (formerly Cabot Wrought Products and Kawecki- Berylco) in Reading, Pennsylvania (EPA 1987; USDI 1990). The facilities in the United States that produce, process, import, and use beryllium and its compounds can be obtained from the Toxics Release Inventory

import, and use beryllium and its compounds can be obtained from the Toxics Release Inventory (TRI) data maintained by the EPA that are shown in Table 4-1 (TRI88 1990). The TRI88 data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. The reported consumption of beryllium products has steadily declined since 1987 because of the decrease in production activities in defense, semiconductor, and computer industries, and the growing concern about the potential health hazards of beryllium oxide ceramic components.

TABLE 4-1. Facilities That Manufacture or Process Beryllium[a]

Facility	Location[b]	Range of maximum amounts on site in pounds	Activities and uses
Dolphin Inc.	Phoenix, AZ	1,000-9,999	As an article component
Brush Wellman Inc.,	Tucson, AZ	10,000-99,999	As an article component
National-Southwire Aluminum	Hawesville, KY	0-99	As a reactant
Diecast Corp.	Jackson, MI	10,000-99,999	As an article component
Koch Refining Co. Sulfuric Acid Unit	Saint Paul, MN	0-99	Produce; as an impurity Acid Unit
River Cement Co.	Festus, MO	10,000-99,999	As a reactant
Weiss-Aug Co. Inc.	East Hanover, NJ	10,000-99,999	As an article component
Brush Wellman Inc.	Elmore, OH	100,000-999,999	Produce; for sale /distribution
B.P. Oil Co. Toledo Refinery	Oregon, OH	100-999	Import; as an impurity
Mercury Marine Plant 14	Stillwater, OK	1,000-9,999	As an article component
Lukens Steel Co.	Coatesville, PA	100-999	As an impurity
Instrument Specialties Co. Inc.	Delaware Water Ga, PA	10,000-999,999	Produce; import; for on-site use/processing; for sale/distribution; as a byproduct; as a reactant; as a formulation component
Franklin Smelting &			

Refining Corp.	Philadelphia, PA	100,000-999,999	Produce; as a byproduct
Doeh Ler-Jarvis/Farley Inc.	Pottstown, PA	10,000-99,999	As a by product
Brush Wellman Inc.	Shoemakersville, PA	1,000-9,999	In re-packaging
Brunswick Corp. Mercury Marine Div.	Fond Du Lac, WI	1,000-9,999	As an article component

[a]Derived from TRI88 (1990)
[b]Post office state abbreviations used

TABLE 4-1. Facilities That Manufacture or Process Beryllium [a]

TABLE 4-1. Facilities That Manufacture or Process Beryllium a

4.2 IMPORT/EXPORT

In 1989, the United States imported 601 metric tons (total weight) of beryl ore; of this total, 526 metric tons were imported from Brazil (USDI 1990). China, Morocco, and Zimbabwe also exported beryl ore to the United States. The quantity of beryl imported into the United States in 1989 declined from the 1988 total, which was 884 metric tons.

In 1989, the United States exported 34.3 metric tons of beryllium alloys, wrought and unwrought beryllium, and waste and scrap beryllium (USDI 1990). This total was less than the exports for 1988, which were 37.6 metric tons. Tanzania, the Netherlands, and the United Kingdom exported the most significant quantities of beryllium in 1989.

4.3 USE

EPA (1987) estimated that the production of beryllium alloys accounted for 75% of the total usage of technical-grade beryllium hydroxide that resulted from ore processing. The production of beryllium oxide and pure metal represented 15% and 10% of the total usage, respectively.

Pure beryllium metal is used in aircraft disc brakes, X-ray transmission windows, space vehicle optics and instruments, aircraft/satellite structures, missile parts, nuclear reactor neutron reflectors, nuclear weapons, fuel containers, precision instruments, rocket propellants, navigational systems, heat shields, and mirrors (EPA 1987).

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, and laser structural components (EPA 1987).

Beryllium alloys have various uses that include the following: electrical connectors and relays; springs; precision instruments; aircraft engine parts; nonsparking tools; submarine cable housings and pivots; wheels, and pinions; automotive electronics; and molds for injection-molded plastics for automotive, industrial, and consumer applications (EPA 1987; USDI 1990).

4.4 DISPOSAL

The EPA has classified beryllium dust as a hazardous waste. EPA standards require that atmospheric emissions from stationary sources are not $>$10 g of beryllium over a 24-hour period and that the ambient concentration of beryllium near the stationary source is not>0.01 ug/m.^{3} EPA also requires that regulations stated in the Federal Resource Conservation and Recovery Act (RCRA) are complied with when hazardous wastes are disposed of. In addition, EPA has issued final regulations under the Clean Water Act for specific nonferrous metal manufacturing operations. These regulations limit the discharge of pollutants by existing and new operations into navigable waters and into publicly owned treatment works (POTWs) (EPA 1982, 1988a; USDI 1990). EPA relies on state and local POTW authorities to enforce compliance with federal, local, and categorical pretreatment regulations. Discharge limits for beryllium-containing waste water in St. Louis,

Missouri, have been reported (Bennett 1989).

The disposal of beryllium-containing wastes depends on the nature of the wastes. Recovery and recycling is an alternative to disposal for beryllium scrap and pickle liquors having a high beryllium content. Powdered wastes containing small amounts of beryllium should be converted into chemically and toxicologically less reactive oxides by incineration before land disposal. However, beryllium dust is a poor candidate for incineration. Waste waters containing beryllium should be subjected to treatment processes to reduce the concentration of beryllium. Waste waters containing permissible levels of beryllium can be discharged into water. Some aqueous wastes can be converted to chemically and toxicologically less reactive oxides either by direct incineration (where such provisions are available) or by incineration after sorption onto suitable combustible material, such as sawdust (HSDB 1990; TRI88 1990).

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. Although the most desirable method of handling beryllium wastes is to recycle them to the producers, burial in plastic-lined metal drums has also been recommended (Fishbein 1981). According to TRI88, a total of =54,000 pounds of beryllium wastes was released to the environment by various industries in 1988 (see Chapter 5). Of the total release, 90.8% was disposed in land, 8.6% was released to air, and 0.6% into surface water. Therefore, land burial is the primary disposal method for beryllium wastes. An additional 11,700 pounds of beryllium wastes were transferred to off-site locations, perhaps for incineration to convert the wastes into chemically inert oxide (HSDB 1990). It is likely that most of the beryllium oxide produced from incineration will be disposed of by land burial. Data regarding the trend in disposal practices for beryllium wastes in recent years were not located.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Beryllium is naturally emitted to the atmosphere by windblown dusts and volcanic particles (EPA 1987). The major emission source to the environment is the combustion of coal and fuel oil, which releases particulates and fly ash that contains beryllium into the atmosphere. 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 are 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 in soil. Beryllium has been identified in 349 of the 1,300 NPL hazardous waste sites, including 5 in Puerto Rico, that have been proposed for inclusion on the NPL. The frequency of these sites within

the United States can be seen in Figure 5-1.

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. 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). The geometric mean concentration of total beryllium in U.S. surface water is 70 ng/L (Eckel and Jacob 1989). In an analysis of 1,577 U.S. drinking water samples, beryllium was detected in 5.4% of the samples at a detection limit of 10 ng/L. The mean beryllium concentration in samples in which it was detected was 190 ng/L (EPA 1980). 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 ug/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).

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

Anthropogenic and natural emissions of beryllium to the atmosphere from various sources are reported in Table 5-1. In addition to ore processing, beryllium is also released into the atmosphere during the production and use of beryllium alloys and chemicals. According to the TRI88 data shown in Table 5-2, =2.3 additional tons (4,625 pounds) of beryllium were released in the atmosphere from alloys, chemicals, and user industries in 1988 (TRI88 1990). The TRI88 data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Beryllium emissions from coal and fuel oil combustion account for 96% of the U.S. beryllium emissions from all natural and anthropogenic sources. The average beryllium concentration in coal is etween 1.8 and 2.2 ug/g (EPA 1987). Based on data from various sources, it has been estimated that 70-90% of the beryllium in the coal fly ash is captured by emission control devices, and 10-30% is emitted to the ambient atmosphere. The beryllium concentration in coal ash is =5-23 ug/g (Holcombe et al. 1985; Pougnet et al. 1985). Fuel oil can contain =0.08 ppm beryllium (Fishbein 1981). It has been assumed that =40% of the beryllium contained in fuel oil is lost to the atmosphere because of burning (EPA 1987).

FIGURE 5-1. FREQUENCY OF NPL SITES WITH BERYLLIUM CONTAMINATION *

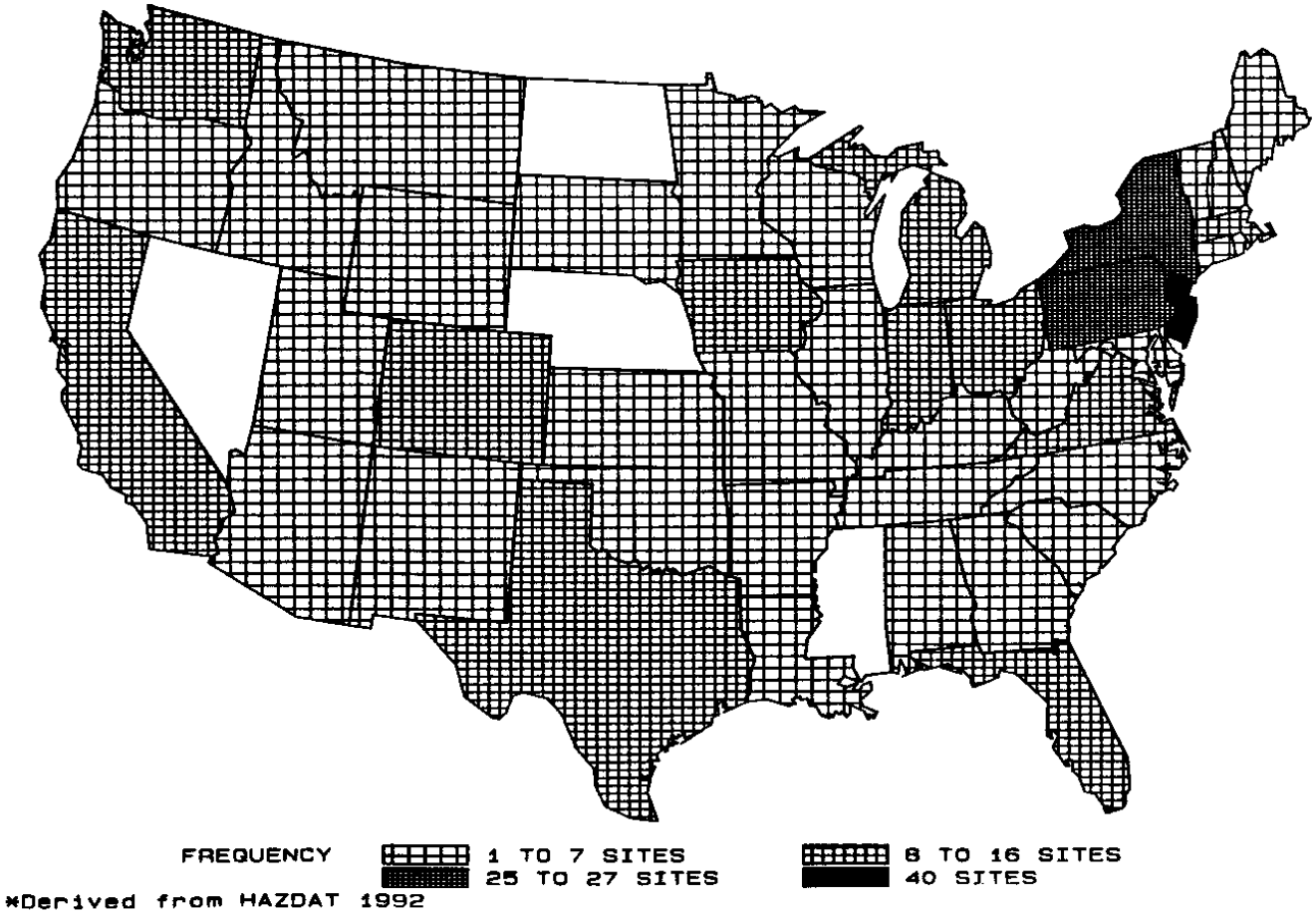


FIGURE 5-1. FREQUENCY OF NPL SITES WITH BERYLLIUM CONTAMINATION*

TABLE 5-1. Natural and Anthropogenic Emissions of Beryllium to the Atmosphere[a]

Emission source	Total U.S. production[b] (10^6 tons/year)	Emission factor (g/ton)	Emission (ton/year)
Natural			
Windblown dust	8.2	0.6	5
Volcanic particles	0.41	0.6	0.2
Total			5.2
Anthropogenic			
Coal combustion	640	0.28	180
Fuel oil	148	0.048	7.1
Beryllium ore processing	0.008[c]	37.5[b]	0.3
Total			187.4

[a]Adapted from EPA 1987
[b]Units are in metric tons.
[c]The production of beryllium ore is expressed in equivalent tons of beryl; the emission factor of 37.5 is estimated. Production of 8,000 tons/year of beryl is equivalent to =400 tons/year of contained metal. The actual amount produced in 1989 was about one-half of this amount (see Section 4.1).

TABLE 5-1. Natural and Anthropogenic Emissions of Beryllium to the Atmosphere a

TABLE 5-2. Releases to the Environment from Facilities That Manufacture or Process Beryllium[a]

		Reported amounts released in pounds						
Facility	Location[b]	Air	Underground injection	Water	Land	Total environment[c]	POTW transfer	Off-site waste transfer
Dolphin Inc.	Phoenix, AZ	0	0	0	0	0	0	0
Brush Wellman Inc.	Tucson, AZ	1	0	0	0	1	3	6,933
National-Southwire Aluminum	Hawesville, KY	1	0	20	0	21	0	0
Diecast Corp.	Jackson, MI	0	0	0	0	0	0	750
Koch Refining Co. Sulfuric Acid Unit	Saint Paul, MN	1	0	0	0	1	0	0
River Cement Co.	Festus, MO	250	0	0	0	250	0	0
Weiss-Aug Co. Inc.	East Hanover, NJ	0	0	0	0	0	0	0
Brush Uellman Inc.	Elmore OH	1,200	0	40	37,000	38,240	0	0
								2,400
B. P. Oil Co. Toledo Refinery	Oregon OH	0	0	0	0	0	0	250
Mercury Marine 14 Plant	Stillwater, OK	0	0	0	0	0	0	0
Lukens Steel Co.	Coatesville, PA	500	0	0	0	500	0	0
Instrument Specialties	Delaware Water, PA	0	0	0	0	0	0	0

Co. Inc.								
N. G. K. Metals Corp.	Muhlenberg Tow, PA	361	0	17	12,000	12,378	0	1,358
Franklin Smelting & Refining Corp.	Philadelphia, PA	1,000	0	250	0	1,250	0	0
Doehler-Jarvis /Farley Inc.	Pottstown, PA	250	0	0	0	250	0	0
Brush Uellman PA Inc.	Shoemakersvill,	1	0	14	0	15	0	4
Brunswick Corp. Mercury Marine Div.	Fond Du Lac, WI	1,060	0	0	0	1,060	4	4
Totals		4625	0	34	49000	53966	7	11699

[a]Derived from TR188 1990
[b]Post office state abbreviations used
[c]The sum of all releases of the chemical to air, land, water, and undergrourd injection ¯ells by a given facility
POTU = publicly-owned treatment works

TABLE 5-2. Releases to the Environment from Facilities That Manufacture or Process Beryllium a

TABLE 5-2. Releases to the Environment from Facilities That Manufacture or Process Beryllium a

Municipal waste combustors are also a small source of beryllium emissions into the atmosphere. The beryllium emission factors (the concentration of pollutant emitted in flue gas to the amount present in combusted waste) into the air from waste combustors depend on the type of combustors, combustor operating conditions, and feed materials. When electrostatic precipitators are used as emission controls, the beryllium emission factors from the combustors are <2 ug/g (Epner and Vancil 1989; Lisk 1988). It has been estimated that the beryllium emissions from the existing municipal waste combustors in 1986 totalled 0.1 metric ton. This amount is expected to increase to 0.6 metric tons per year in the 1990s (Cleverly et al. 1989).

Natural emission sources include windblown dusts and volcanic particles. The beryllium amounts released to the atmosphere from these sources are small compared with anthropogenic sources (see Table 5-1).

5.2.2 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). Beryllium concentrations may be the highest in treated waste waters from nonferrous metal manufacturing industries. The highest total discharge of beryllium via treated waste water results from iron and steel manufacturing and nonferrous manufacturing industries. The industrial release of beryllium into surface water and into waste water of POTWs is shown in Table 5-2.

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.

According to the Contract Laboratory Program Statistical Database (CLPSD), beryllium was detected in surface water and in groundwater samples from an estimated 5.7% and 17.7% of the NPL hazardous waste sites, respectively. The geometric mean beryllium concentrations in samples of surface and ground waters with detectable levels of beryllium were 5.6 and 6.1 ppb, respectively (CLPSD 1989). The information used from the CLPSD includes data from NPL sites only.

5.2.3 Soil

Beryllium compounds are naturally present in soil. One source of beryllium in soil is coal ash and municipal waste combustor ash that are disposed into landfills. Both types of ash contain beryllium. Another source of beryllium in soil results from the land disposal of solid waste generated from industries that process or use beryllium. The amount of beryllium waste released in U.S. soils in 1988 is shown in Table 5-2. It is apparent from Table 5-2 that land burial constitutes by far the largest method for beryllium disposal by industries (see Section 4.4). It should be noted that data regarding wastes from the beryllium ore processing industry are not included in Table 5-2. Similarly, application of sewage sludge containing higher than background concentrations of beryllium on land

can be a beryllium source in soil. Deposition of atmospheric aerosols on terrestrial surfaces is another source of beryllium in soil. However, quantitative data regarding the relative significance of each of these sources were not located. According to CLPSD, beryllium was detected in soil samples from an estimated 30% of the NPL hazardous waste sites included in the CLPSD at a geometric mean concentration of 1.1 ppm (CLPSD 1989). Only 1.2% of the soil samples in the CLPSD contained beryllium exceeding maximum concentration in background U.S. soils (Eckel and Langley 1988). The information used from the CLPSD includes data from NPL sites only.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

The transport of beryllium from the atmosphere to terrestrial and aquatic surfaces occurs through wet and dry deposition (EPA 1987). The dry deposition rate of aerosol particles is a function of particle aerodynamic size, windspeed, and surface roughness. A study of stack emissions from coal combustion reported that most beryllium is found on particles of median aerodynamic diameter $<$2.5 um (Gladney and Owens 1976); particles of this size can remain airborne for =10 days. By analogy to other elements, a typical dry deposition velocity for beryllium particles over a vegetative surface would be 0.25 cm/second (EPA 1987).

The portion of beryllium particles transported from the atmosphere by wet deposition has not been determined experimentally. Rainwater in Australia had an average beryllium concentration of 0.05-0.08 ug/L (Meehan and Smythe 1967). Beryllium was detected (concentration not quantitated) in rainwater from Fresno, California (Salo et al. 1986), which indicates that transport of beryllium from the atmosphere to terrestrial and aquatic surfaces occurs by wet deposition.

The beryllium concentration measured in water and sediment of the Great Lakes indicates that beryllium is present in sediment at concentrations several orders of magnitude higher than its concentration in water (Bowen 1979; Lum and Gammon 1985; Rossmann and Barres 1988). Therefore, most of the beryllium is expected to be present either in the sorbed state in suspended matter or in the sediment rather than in a dissolved form in most natural waters. Beryllium in sediment is usually associated with the aluminum part (clay content) of the sediment, which is probably a result of adsorption onto clay particles. This association is expected because of the geochemical similarity of beryllium and aluminum. Some beryllium may also be present in the sediment as a result of formation and subsequent precipitation of insoluble complexes. A high percentage of beryllium is expected to have low mobility in water due to association in the sediment, although at a high water pH, formation of water- soluble complexes with hydroxide ions may increase the solubility and mobility of beryllium (Callahan et al. 1979).

The estimated residence time of beryllium in ocean water (before it is removed from the aquatic phase by sedimentation or other removal processes) is about a few hundred years (Bowen 1979; Merrill et al. 1960).

No evidence was found to substantiate that biomethylation or any other environmental process results in the volatilization of beryllium into the atmosphere from water or soil.

Beryllium is extremely toxic to warmwater fish in soft water. The degree of toxicity decreases with

increasing water hardness (Callahan et al. 1979). Bioconcentration of beryllium in fish to high levels is not likely due to the low uptake of beryllium from water by aquatic animals. 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, invertebrates, and fish (Callahan et al. 1979). According to Kenaga (1980), chemicals with BCFs <1000 will not bioaccumulate significantly in aquatic organisms. It is possible that bottom-feeding crustaceans, such as clams and oysters, could accumulate beryllium from sediment and show higher bioconcentration than freshwater fish. Comparisons of the beryllium levels in biota and surface sediments from Lake Pontchartrain, Louisiana, indicated similar, but somewhat lower, beryllium concentrations in biota (Byrne and DeLeon 1986). The BCFs for beryllium in bottom-feeding animals could not be estimated from this investigation since the authors did not report the beryllium concentration in water. No evidence for significant biomagnification of beryllium within food chains was found (Fishbein 1981).

In most types of soil, beryllium is expected to be tightly adsorbed because it displaces divalent cations that share common sorption sites (Fishbein 1981). Due to its geochemical similarity to aluminum, beryllium may be expected to adsorb onto clay surfaces at low pHs, and it may remain precipitated as insoluble complexes at higher pHs (Callahan et al. 1979); therefore, beryllium is expected to have limited mobility in soil. At high soil pH, the mobility of beryllium in soil may increase as a result of formation of soluble polynuclear hydroxide complexes (Callahan et al. 1979). However, beryllium was not detected (detection limit not stated) in soil water or groundwater in Fresno, California (Salo et al. 1986). Beryllium is, therefore, not likely to be found in a soluble state in most soils, and it may not leach through soil to contaminate most groundwaters.

5.3.2 Transformation and Degradation

5.3.2.1 Air

Beryllium is probably emitted into the atmosphere as beryllium oxide (BeO). The atmospheric emission of beryllium during ore-crushing processes is likely to occur in the form of BeO because the two commonly used beryllium ores, beryl and bertrandite, both contain BeO. The atmospheric emission of beryllium during thermal processes, such as coal and refuse combustion, is also likely to produce BeO in the stack emission. As is the case with other metallic compounds, BeO cannot be destroyed; however, it could be transformed from one form to another. It is not known whether BeO in air will react with sulfur or nitrogen oxides to produce beryllium sulfate or nitrate. If such conversion occurs, the removal of beryllium from the atmosphere by wet deposition will be accelerated since both beryllium sulfate and nitrate are water-soluble. Experimental data that would substantiate the possibility of any reaction of BeO in air were not located.

5.3.2.2 Water

The likely reaction for beryllium in water is chemical speciation by which one species is converted to another. One such possible reaction in water is hydrolysis. Soluble beryllium salts in water are hydrolyzed to form relatively insoluble beryllium hydroxide, which would have a low solubility in the pH range of most natural waters (Callahan et al. 1979). Complexation with hydroxide ions to form soluble polynuclear hydroxide complexes is another possible reaction, although the pH range necessary for this reaction is probably not available in most natural waters. This is substantiated by

empirical data that indicate that, even in polluted rivers where the concentration of complexing agents is high, dissolved beryllium levels are very low (Callahan et al. 1979).

No data were located suggesting the biotransformation of beryllium or its compounds in water.

5.3.2.3 Soil

The possible reactions of beryllium in soil are hydrolysis of soluble salts, anion exchange reaction by which one salt is converted to another (e.g., beryllium sulfate may be converted to beryllium carbonate), and complexation reactions with ligands present in soil (e.g., humic substances). Reactions of beryllium in soil are likely to be responsive to pH (Drury et al. 1978); however, experimental evidence of any such reactions in soil was not located in the literature. Data suggesting the biotransformation of beryllium or its compounds in soil were not located.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Beryllium in the ambient air is measured at many of the State and Local Air Monitoring Stations and National Air Monitoring Stations. The data are available from the Storage and Retrieval of Aerometric Data database (EPA 1987). The beryllium detection limit for these analyses is 0.03 ng/m^3, and the annual averages at most of the monitoring stations are listed at this concentration. Between 1977 and 1981, annual averages were >0.1 ng/m^3 in 50 U.S. cities; the highest average was 0.4 ng/m^3 in Dallas, Texas, in 1979. The median atmospheric concentration of beryllium in contaminated air in North America is 0.2 ng/m^3 (Bowen 1979). Based on earlier monitoring data from the National Air Surveillance Network, the atmospheric level of beryllium in an uncontaminated location was estimated to be <0.1 ng/m^3 (Drury et al. 1978).

5.4.2 Water

The concentration of total beryllium in ocean water 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 median total beryllium concentration in Great Lakes water samples ranged from <4 to 120 ng/L (Rossmann and Barres 1988). In Australian river waters, the total beryllium concentration ranged from <10 to 120 ng/L, with an average of 10-30 ng/L (Meehan and Smythe 1967). Using the data of ambient, lake, and stream stations monitored by the U.S. Geological Survey and EPA's STORET database from ÷1960 to 1988, the geometric mean concentration of total beryllium in U.S. surface water was estimated to be 70 ng/L (Eckel and Jacob 1989). The total beryllium concentrations in various freshwaters ranged from 10 to 1000 ng/L (Bowen 1979). Beryllium has been detected in treated waste waters from nonferrous metal manufacturing industries at a maximum concentration of 170 µg/L and at a mean concentration of 30 µg/L in treated waste water from paint and ink formulation industries (EPA 1981). The average beryllium concentration in Australian rainwater ranged from 0.05-0.08 µg/L (Meehan and Smythe 1967).

In an analysis of 1,577 drinking water samples obtained throughout the United States, beryllium was detected (detection limit of 10 ng/L) in 5.4% of the samples. The beryllium concentrations in

samples where it was detectable ranged from 10 to 1,220 ng/L, with a mean concentration of 190 ng/L (EPA 1980). The concentration of several metals in drinking waters from two New York City municipalities was measured. Beryllium was not detected in any samples at a detection limit of 10 µg/L (Iwan 1987).

5.4.3 Soil

The average beryllium concentration in the Earth's crust is ÷2.8-5.0 mg/kg (Mason 1966; Reeves 1986). Various geochemical surveys have found typical beryllium concentrations in soil to range from 0.01 to 40.0 mg/kg, with a median value of 0.3 mg/kg (Bowen 1979). Using the U.S. Geological Survey data, the mean concentration of beryllium in U.S. soil was estimated to be 0.6 mg/kg (Eckel and Langley 1988). The concentration range of beryllium in 15 soil samples obtained from six states in the United States was 0.13-0.88 mg/kg, with an average concentration of 0.4 mg/kg (Drury et al. 1978). The beryllium concentration in an English peat bog ranged from 0.06 to 0.3 mg/kg (Markert and Thornton 1990).

5.4.4 Other Environmental Media

Several foodstuffs from New South Wales, Australia, were analyzed, and the following average beryllium concentrations were found (in µg/kg fresh weight): beans (0.065); cabbage (0.234); hen eggs yolk and whites (0.061); milk (0.166); mushrooms (1.58); edible nuts (0.21-0.52); tomatoes (0.21); crabs (15.4-26.2); fish fillets (0.16-1.48); oyster flesh (0.6-2.0); and scallops (0.34) (Meehan and Smythe 1967). The following beryllium concentrations (µg/kg dry weight) were reported in West German food samples: polished rice (80); toasted bread (120); potatoes (170); tomatoes (240); and green head lettuce (330) (Reeves 1986). The reported beryllium concentrations (µg/kg dry weight) in crops from Egypt were as follows: eggplant (370); potatoes (300); green pepper (400); kidney bean (2,500); garden pea (430); vegetable marrow (400); pear (400); lettuce (600); dill (420); and parsley (400) (Awadallah et al. 1986).

The beryllium concentrations, expressed in fresh weight, in both raw carrots and field corn grown in the United States were <25 µg/kg, with a sample detection limit of 25 µg/kg (Wolnik et al. 1984). The beryllium concentration in tissue of bottom fish (English sole, Parophrys vetulus) caught in Commencement Bay, Tacoma, Washington, was 6 µg/kg (Nicola et al. 1987). If a factor of 10 is used for conversion of fresh weight to dry weight, it is apparent that the beryllium levels in the German and Egyptian crops that were sampled are higher by at least two orders of magnitude than the beryllium levels in the Australian crops. The discrepancy may result from errors in the method used for the determination of beryllium, the lower levels of environmental contamination of Australian food, or a possible combination of both.

The beryllium levels in the sediments of Lake Pontchartrain, Louisiana, were 0.05-0.5 mg/kg (dry weight) (Byrne and DeLeon 1986). In sediments of the Detroit River and western basin of Lake Erie, the levels were 0.1-3.8 mg/kg (dry weight) (Lum and Gammon 1985).

Beryllium has been detected in U.S. orchard leaves and in various trees and shrubs at concentrations of 26 µg/kg and ≤1 mg/kg, respectively (IARC 1980).

Beryllium levels of 0.47-0.74 µg/cigarette have been detected in three brands of West German

cigarettes; 2-10% of the beryllium was found in the cigarette smoke (Reeves 1986).

5.5 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/m^3 (see Section 5.4.1), and it is further assumed that a normal U.S. adult inhales 20 m^3 of air per day, the daily inhalation exposure to beryllium for a U.S. adult would be 0.0006 µg. Similarly, if the concentration of beryllium in average U.S. drinking water is 0.2 µg/L (see Section 5.4.2), and the consumption rate of drinking water by a normal adult is assumed to be 2 L/day, the daily exposure from drinking water would be 0.4 µg. 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/g and a daily consumption of 1,200 g of food (EPA 1987). Other investigators have reported the total daily intake of beryllium to range from 10 to 20 µg of which ÷12 µg is contributed by food. These values, however, are approximated and need to be verified (Tsalev and Zaprianov 1984).

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 the metal were >50 µg/m^3 during the mid-1960s; the levels were >30 µg/m^3 during the mid-1970s. After 1977, the plant complied with the permissible exposure limit of 2.0 µg/m^3 (Kriebel et al. 1988). The time-weighted average 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). Determination of beryllium concentrations in the lungs at autopsy of deceased German mine workers revealed 2.3-34 times higher lung levels than in an unexposed control group (Baumgardt et al. 1986). 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 metal and 4,305 workers to beryllium oxide in the workplace (NIOSH 1989a).

5.6 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; however, there have been no reports of disease 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 restricts the

amount of beryllium emitted into the environment by industries that process beryllium ores, metals, oxides, alloys, or wastes to 10 g in a 24-hour period (EPA 1982). 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).

Smokers may inhale unusually high concentrations of beryllium. Based on an analysis of West German cigarettes and smoke (Reeves 1986), an average of 35 ng of beryllium may be inhaled per cigarette. A person smoking one pack of cigarettes each day would inhale ÷700 ng of beryllium, which is nearly twice the daily consumption from other sources (EPA 1987). This estimate depends on the amount of beryllium contained in the native tobacco leaf, and it may vary depending on the source of tobacco.

It is also possible that certain individuals may be exposed to higher than normal beryllium from implanted dental prostheses, although no studies on beryllium leaching from dental prostheses are available (EPA 1987). The mantles of some lanterns used by campers contain ÷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).

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA 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 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 or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. The relevant physical and chemical properties of beryllium are known (see Section 3.2). However, many of the physical properties, such as the octanol/water partition coefficient and Henry's law constant, that are important for prediction of environmental behavior of organic compounds are neither available nor relevant for beryllium. Additional information regarding the chemical forms of beryllium in coal fly ash, tobacco smoke, and aerosols produced by specific industrial processes and the mode by which beryllium compounds are

incorporated into biological systems would be useful.

Production, Import/Export, Use, and Release and Disposal. Knowledge of a chemical's production volume is important because it may indicate environmental contamination and human exposure. If a chemical's production volume is high, there is an increased probability of general population exposure via consumer products and environmental sources. More workers may be occupationally exposed to a chemical that is produced in high volumes. Data regarding the production, import/export, and use of commercially significant beryllium compounds are available (EPA 1987; USDI 1990). The demand for beryllium has declined each year since 1987 (USDI 1990). This trend is not expected to continue over the next few years because the use of beryllium alloys in automotive electronic components is expected to increase (USDI 1990). Beryllium is rarely used in consumer products where it is a viable source of exposure to the general population. One known source of consumer exposure to beryllium results from ignition of mantles of new camp lanterns. The beryllium is vaporized and becomes airborne during the first 15 minutes of use of the new mantle (Fishbein 1981). There is no known food additive that contains beryllium. Due to the transport characteristics (Bowen 1979; Fishbein 1981) and the disposal practice (TRI88 1990), soil is the primary environmental medium where contamination of beryllium will occur.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1987, became available in May of 1989. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

As reported in Table 5-1, the most significant amount of beryllium from production and user 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 (TRI88 1990). There are EPA regulations regarding the disposal of beryllium wastes (EPA 1982, 1988a; USDI 1990) and OSHA regulations regarding the allowable levels of beryllium in workplaces (OSHA 1989). 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. Beryllium is removed from the atmosphere by wet and dry deposition (EPA 1987). Additional data examining the possible chemical transformation reactions of beryllium and its half-life in air would be useful. Similarly, it is known that sediment will be the ultimate sink for beryllium in water (Bowen 1979; Lum and Gammon 1985; Rossmann and Barres 1988), and its association with sediment would decrease the mobility in water. However, data regarding the physical and chemical processes that induce association of beryllium in sediment are lacking. Very little is known regarding the chemical species and the exact chemical processes involved in the formation of soluble chelates responsible for increased beryllium mobility in water. Additional information elucidating the fate of beryllium with respect to its chemical speciation in soil would be useful.

Bioavailability from Environmental Media. Although the absorption of specific beryllium compounds from skin contact, inhalation, and ingestion have been studied in animals (see Section 2.3.1), the bioavailability of beryllium or its compounds from contaminated air, water, soil, or plant material may differ significantly from the studied values. The absorption may depend on the chemical form and the physical state (e.g., extent of adsorption on soil particles) of beryllium compounds present in the

environment. For example, absorption of beryllium from inhalation of aerosols from disposal sites may vary depending on the extent of beryllium sorption on soil particles. 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 nonbottom-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.

Exposure Levels in Environmental Media. Although some data on the levels of beryllium in air and drinking water are available (Bowen 1979; EPA 1980, 1987; Iwan 1987), these data are not current. Limited data regarding the ambient concentration of beryllium near beryllium-containing hazardous waste sites are available. These monitoring data are important for assessing the potential health risk for individuals living near the waste sites (Eckel and Longley 1988). In an EPA survey, beryllium was not detected in ÷95% of 1,577 drinking water samples analyzed at a detection limit of 10 ng/L (EPA 1980). Although the impact of beryllium in drinking water on the health effects of the general population may not be significant, the determination of the beryllium level in drinking water is important in assessing its contribution towards total intake in humans. Nationwide monitoring data determining the levels of beryllium in U.S. drinking water at a detection limit $<$10 ng/L should be developed. Data regarding the intake of beryllium from food are lacking (Wolnik et al. 1984). Such information would be important in assessing the contribution of food to the total intake of beryllium from different pathways. 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.

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.

Exposure Registries. The Beryllium Case Registry was begun at Massachusetts General Hospital, Boston, Massachusetts. This compound is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The compound will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this compound.

5.7.2 On-going Studies

A search of federal research in progress indicates that there is no on-going research project that would fill the data gaps discussed in Section 5.7.1. 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 and in humans and will contribute information for exposure registries. Investigations at these sites will also increase the current knowledge regarding the transport and transformation of beryllium at hazardous waste sites. No other long-term research studies regarding the environmental fate and transport of beryllium or the occupational and general population exposure to beryllium were identified.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring beryllium in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify beryllium. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect beryllium in environmental samples are the methods approved by federal 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 refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL MATERIALS

Methods used for the analysis of beryllium in biological materials are reported in Table 6-1. Reviews of beryllium analysis methods in biological media have been published (Delves 1981; Tsalev and Zaprianov 1984). Although the beryllium level in urine may be informative of the current exposure level, it is not useful as a diagnostic criterion. However, the level of beryllium in blood/serum/plasma is predictive of the intensity of current exposure (Tsalev and Zaprianov 1984) from certain beryllium compounds (see Section 2.3.2). Flame atomic absorption spectroscopy or atomic emission spectroscopy is not sensitive enough for measuring the beryllium concentration in body fluids and tissues. The determination of beryllium levels in these matrices requires elimination of severe matrix interference. In particular, Ca^{+2} and Mg^{+2} enhance and CI- and ClO_4^- cause severe suppression of beryllium absorption in atomic spectroscopy. Electrothermal or graphite furnace atomic absorption spectroscopy with background correction (deuterium or Zeeman effect background corrector) is the commonly used method, and it has the sensitivity and accuracy to determine beryllium content 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 time-consuming 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). A relatively recent technique called the Laser Ion Mass Analyzer (LIMA) uses a laser beam to ionize elements in a small section of tissue and detects ions including beryllium by a time-of-flight mass spectrometer (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).

6.2 ENVIRONMENTAL SAMPLES

Methods used to analyze beryllium in environmental media are presented in Table 6-2. The standard test methods approved by EPA and NIOSH for beryllium analysis in ambient and occupational samples are included in Table 6-2. Environmental samples analyzed by atomic absorption spectroscopy and gas chromatography require pretreatment to remove interfering substances and increase sensitivity (EPA 1987). At high concentrations (500 mg/kg), aluminum and silicon interfere with beryllium analysis by atomic absorption spectroscopy. Separation of these elements is achieved by chelation and extraction with an organic solvent. A method using laser spark spectroscopy has been used for the direct determination of trace quantities of airborne beryllium collected on filters (Cremers and Radziemsky 1985).

The following SRMs for beryllium in environmental samples are available from the National Institute of Standards and Technology: 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). In addition, SRMs MESS-1 and BCSS-1 for beryllium in sediments are available from the National Research Council of Canada (Waldichuk et al. 1987).

TABLE 6-1. Analytical Methods for Determining Beryllium in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
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 (human and rat)	Add EDTA to aqueous sample; adjust to pH 6; add trifluoroacetylacetone in benzene; extract	GC/EC	1 μg/L	67.6-123%	Foreman et al. 1970
Urine	Sample mixed with ascorbic acid and ammonium phosphomolybdate	GFAAS	0.05 μg/L	94-98%	Shan et al. 1989
Urine (human)	Urine sample is a matrix modifier (aqueous $Mg(NO_3)_2$, Triton X-100, HNO)	Electrothermal atomic absorption (stabilized temprature	0.05 μg/L	107%	Paschal and Bailey 1986

		platform furnace)			
Fecal sample	Heat with nitric acid and hydrogen peroxide; add ferrous chloride; evaporate to dryness; dissolve residue in nitric acid containing lanthanum	GFAAS	1 μg/kg	108%	Hurlburt 1978
Dog blood; rat liver homogenates	Add sodium hydroxide; dissolve by heating; chelate with trifluoroacetylacetone; extract with benzene	GC/EC	No data	95-117%	Frame and Ford 1974
Lung tissue	Sample subjected to dry or wet ashing	ICP-AES	0.075 mg/kg	No data	Mortisen and Thomassen 1986
Bovine liver	Wet-ash tissue in a mixture of acids; chelate with acetylacetone; extract (chloroform); acidify a chelate with 2-hydroxy-3-naphthoic acid reagent	Fluorescence spectrometry	No data	No data	IARC 1980

Hair-fingernails	Dissolve sample with nitric acid: perchloricacid (1:1)	GFAAS	<1 μg/kg	97.5-105%	Hurlburt 1978

EDTA = ethylenediaminetetraacetic acid; GC/EC = gas chromatography-electron capture; GFAAS = graphite furnace atomic absorption spectrometry; ICP-AES = inductively coupled plasma-atomic emission spectrometry; HNO_3 = nitric acid; $Mg(NO_3)_2$ = magnesium nitrate

TABLE 6-1. Analytical Methods for Determining Beryllium in Biological Materials

TABLE 6-2. 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 nitric and hydrochloric acids; concentrate; add nitric acid and lithium chloride solution	Optical emission spectroscopy	5.3 μg/L (in dissolved particles)	96-108%	Scott et al. 1976
Air	Dissolve collection filter matrix in hydrofluoric acid; and nitric acid; water; boil; dilute	GFAAS FAAS	0.05 ng/m^3 2.5 ng/m^3	No data	Zdrojewski et al.1976
Occupational air	Dry collection filter; add nitric acid and sulfuric acid; solubilize with concentrated HCl	Direct current plasma AES	0.0036 μg/ sample	100%	Chang et al. 1982

Occupational air	Filter collecting; acid digestion	GFAAS (method 7102)	5 pg/sample	108%	NIOSH 1989b
Water	Acidify with nitric acid; evaporate under heat; add hydrochloric acid or nitric	AAS (direct aspiration method 210.1)	0.005 mg/L	97-100%	EPA 1983
		AAS (furnace technique-method 210.2)	0.2 µg/L	No data	
Water	Acidify with nitric acid	GFAES	2 µg/L	112% (average)	Epstein et al. 1978
		GFAAS	0.06 µg/L	98% (average)	
Seawater	Add specific volumes of EDTA, sodium benzene and Hfta to collected seawater; rinse organic phase with NaOH; UV oxidize	GC/EC	0.02 µg/L	93-104%	Measures and Edmond 1986
Sediment	Extract dry sample with HCl solution	Direct current plasma AES	0.02 µg/g	No data	Lum and Gammon 1985
Soil, sludge, sediments, and other	Acid digestion of sample	ICP-AES (method (6010)	0.3. µg/L	97.7-100%	EPA 1988c

solid wastes					
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 nitric, perchloric; sulfurnic, or hydrochloric acid	ICP-AES	2.5 µg/kg	No data	Wolnick et al. 1984

AAS = atomic absorption spectrometry; AES = atomic emission spectrometry; EDTA = ethyhlenediaminetetraacetic acid; FAAS = flame atomic absorption spectrometry; GFAAS = graphite furnace atomic absorption spectrometry; GFAES = graphite furnace atomic emission spectrometry; GC/EC = gas chromatography-electron capture; HCl = hydrochloric acid; $HClO_4$ = perchloric acid; Hfta = 1, 1, 1-trifluoro-2,4-pentanedione; HNO_3 = nitric acid; ICP-AES = inductively coupled plasma-atomic emission spectrometry; NaOH = sodium hydroxide; UV = ultraviolet

TABLE 6-2. Analytical Methods for Determining Beryllium in Environmental Samples

TABLE 6-2. Analytical Methods for Determining Beryllium in Environmental Samples

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA 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 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 or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. As discussed in Section 2.5.1, 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 is currently available. The routine analytical methods presently available are useful for detecting beryllium levels in the blood of occupationally exposed persons.

There are several methods for measuring effects due to beryllium exposure (see Section 2.5.2). 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 (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. The LIMA can detect ppm 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 = 95% of drinking waters in the United States is <0.01 μg/L (EPA 1980; Iwan 1987). Although a few special methods are available (see Table 6-2) 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 6-2) is 25 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 beryllium in foods would be useful. The data on the levels of beryllium in drinking water and total diet samples with no apparent source of pollution are significant in determining background levels of daily intake from these routes.

Unlike organic compounds, inorganic metallic compounds do not degrade in the environment; however, they may transform from one form to another. The analytical methods most commonly used for such compounds determine only the cationic portion of the compound. Therefore, routine analytical methods for the determination of changes of beryllium forms (e.g., BeO changing to $BeSO_4$) occurring as a result of environmental reactions are lacking.

6.3.2 On-going studies

A Department of Energy (DOE)-funded project is currently being conducted at Los Alamos National Laboratory to develop a near real-time analyzer for beryllium using laser ionization spectroscopy.

7. REGULATIONS AND ADVISORIES

National and state regulations and guidelines pertinent to human exposure to beryllium are summarized in Table 7-1.

Beryllium exposure is regulated by the Clean Water Act Effluent Guidelines for the following point sources: nonferrous metals manufacturing, steam electric, asbestos, timber products processing, mineral mining, paving and roofing, paint formulating, and ink formulating (EPA 1988b).

A chronic oral reference dose (RfD) of 0.005 mg beryllium/kg/day has been derived and verified by EPA for beryllium (IRIS 1992). The RfD is based on a NOAEL for systemic effects in rats chronically exposed to 0.5 ppm as beryllium sulfate in the drinking water in the study by Schroeder and Mitchner (1975a). EPA has not derived a reference concentration (RfC) for inhalation exposure to beryllium.

TABLE 7-1. Regulations and Guidelines Applicable to Beryllium

Agency	Description	Compound	Information	References
INTERNATIONAL				
IARC	Carcinogenic classification	Beryllium and beryllium compounds	Group 2A[a]	IARC 1987
NATIONAL				
Regulations:				
a. Air:				
OSHA	TWA	Beryllium and beryllium compounds (as Be)	0.002 mg/m^3	OSHA 1989; 29 CFR 1910
	STEL	Beryllium and beryllium compounds (as Be)	0.005mg/m^3 (30 min)	
	Ceiling	Beryllium and beryllium compounds (as Be)	0.025 mg/m^3	
Guidelines:				
a. Air:				
ACGIH	TLV-TWA	Beryllium and beryllium compounds	0.002 mg/m^3; suspected human carcinogen	ACGIH 1990
NIOSH	REL-TWA	Beryllium and beryllium compounds	Carcinogen; not to exceed 0.0005 mg/m^3	NIOSH 1992

b. Water:				
EPA OWRS	Ambient water quality criteria for protection of human health			
	Water and fish consumption	Beryllium	0.68-68 ng/L	EPA 1986
	Organism consumption only	Beryllium	11.7-1,170 ng/L	
EPA OWRS	Ambient water quality criteria for protection of aquatic organisms			
	Acute lowest effect level	Beryllium	130 µg/L	EPA 1980
	Chronic lowest effect level	Beryllium	5.6 µg/L	
c. Other:				
EPA	RfD (oral)	Beryllium	0.005 mg/kg/day	IRIS 1992
	Carcinogenic classification	Beryllium	Group B2[b]	
	unit risk (inhalation)	Beryllium	$2.4x10^{-3}$ $(mg/kg/day)^{-1}$	
	$q1^*$ (oral)	Beryllium	$4.3\ (mg/kg/day)^{-1}$	
EPA OERR	RQ	Beryllium dust	10 pounds	EPA 1989b (40 CFR
		Beryllium chloride	1 pound	116, 117, 302)
		Beryllium fluoride	1 pound	
		Beryllium nitrate	1 pound	
EPA	Emissions from stationary source	Beryllium	10 g (24 hr)	EPA 1988d
			0.01 µg/m^3	(40 CFR

	Ambient air concentration		(30-day avg)	61.32)
STATE Regulations and Guidelines:				
a. Air:	Acceptable ambient air concentration			
Arizona		Beryllium	0.016 μg/m^3 (24-hr avg)	NATICH 1992
Arizona		Beryllium	0.0005 μg/m^3 (1-hr avg)	NATICH 1992
Colorado		Beryllium	0.01 μg/m^3 (30-day avg)	CELDS 1990
Connecticut		Beryllium	0.01 μg/m^3 (8-hr avg)	NATICH 1992
Delaware		Beryllium	0.01 μg/m^3 (30-day avg)	CELDS 1990
Florida (Fort Lauderdale)		Beryllium	0.02 μg/m^3 (8-hr avg)	NATICH 1992
Florida (Pinella)		Beryllium	0.06 μg/m^3 (8-hr avg)	NATICH 1992
Florida (Pinella)		Beryllium	0.0048 μg/m^3 (24-hr avg)	NATICH 1992
Florida (Pinella)		Beryllium	0.000426 μg/m^3 (1-hr avg)	NATICH 1992
Kansas		Beryllium	0.000417 μg/m^3 (1-hr avg)	NATICH 1992
Kentucky		Beryllium	0.001 μg/m^3 (24-hr avg)	CELDS 1990
Massachusetts		Beryllium	0.0004 μg/m^3	NATICH 1992

		(1-hr avg)	
Massachusetts	Beryllium	0.001 μg/m^3	NATICH 1992
		(24-hr avg)	
Nevada	Beryllium	0.1 μg/m^3	NATICH 1992
		(8-hr avg)	
New Hampshire	Beryllium	0.01 μg/m^3	CELDS 1990
		(30-hr avg)	
New York	Beryllium	0.007 μg/m^3	NATICH 1992
	sulfate	(1-hr avg)	
North Carolina	Beryllium	0.0041 μg/m^3	NATICH 1992
North Carolina	Beryllium	0.0041 μg/m^3	NATICH 1992
	chloride	(1-hr avg)	
North Carolina	Beryllium	0.0041 μg/m^3	NATICH 1992
	nitrate	(1-hr avg)	
North Dakota	Beryllium	0.01 μg/m^3	CELDS 1990
		(30-hr avg)	
Oklahoma	Beryllium	0.02 μg/m^3	NATICH 1992
		(24-hr avg)	
Oregon	Beryllium	0.01 μg/m^3	CELDS 1990
		(30-hr avg)	
Pennsylvania	Beryllium	0.01 μg/m^3	NATICH 1992
		(1-hr avg)	
South Carolina	Beryllium	0.01 μg/m^3	NATICH 1992
		(8-hr avg)	
South Carolina	Beryllium	0.01 μg/m^3	NATICH 1992
	sulfate	(24-hr avg)	
South Dakota	Beryllium	0.02 μg/m^3	NATICH 1992
Vermont	Beryllium	0.0013 μg/m^3	NATICH 1992
		(1-hr avg)	
Virginia	Beryllium	0.02 μg/m^3	NATICH 1992

			(24-hr avg)	
b. Water:	Drinking water quality standards			FSTRAC 1990
Arizona		Beryllium	0.007 µg/L	
Kansas		Beryllium	0.13 µg/L	
New Hampshire		Beryllium	0.004 µg/L	

[a] Group 2A: Probable human carcinogen
[b] Group B2: Probable human carcinogen
ACGIH = American Conference of Governmental Industrial Hygienists; avg = average; Be = beryllium; EPA = Environmental Protection Agency; IARC = International Agency for Research on Cancer; NIOSH = National Institute for Occupational Safety and Health; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OWRS = Office of Water Regulations and Standards; REL = Recommended Exposure Limit; RfD = Reference Dose; RQ = Reportable Quantity; STEL = Short-term Exposure Level; TLV = Threshold Limit Value; TWA = Time Weighted Average.

TABLE 7-1. Regulations and Guidelines Applicable to Beryllium

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9. GLOSSARY

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

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 a mount 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.

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.

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.

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

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 development effects may be detected at any point in the life span of the organism.

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

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.

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

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

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$^{(50)}$ (LD^{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 is expected 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}) -- The 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 dose 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.

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

Minimal Risk Level -- An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effect over a specified duration of exposure.

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

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

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of 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.

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

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).

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 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 effect such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 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.

Short-Term Exposure Limit (STEL) -- The 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 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) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may expressed as a TWA, as a STEL, or as a CL.

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

Toxic Dose (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.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD 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 LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

Appendix A

User's Guide

Chapter 1

Public Health Statement

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

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

Tables and Figures for Levels of Significant Exposures (LSE)

Tables (2-1, 2-2. and 2-3) and figures (2-1 and 2-2) are used to summarize health effects by duration of exposure and end point and to illustrate graphically levels of exposure associated with those effects. 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) for Less Serious and Serious health effects, or Cancer Effect Levels (CELs). In addition, these tables and figures illustrate 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. The LSE tables and figures can be used 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.

LEGEND

TABLE 2-1. Levels of Significant Exposure to [Chemical x] - Inhalation

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

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

[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).

CEL = cancer effect level; d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

LSE Table 2-1

(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 exist, three LSE table and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes.

(2). Exposure Duration Three exposure periods: acute (14 days or less); intermediate (15 days to 364 days); and chronic (365 days or more) and presented within each route of exposure. In this example, an inhalation study of intermediate duration exposure is reported.

(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.

(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 define a NOAEL and a Less Serious LOAEL

(also see the two "18r" data points in Figure 2-1).

(5). Species The test species, whether animal or human, are identified in this column.

(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 [substance x] via inhalation for 13 weeks, 5 days per week, for 6 hours per day.

(7). System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "other" refers to any systemic effect (e.g. a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated in this study.

(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 exposure level 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 "Less Serious" respiratory effect reported in key number 18 (hyperplasia) occurred at a LOAEL of 10 ppm.

(10). Reference The complete reference citation is given in Chapter 8 of the profile.

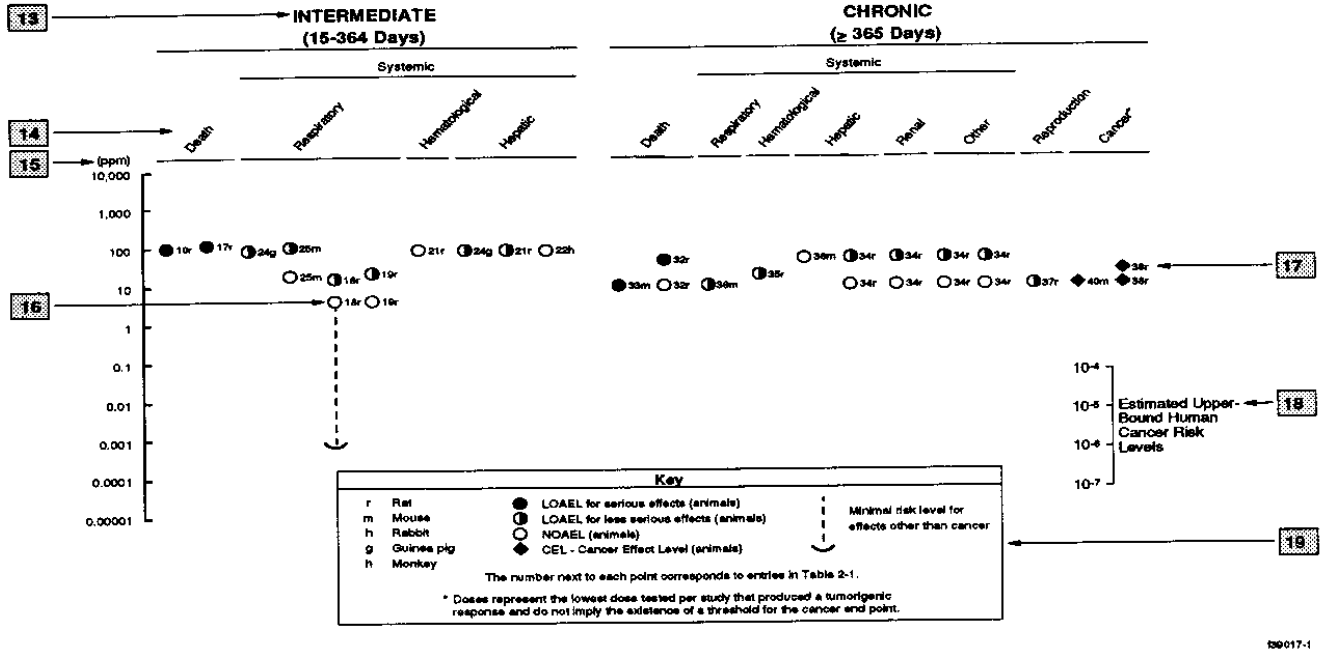
(11). CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiological studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses which did not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

(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

SAMPLE

FIGURE 2-1. Levels of Significant Exposure to [Chemical X] - Inhalation



LSE Figure 2-1

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

(13).Exposure Duration 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 exist. The same health effects appear in the LSE table.

(15).Levels of Exposure Exposure levels for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure levels are reported 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 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 one of three studies for which Cancer Effect Levels (CELs) were derived. The diamond symbol refers to a CEL for the test species (rat). 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 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.

Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicological, epidemiological, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section discusses health effects by end point. Human data are presented first, then animal data. Both are organized by route of exposure (inhalation, oral, and dermal) and by duration (acute, intermediate, and chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency of perform cancer risk assessments. MRLs for noncancer end points if derived, and the end points from which they were derived are indicated and discussed in the appropriate sections(s).

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

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information was available, MRLs were derived. MRLs are specific for route (inhalation or oral) and duration (acute, intermediate, or chronic) of exposure. Ideally, MRLs can be derived from all six exposure scenarios (e.g., Inhalation - acute, -intermediate, -chronic; Oral - acute, -intermediate, - 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 substance emission, given the concentration of a contaminant in air or the estimated daily dose received via food or water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicological information on which the number is based. Section 2.4, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.6, "Interactions with Other Chemicals" and 2.7, "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 used by the Environmental Protection Agency (EPA) (Barnes and Dourson 1988; EPA 1989a) to derive reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the 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 effects (e.g., systemic, neurological, and developmental). In order to compare NOAELs and LOAELs for specific end points, all inhalation exposure levels are adjusted for 24hr exposures and all intermittent exposures for inhalation and oral routes of intermediate and chronic duration are adjusted for continuous exposure (i.e., 7 days/week). If the 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. The NOAEL is the most suitable end point for deriving an MRL. When a NOAEL is not available, a Less Serious LOAEL can be used to derive an MRL, and an uncertainty factor of (1, 3, or 10) is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of (1, 3, or 10) are used for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and (1, 3, or 10) are used for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual MRL workgroup reserves the right to use uncertainty factors of (1, 3, or 10) based on scientific judgement. The product is then divided into the adjusted 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.

Appendix B
Acronyms, Abbreviations, and Symbols

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
AML	acute myeloid leukemia
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry

BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram

kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	trans,trans-muconic acid
mCi	millicurie
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
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
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
PCE	polychromatic erythrocytes

pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard morality ratio
STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
UMDNJ	University of Medicine and Denistry New Jersey
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram

Appendix C
PEER REVIEW

A peer review panel was assembled for beryllium. The panel consisted of the following members: Dr. Finis Cavender, Associate Professor, College of Natural and Applied Science, Abilene Christian University, Abilene, Texas; Dr. Andrew Reeves, Professor, Department of Occupational and Environmental Health, Wayne State University, Detroit, Michigan; and Dr. Milton Rossman, Associate Professor of Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania; Dr. Alan Hall, Private Consultant, Evergreen Colorado; Dr. James Gallo, Associate Professor of Pharmaceutics, College of Pharmacy, University of Georgia, Athens, Georgia; Dr. Peter Lacouture, Associate Director, Clinical Research, The Purdue Frederick Company, Norwalk, Connecticut; Dr. Gregory Finch, Staff Scientist, Lovelace Inhalation Toxicology Research Institute, Alburquerque, New Mexico. 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 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.