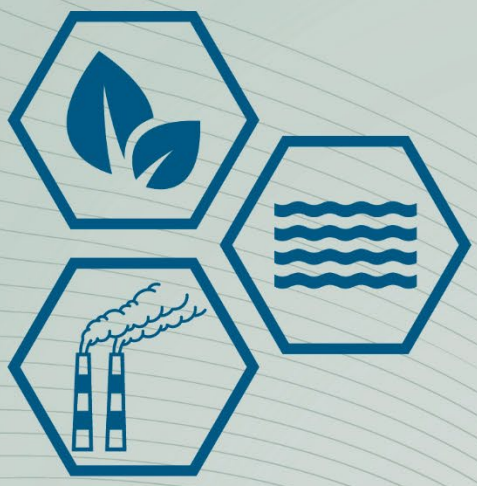

Toxicological Profile for Beryllium

Draft for Public Comment

January 2022

U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

CS274127-A

FOREWORD

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

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

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. 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 the protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, intermediate, 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 the levels of exposure that present a significant risk to human health due to acute, intermediate, and chronic duration exposures.

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

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. ATSDR plans to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov. Follow the on-line instructions for submitting comments.

Written comments may also be sent to: Agency for Toxic Substances and Disease Registry
Office of Innovation and Analytics
Toxicology Section
1600 Clifton Road, N.E.
Mail Stop S102-1
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The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA Section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and 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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VERSION HISTORY

Date	Description
January 2022	Draft for public comment released
June 2015	Addenda released
September 2002	Final toxicological profile released
April 1993	Final toxicological profile released
December 1988	Final toxicological profile released

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These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers were selected in conformity with Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Beryllium is a lightweight metal that occurs naturally in rocks, coal, soil, and volcanic dust. Commercially, bertrandite and beryl ore are mined for the recovery of beryllium. Because beryllium is one of the lightest metals and is very rigid, it has many uses in the electronics, aerospace, and defense industries. Beryllium is released into the atmosphere by windblown dust, volcanic particles, and the combustion of coal and fuel oil.

As an element, beryllium does not degrade in the environment; it only changes form. Beryllium particulates in the atmosphere will settle out or be removed by precipitation. The annual average concentration of beryllium in ambient air in the United States is typically below 0.2 ng/m^3 (EPA 2018a). Beryllium concentration in urban air is usually higher, possibly due to burning of coal and fuel oil. Sax et al. (2006) analyzed indoor and outdoor home air in New York City and Los Angeles. The mean concentration of beryllium in indoor home air was 0.0015 ng/m^3 for New York City and 0.0018 ng/m^3 in Los Angeles; the mean concentration in air outside the home was 0.0028 ng/m^3 in New York City and 0.0018 ng/m^3 in Los Angeles.

Beryllium can be released into waterways by the weathering of soil and rocks. Beryllium entering surface water and soil will be retained in the sediment and soil and will be generally immobile. Drinking water samples taken as part of a review of national drinking water regulations contain beryllium in concentrations ranging from 0.002 to 2000 µg/L (0.000002 to 0.2 mg/L) (EPA 2016).

Although beryllium is found in water and soil, most human exposure to beryllium and its compounds occurs in the workplace. People who work in beryllium manufacturing, fabricating, and reclaiming industries have a greater probability of inhalation exposure than non-occupational groups. The general population can be exposed to trace amounts of beryllium through inhalation of air, consumption of food, water and incidental soil ingestion, and skin contact with air, water, or soil that contains beryllium. Individuals living near sources of beryllium emissions, such as beryllium manufacturing facilities or municipal waste sites, are potentially at risk of exposure to beryllium levels above background. Dental technicians are exposed to beryllium through inhalation exposure (Stark et al. 2014). People working in aeronautics and aircraft industries are exposed to beryllium through altimeters, braking systems, bushings, and bearings for landing gear (Kreiss et al. 2007). Beryllium has been identified in at least 540 hazardous waste sites that have been proposed for inclusion on the EPA NPL. Measurements in water and soil at these sites are generally higher than background levels. Therefore, individuals living near these sites may

be at risk of exposure to higher levels of beryllium than background levels of beryllium. Air levels in the vicinity of active beryllium use facilities may also be elevated.

1.2 SUMMARY OF HEALTH EFFECTS

The general population can be exposed to beryllium via inhalation, oral, and dermal routes of exposure. The inhalation route is of greatest concern. In inhalation exposures, the lung appears to be the deposition spot from which beryllium is distributed throughout the body. Beryllium and its compounds are poorly absorbed after oral and dermal exposure, although dermal exposure can result in beryllium sensitization. Typically, oral exposures result in the most beryllium accumulation in the bone or liver. Nonetheless, distribution may be dependent on the form and solubility of beryllium and its particle size.

The primary adverse health effects of beryllium are respiratory effects and lung cancer following inhalation exposure, and skin effects following dermal exposure; these effects, along with beryllium sensitization, are discussed in greater detail below. The reader is referred to Chapter 2, Discussion of Health Effects, for additional information. Human and animal data provide evidence that inhaled beryllium is a human lung carcinogen; oral data are inadequate for the assessment of carcinogenic potential.

Beryllium exposure may result in acute beryllium disease, beryllium sensitization, subclinical chronic beryllium disease, and clinical chronic beryllium disease . Each of these diseases have their own diagnostic criteria. A person with any form of chronic beryllium disease will also be diagnosed with beryllium sensitization.

Occupational exposure to higher concentrations of soluble beryllium compounds can result in acute beryllium disease, while exposure to relatively low concentrations of soluble or insoluble beryllium compounds can result in chronic beryllium disease. Adherence to environmental controls in the workplace have now made the occurrence of acute beryllium disease rare.

Acute beryllium disease is characterized by inflammation of the respiratory tract tissues, is usually resolved within several months of exposure termination, and has been reduced by control measures implemented in the workplace. In contrast, chronic beryllium disease is an immune response to beryllium observed in individuals who are sensitized to beryllium. Individuals with severe cases of chronic beryllium disease may also have damage to the right heart ventricle (not a direct effect, but secondary effect), hepatic necrosis, kidney stones, and weight loss. Registries are available for exposed workers to allow researchers to further study and understand the incidence of beryllium sensitization and chronic

beryllium disease. The Beryllium-Associated Worker Registry is maintained by Oak Ridge Institute for Science and Education, and information can be found at https://oriseapps.orau.gov/BAWR/Default.aspx.

As with inhalation exposure, dermal contact with beryllium may result in an allergic response, such as skin granulomas or edema. Dermatitis has been observed in workers exposed to high concentrations of airborne beryllium. Workers with abraded skin have also been found to have skin ulcerations.

Unlike inhalation and dermal exposure routes, oral exposures to beryllium have not been shown to have an immune response as the primary effect. There is no reliable human data for oral exposure to beryllium. In animals, the most sensitive effects after oral exposure appear to be ulcerative gastrointestinal lesions and beryllium rickets. Beryllium rickets do not appear to be due to a direct effect of beryllium on the bone. Rather, the rickets are due to a phosphorus deficiency, which is hypothesized to result from the precipitation of beryllium with dietary phosphorus in the acidic environment of the digestive tract (Kay and Skill 1934). Additionally, these effects have only been observed following exposure to beryllium carbonate.

Respiratory Effects. The toxicity of beryllium to the respiratory tract usually manifests as one of two syndromes: acute beryllium disease or chronic beryllium disease. Acute beryllium disease has a short period of induction and is usually resolved within a couple of months after exposure. Acute beryllium disease may be an inflammatory and/or immunological response to beryllium and has been hypothesized to be part of the continuum of chronic beryllium disease. Most regions of the respiratory tract are affected by acute beryllium disease; some reported symptoms include nasopharyngitis, shortness of breath, labored breathing, and chemical pneumonitis.

Chronic beryllium disease is a systemic granulomatous disorder of the lungs caused by an immune reaction to inhaled beryllium. In general, chronic beryllium disease has been confined to workers exposed to beryllium metal and to less soluble beryllium compounds in the workplace, such as beryllium oxide. However, there have been a few reported cases among residents living near beryllium manufacturing facilities (Maier et al. 2008), and in families of workers who wore contaminated clothing at home (Chesner 1950; Dattoli et al. 1964; Eisenbud et al. 1949; Lieben and Metzner 1959; Lieben and Williams 1969). When individuals inhale beryllium, it binds to proteins/peptides and elicits a proliferation of T lymphocytes, a release of inflammatory mediators, and an accumulation of inflammatory cells in the lungs. This causes sensitization that results in the formation of noncaseating granulomas, the accumulation of mononuclear cell infiltrates, and the development of fibrosis.

Beryllium sensitization is usually diagnosed as more than one abnormal beryllium lymphocyte proliferation test (BeLPT) result, and can progress to chronic beryllium disease, but not all sensitized

individuals will develop chronic beryllium disease. As shown in Table 2-5 in Chapter 2, many of the occupational studies do not rely on beryllium lymphocyte proliferation tests to confirm a diagnosis of chronic beryllium disease. Individuals with subclinical chronic beryllium disease are sensitized to beryllium and have histological evidence of lung granulomas, but no clinical signs. Although no clinical signs are observed, there is evidence to suggest that there may be some impairment of lung function. Individuals with clinical chronic beryllium disease are beryllium sensitized and have histological evidence of lung granulomas, respiratory symptoms, changes on chest radiographs, and/or altered lung function. Beryllium sensitization and/or chronic beryllium disease have been detected at exposure levels of 0.2 μg/m^3. Respiratory disease is not likely to occur from exposure to beryllium levels in the general environment because ambient air levels of beryllium (0.03–0.2 ng beryllium/m^3) are very low.

Gastrointestinal Effects. No human data were located regarding gastrointestinal effects following exposure to beryllium. Extensive ulcerative and inflammatory lesions of the small intestine, stomach, and large intestine have been observed in dogs exposed to dietary beryllium over 143-172 weeks (2.7-3.3 years) (Morgareidge et al. 1976). In a study by the same group, no lesions in small and large intestines were observed in rats exposed to a similar beryllium-containing diet for 2 years (Morgareidge et al. 1975). The difference in observed gastrointestinal outcomes between dogs and rats may be associated with the difference in the frequency of beryllium exposure due to different eating patterns. Dogs who had access to the beryllium-containing diet for one hour per day, showed higher concentrations of beryllium in gastrointestinal tract tissues than rats who had unlimited access to the diet.

Dermal Effects. Dermal responses to beryllium exposure involve the immune system. Edematous papulovesicular dermatitis was observed in workers exposed to airborne beryllium sulfate, beryllium fluoride, or beryllium oxyfluoride; this is likely an inflammatory response to beryllium (VanOrdstrand et al. 1945). Beryllium exposure may also cause a delayed, hypersensitive reaction in the skin (Maier et al. 2003). Biopsied skin granulomas from beryllium workers had the same mononuclear infiltrates as detected in the lungs (McConnochie et al. 1988). Guinea pigs sensitized with beryllium sulfate developed granulomatous lesions and other delayed hypersensitive reactions following dermal exposure to beryllium sulfate, beryllium fluoride, beryllium oxide, or beryllium chloride (Belman 1969; Marx and Burrell 1973).

Immunological Effects. Beryllium exposure may cause an immune reaction that presents with respiratory, dermal, or other symptoms. 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 (NRC 2008). Granuloma formation and dermatitis are

the principal immunological effects caused by exposure to beryllium. Certain polymorphisms can cause increased beryllium sensitization.

Cancer Effects. Fifteen epidemiology studies have assessed the carcinogenic potential of beryllium inhalation exposure. Several retrospective cohort mortality studies have observed increased incidence of lung cancer mortality among workers at beryllium extraction, processing, and fabrication facilities. Increased lung cancer mortality was also seen in studies looking at entrants to the Beryllium Case Registry administered by Massachusetts General Hospital (Infante et al. 1980; Steenland and Ward 1991). In addition, a positive association between length of latency (length of time since onset of exposure) and lung cancer mortality was observed, with the highest mortality rate among workers with a latency of 25 years (Wagoner et al. 1980). Increased bronchiole tumor incidence has also been observed in rats and monkeys exposed to beryllium (Vorwald and Reeves 1959; Vorwald 1968).

The National Toxicology Program lists beryllium and certain beryllium compounds (beryllium-aluminum alloy, beryllium chloride, beryllium fluoride, beryllium hydroxide, beryllium oxide, beryllium phosphate, beryllium sulfate, beryllium zinc silicate, and beryl ore) as human carcinogens. EPA concluded that the human data provided limited evidence and the animal data sufficient evidence of carcinogenicity and therefore classified inhaled beryllium as a probable human carcinogen. They determined that beryllium had inadequate evidence to be able to classify it as carcinogenic by the oral route. Studies in different species of animals demonstrate a similar immunological response as humans as well as other toxicity. However, there are deficiencies in these studies; they do not adequately reproduce features of human chronic beryllium disease. Therefore, these studies cannot reliably predict exposure-response effects of beryllium exposure (NRC 2008). Humans are exposed to lower concentrations of beryllium than levels used in most animal studies, hence it is pertinent to examine the physiological changes happening at those lower doses. It is potentially likely that prior sensitization in humans is exacerbating the toxic effects. The International Agency for Research on Cancer (IARC) has classified beryllium and beryllium compounds as carcinogenic to humans.

Figure 1-1 summarizes the health effects observed in animals and humans after inhalation exposure, and Figure 1-2 summarizes the health effects observed after oral exposure to beryllium.

Figure 1-1. Health Effects Found in Animals and Humans Following Inhalation Exposure to Beryllium

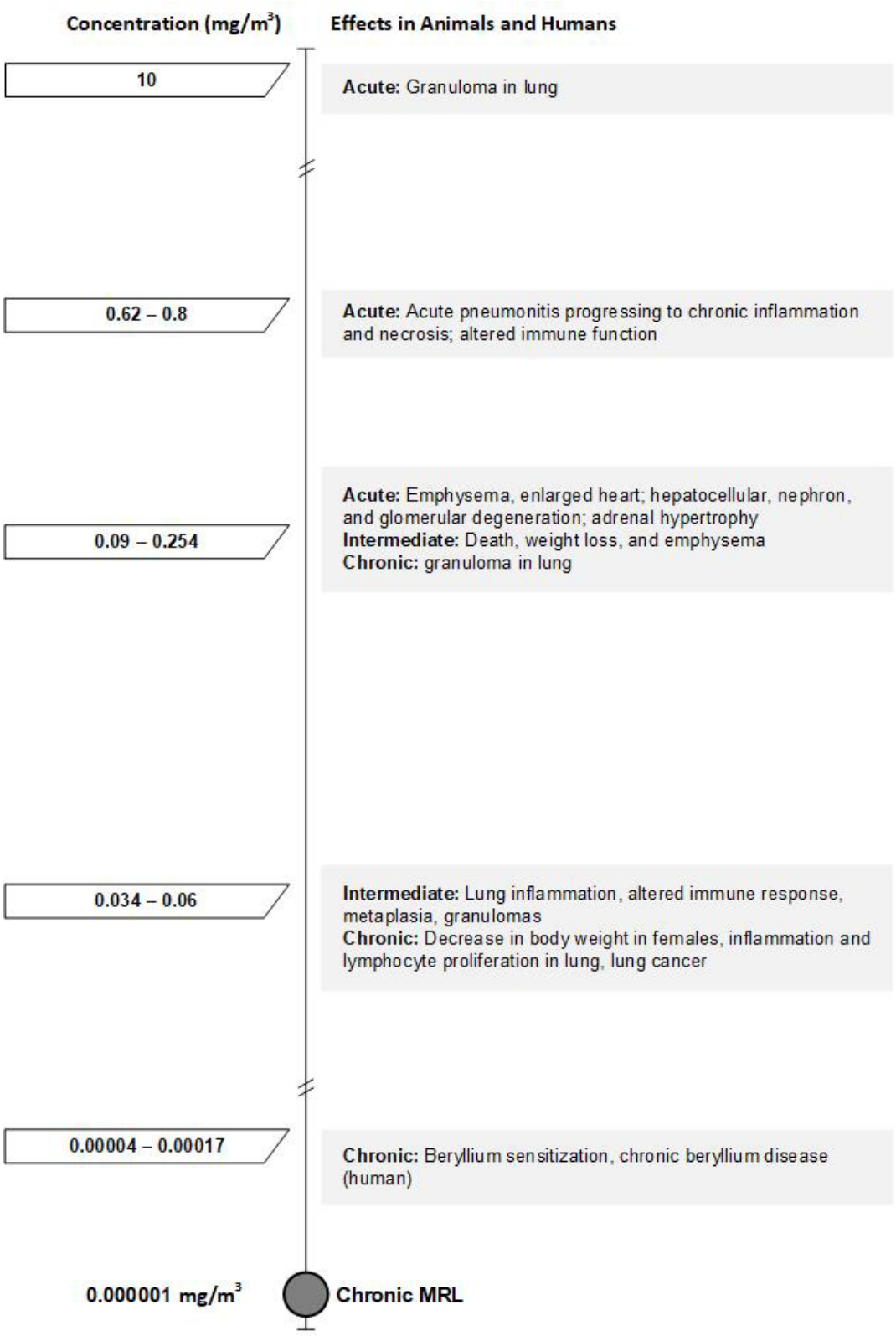
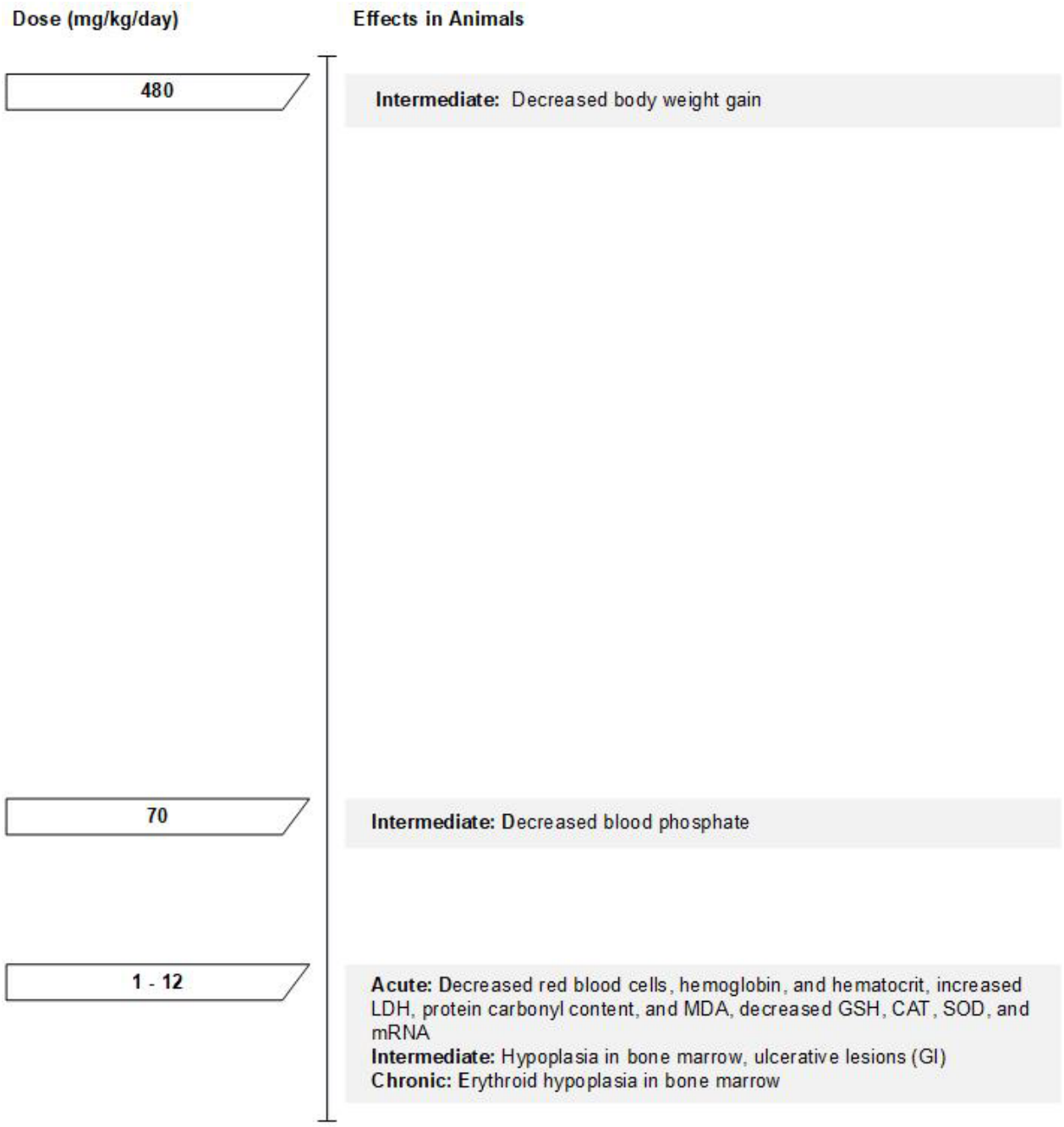


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Beryllium



1.3 MINIMAL RISK LEVELS (MRLS)

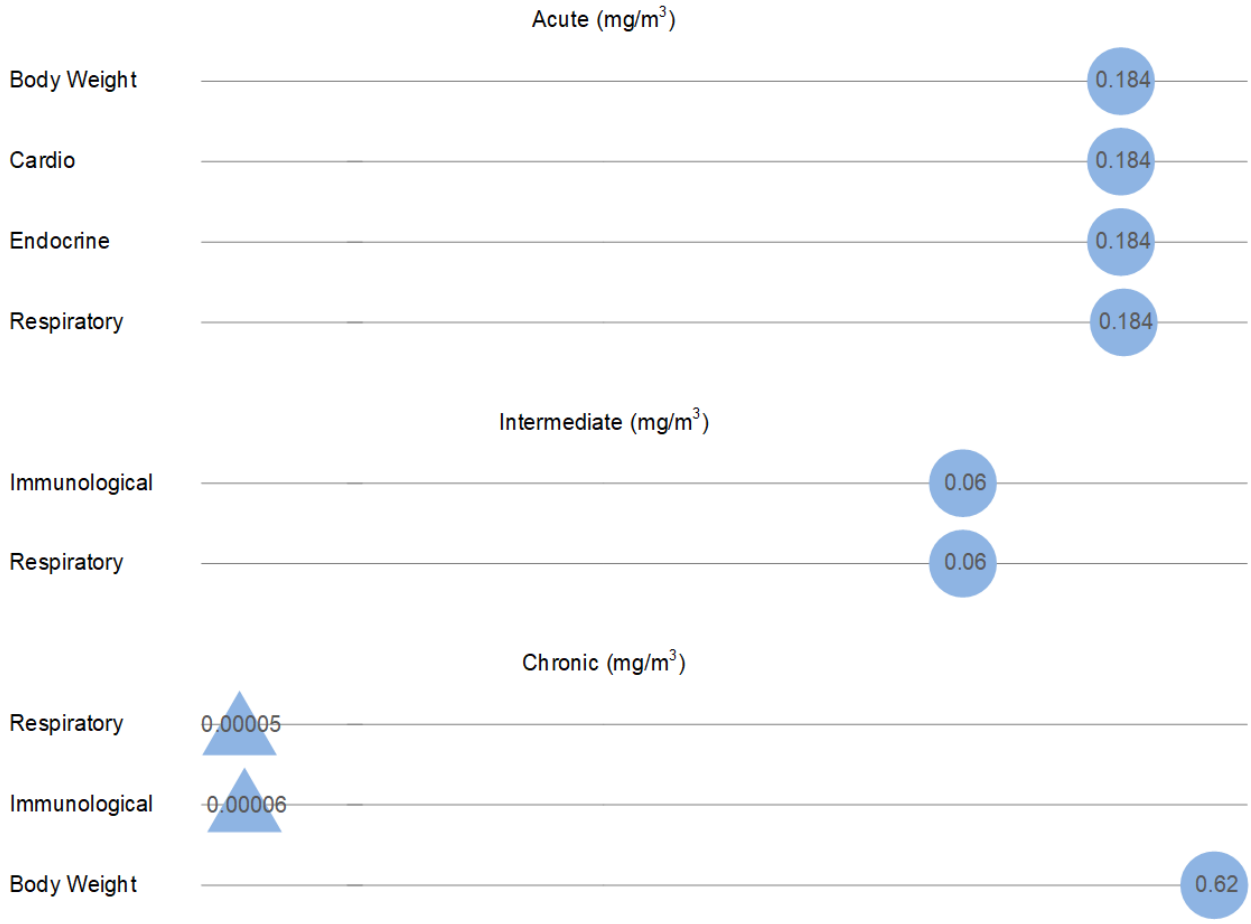
Based on the available human and animal data, the respiratory tract is the critical target of beryllium after inhalation exposures. However, except for the chronic duration, available data were deemed insufficient for deriving inhalation MRLs. The existing animal database is inadequate for developing provisional inhalation MRLs for both acute and intermediate duration exposures. In general, animal studies have not identified a reliable no-observed-adverse-effect level (NOAEL) for respiratory effects, and the lowest-observed-adverse-effect levels (LOAELs) are several orders of magnitude higher than the lowest LOAEL identified in occupational exposure studies, suggesting that humans may be the most sensitive species.

As presented in Figure 1-3, following inhalation exposure, the respiratory system is consistently the most sensitive target of beryllium toxicity and immunological health effects manifest as the duration of the exposure increases. The hematological system appears to be the sensitive target of oral beryllium toxicity, as shown in Figure 1-4. The oral database was considered inadequate for derivation of provisional chronic-, intermediate-, and acute-duration oral MRLs. The provisional chronic duration inhalation MRL is listed in Table 1-1, and the MRL details are discussed in greater detail in Appendix A.

Figure 1-3. Summary of Sensitive Targets of Beryllium – Inhalation

The respiratory endpoint is consistently the most sensitive target of beryllium inhalation exposure across exposure durations

Numbers in triangles and circles are the lowest LOAELs among health effects in humans and animals, respectively.[1]



[1]For acute inhalation exposure, death, hepatic, and body weight effects were also seen at this dose.

Figure 1-4. Summary of Sensitive Targets of Beryllium – Oral

The hematological endpoint is the most consistently sensitive target of beryllium oral exposure across durations.

Numbers in circles are the lowest LOAELs for all health effects in animals.

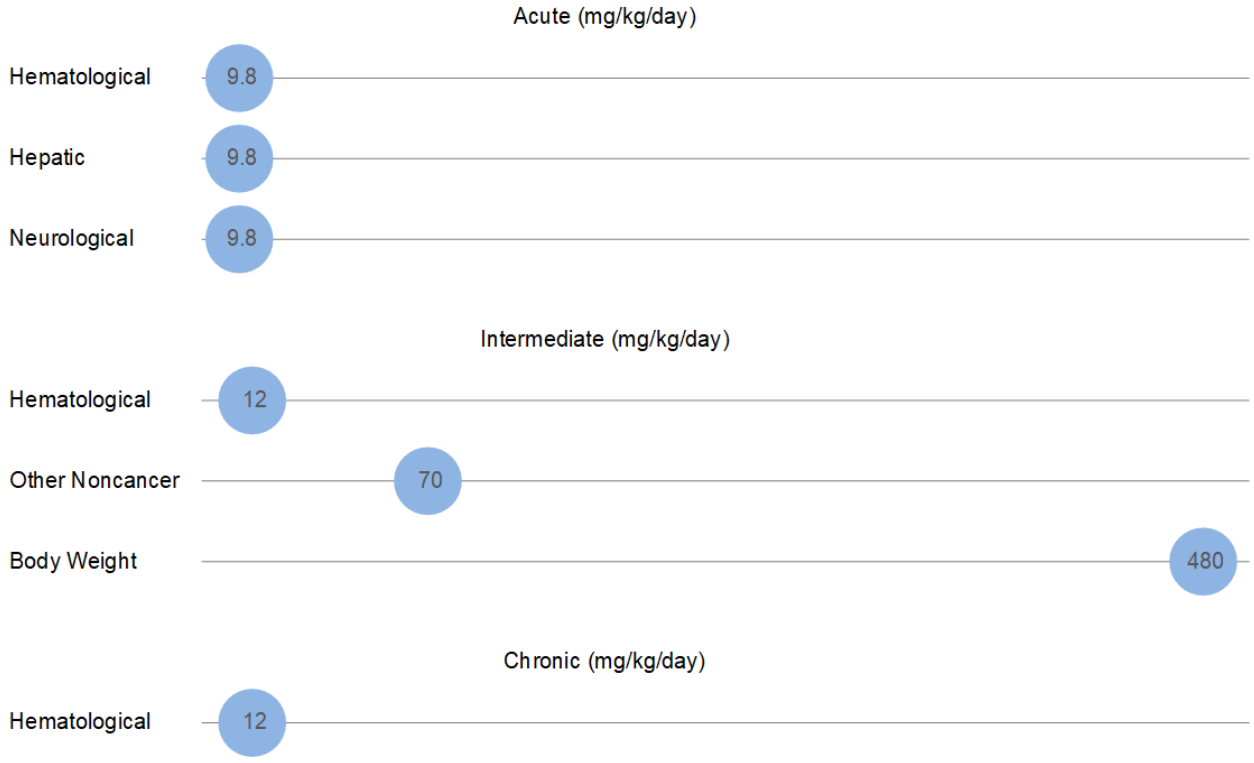


Table 1-1. Provisional Minimal Risk Levels (MRLs) for Beryllium[a]

Exposure duration	Provisional MRL	Critical effect	Point of departure	Uncertainty/ Modifying factor	Reference
Inhalation exposure (µg/m^3)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	0.001 µg/m^3 (0.0036 ppb)[b]	BeS	0.04 µg/m^3 (LOAEL)	30	Schuler et al. 2012
Oral exposure (mg/kg/day)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				

[a]See Appendix A for additional information. [b]0.000001 mg/m^3
BeS- beryllium sensitization

CHAPTER 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 on the toxicology of beryllium. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to beryllium, but may not be inclusive of the entire body of literature.

Summaries of the human observational studies are presented in Table 2-4, Table 2-5, and Table 2-8. Animal and select occupational inhalation studies are presented in Figure 2-2, animal oral studies are presented in Figure 2-3; and animal dermal data are presented in Table 2-3.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects (SLOAELs) are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints.

ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

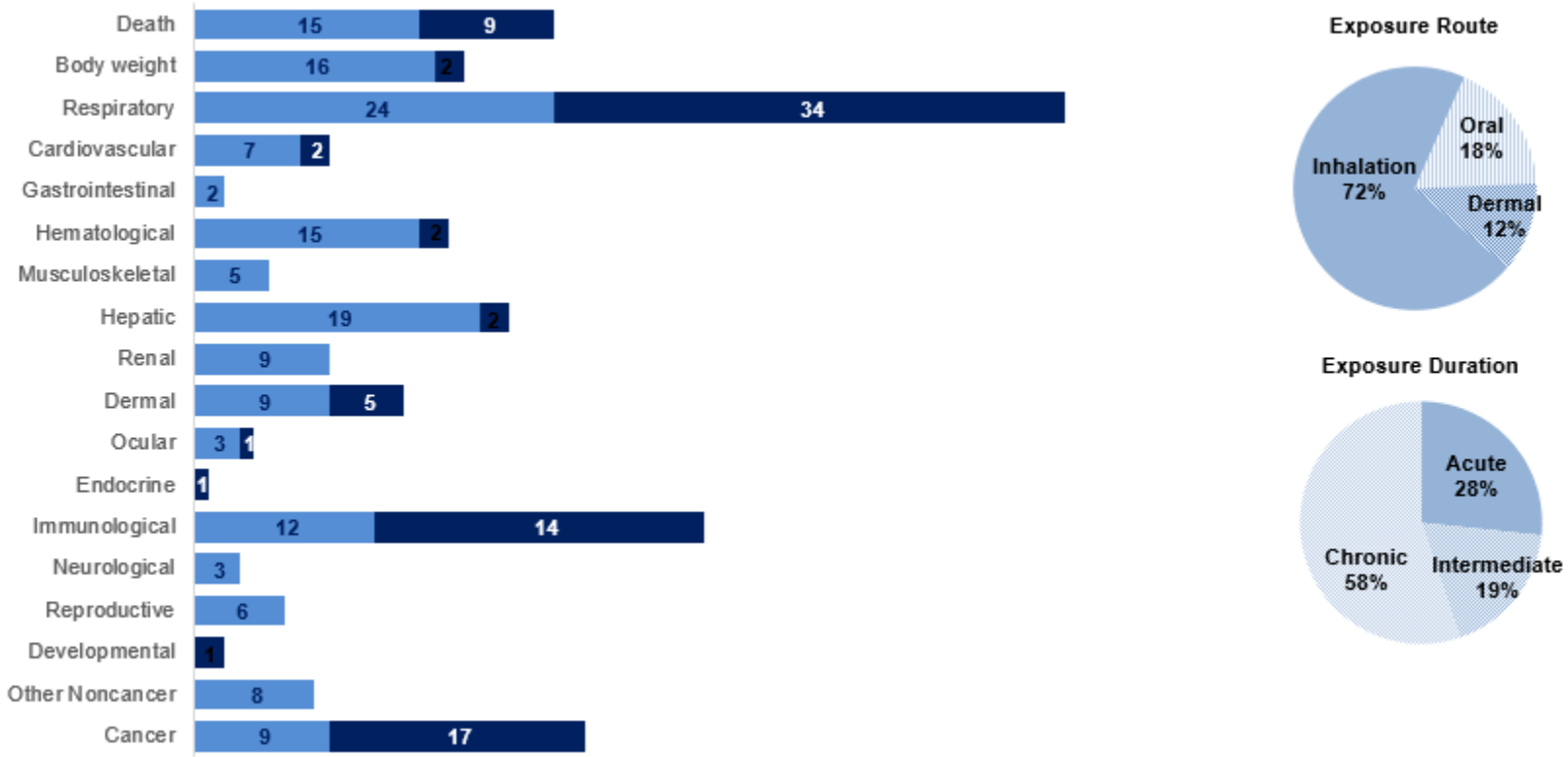
Due to the limitations of the available occupational epidemiological studies in terms of quantitative exposure information, many of the studies identified in the literature were not included in the LSE table. Specifically, the epidemiologic studies identified generally relied on exposure data captured from a limited period of time (e.g., a year), extrapolated over the exposure time period of interest, and used a mixture of multiple exposure estimation methods (e.g., area-wide, personal monitor), often to create job-specific exposure averages. In addition, a worker’s estimated exposure was often analyzed and presented as a single number (e.g., mean or cumulative exposure), while their true exposure was likely a range of concentrations. Thus, there was a large degree of uncertainty in the exact concentration workers were exposed to that would cause a health effect. These epidemiological studies are discussed in detail in the text and summarized in Table 2-4, Table 2-5, and Table 2-8.

Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of beryllium are indicated in Table 2-1.

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

Figure 2-1. Overview of the Number of Studies[1] Examining Beryllium Health Effects

Most studies examined the respiratory and cancerous effects of beryllium.
Fewer studies evaluated health effects in **humans** than **animals** (counts represent studies examining endpoint).



[1] Includes studies discussed in Chapter 2. A total of 142 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to Beryllium–Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
ACUTE EXPOSURE									
1	MONKEY (Macaca mulatta) 4 F	8-10 days 6 hours/day	0, 1.13, 8.3	BW OW FI GN HP	Death			1.13	4/4 died
					Bd wt			1.13	Severe weight loss, 8-34%
					Resp			1.13	Emphysema
					Cardio		1.13		Enlarged heart
					Hepatic		1.13		Hepatocyte degeneration
					Renal	1.13	8.3		Degeneration of the nephrons
					Endocr		1.13		Hypoplasia of the adrenal gland
Beryllium Phosphate Schepers 1964									
2	MONKEY (Macaca mulatta) 4 F	7 days 6 hours/day	0, 0.198	BW OW FI GN HP	Death			0.198	1/4 died
					Bd wt			0.198	24% average weight loss
					Resp			0.198	Emphysema
					Cardio		0.198		Enlarged heart
					Hepatic	0.198			
					Renal		0.198		Glomerular degeneration
Beryllium Sulfate; pre-sensitized Schepers 1964									

Table 2-1. Levels of Significant Exposure to Beryllium–Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
3	MONKEY (Macaca mulatta) 3 F	7-13 days 6 hours/day	0, 0.184	BW OW FI GN HP	Death			0.184	2/3 died
					Bd wt			0.184	19-23% weight loss
					Resp			0.184	Emphysema
					Cardio		0.184		Enlarged heart
					Hepatic		0.184		Hepatocellular degeneration
					Renal		0.184		Nephron degeneration
					Endocr		0.184		Adrenal hypotrophy
Beryllium Fluoride; pre-sensitized Schepers 1964									
4	RAT (Fischer- 344) 20M	1 hour	0, 0.447	BI HP	Resp		0.447 M		Increased lactic dehydrogenase, acid phosphatase, and alkaline phosphatase in lavage fluids 2 days post-exposure: lung inflammation
					Immuno		0.447 M		Reduced macrophagocytic function on day 2, 5 and 12 post-exposure
Beryllium Oxide Hart et al. 1984									
5	RAT (Fischer- 344) 36 M	1 hour	0, 13	HP	Resp			13	Pneumonitis
Beryllium Sulfate; pre-sensitized Sendelbach et al. 1986									
6	RAT (Fischer- 344) 12-16 M	1 hour	0, 4.05	HP BI	Resp			4.05	Pneumonitis
Beryllium Sulfate; pre-sensitized Sendelbach et al. 1989									

Table 2-1. Levels of Significant Exposure to Beryllium–Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
7	RAT (Fischer- 344) 54-74 M	50 minutes	0, 0.8	BI CS GN HP	Death			0.8	20/74 died
					Resp			0.8	Acute pneumonitis progressing to chronic inflammation and necrosis
Beryllium Haley et al. 1990									
8	RAT (Fischer- 344) 20 M	14 days 2 hours/day	0, 2.59	LE	Death			2.6	20/20 died
Beryllium Sulfate; pre-sensitized Sendelbach and Witschi 1987b									
9	MOUSE (BALB/c) 44 M	1 hour	0, 13	HP	Resp		13		Lung inflammation
Beryllium Sulfate; pre-sensitized Sendelbach et al. 1986									
10	DOG (Beagle) 8-14 NS	1 day	0, 10	HP BI	Resp			10	Granulomas in lung
					Immuno		10		Lymph node hyperplasia, lymphocyte stimulation
Beryllium Oxide Haley et al. 1989									
INTERMEDIATE EXPOSURE									
11	MONKEY (Macaca mulatta) 4 F	30 days 6 hours/day	0, 0.198	BW OW FI GN HP	Death			0.198	1/4 died
					Bd wt			0.198	15-39% weight loss
					Resp			0.198	Emphysema
					Hepatic	0.198			
					Renal	0.198			
Beryllium Phosphate Schepers 1964									

Table 2-1. Levels of Significant Exposure to Beryllium–Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
12	MONKEY (Saimiri sciureus) 2-12 M	6 months 5 days/week 6 hours/day	0, 0.620	BI BW GN HE HP	Bd wt	0.62			
					Resp		0.62		Inflammation of lungs
					Hemato	0.62			
					Hepatic	0.62			
					Renal	0.62			
Beryllium Oxide Wagner et al. 1969									
13	MONKEY (Saimiri sciureus) 2-12 M	6 months 5 days/week 6 hours/day	0, 0.210	BI BW GN HE HP BI	Resp		0.21		Inflammation of lungs
					Hemato	0.21			
					Hepatic	0.21			
					Renal	0.21			
					Other noncancer	0.21			
Beryllium Oxide Wagner et al. 1969									
14	RAT (Wistar) (Sherman) 63 M, 27 F	180 days 5-6 days/week 4-8 hours/day	0, 0.035	HP	Resp			0.035	Metaplasia, granulomas
					Cancer			0.035	CEL: lung cancer
Beryllium Sulfate; pre-sensitized Schepers et al. 1957									

Table 2-1. Levels of Significant Exposure to Beryllium–Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
15	RAT (Charles River) 33-60 M	6 months 5 days/week 6 hours/day	0, 0.210	BI BW GN HE HP	Bd wt	0.21			
					Resp			0.21	Granuloma in lung
					Hemato	0.21			
					Hepatic	0.21			
					Renal	0.21			
Beryllium Oxide Wagner et al. 1969									
16	RAT (Charles River) 33-60 M	6 months 5 days/week 6 hours/day	0, 0.620	BI BW GN HE HP	Bd wt	0.62			
					Resp	0.62			
					Hemato	0.62			
					Hepatic	0.62			
					Renal	0.62			
Beryllium Oxide Wagner et al. 1969									
17	MOUSE C3H/HeJ 40 M	3 weeks 5 days/week 6 hours/day	0, 0.254	HP IX	Immuno		0.254 M		>50% higher IFN-a, CD4+ and CD8+ T-cells ($p<0.05$); 30% decrease CD19 ($p<0.05$); 77% increase IL12 ($p<0.05$)
Beryllium Muller et al. 2011									
18	MOUSE C3H/HeJ 40 M	3 weeks 5 days/week 6 hours/day	0, 0.09	HP IX	Resp		0.09 M		Lung inflammation scores different ($p<0.05$)
					Immuno		0.09 M		40% higher IFN-a, CD4+T, and CD8+ cells ($p<0.05$); 22% decrease CD19 ($p<0.05$); >120% and 47% increase IL12 and IFN-g respectively ($p<0.05$)
Beryllium Oxide Muller et al. 2011									

Table 2-1. Levels of Significant Exposure to Beryllium–Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
19	MOUSE C3H/HeJ 40 M	3 weeks 5 days/week 6 hours/day	0, 0.06	HP IX	Resp Immuno		0.06 0.06		Lung inflammation scores different ($p<0.05$) >30% higher IFN-g, CD4+, CD8+; 155% increase IFN-g
Beryllium Aluminum Muller et al. 2011									
20	HAMSTER (Golden Syrian) 17-48 M	6 months 5 days/week 6 hours/day	0, 0.620	BI BW GN HE HP	Bd wt Resp Hemato Hepatic Renal	0.62 0.62 0.62 0.62 0.62			
Beryllium Oxide Wagner et al. 1969									
21	HAMSTER (Golden Syrian) 33-60 M	6 months 5 days/week 6 hours/day	0, 0.210	BI BW GN HE HP	Bd wt Resp Hemato Hepatic Renal	0.21 0.21 0.21 0.21		0.21	Granulomas of the lung
Beryllium Oxide Wagner et al. 1969									
CHRONIC EXPOSURE									
22	HUMAN 204 M, 60 F	≤6 years (median of 1.75 years) (Occup)	<0.00006 -0.00356	CS IX	Immuno		0.00004[b]		BeS observed for average lowest respirable Be
Beryllium Schuler et al. 2012									

Table 2-1. Levels of Significant Exposure to Beryllium–Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
23	HUMAN 204 M, 60 F	≤6 years (median of 1.75 years) (Occup)	<0.00005 -0.00356	CS IX	Resp			0.00017	SLOAEL: CBD cases observed for average lowest respirable Be
Beryllium Schuler et al. 2012									
24	MONKEY (Saimiri sciureus) 2-12 M	12-23 months 5 days/week 6 hours/day	0, 0.210	BI BW GN HE HP	Bd wt	0.21			
					Resp		0.21		Inflammation of lungs
					Hemato	0.21			
					Hepatic	0.21			
					Renal	0.21			
Beryllium Oxide Wagner et al. 1969									
25	MONKEY (Saimiri sciureus) 2-12 M	12-23 months 5 days/week 6 hours/day	0, 0.620	BI BW GN HE HP	Bd wt	0.62			
					Resp		0.62		Inflammation of lungs
					Hemato	0.62			
					Hepatic	0.62			
					Renal	0.62			
Beryllium Oxide Wagner et al. 1969									
26	RAT (Sprague-Dawley) 75 M,75 F	72 weeks 5 days/week 7 hours/day	0, 0.034	BW OW HP	Bd wt	0.034 M		0.034 F	27% decrease in body weight
					Resp		0.034		Inflammation and atypical lymphocyte proliferation with scattered dust-laden macrophages in the lung
					Cancer			0.034	CEL: lung cancer
Beryllium Sulfate; pre-sensitized Reeves et al. 1967									
27	RAT		0, 0.620		Bd wt		0.62		15% decreased body weight gain

Table 2-1. Levels of Significant Exposure to Beryllium–Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
	(Charles River) 33-60 M	12-17 months 5 days/week 6 hours/day		BI BW GN HE HP	Resp		0.62		Consolidation of lung
					Hemato	0.62			
					Hepatic	0.62			
					Renal	0.62			
					Cancer			0.62	CEL: lung cancer
Beryllium Oxide Wagner et al. 1969									
28	RAT (Charles River) 33-60 M	12-17 months 5 days/week 6 hours/day	0, 0.210	BI BW GN HE HP	Bd wt	0.21			
					Resp			0.21	Granuloma in lung
					Hemato	0.21			
					Hepatic	0.21			
					Renal	0.21			
Beryllium Oxide Wagner et al. 1969									
29	HAMSTER (Golden Syrian) 17-48 M	12-17 months 5 days/week 6 hours/day	0, 0.620	BI BW GN HE HP	Bd wt	0.62			
					Resp	0.62			
					Hemato	0.62			
					Hepatic	0.62			
					Renal	0.62			
Beryllium Oxide Wagner et al. 1969									
30	HAMSTER (Golden Syrian) 17-48 M	12-17 months 5 days/week 6 hours/day	0, 0.210	BI BW GN HE HP	Bd wt	0.21			
					Resp			0.21	Granulomas in the lung
					Hemato	0.21			
					Hepatic	0.21			
					Renal	0.21			

Table 2-1. Levels of Significant Exposure to Beryllium–Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	LOAEL (mg/m^3)	Effects
Beryllium Oxide									
Wagner et al. 1969									

[a] The number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

[b] Used to derive a provisional chronic inhalation minimal risk level of 0.000001 mg/m^3; LOAEL was divided by a total uncertainty factor of 30 (10 for use of a LOAEL and 3 for human variability). See Appendix A for more detailed information regarding the provisional MRL.

Highlighted row indicates the principal study used for the MRL

BC = blood chemistry; Bd wt or BW = body weight; BI = biochemical changes; BS = beryllium sensitization; Cardio = cardiovascular; CBD = chronic beryllium disease; CD19 = cluster of differentiation 19; CEL = cancer effect level; CI = confidence interval; CS = clinical signs; Endocr = endocrine; F = female(s); FI = food intake; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathological; IFN = interferon; IL 12 = interleukin 12; Immuno = immunological; IX = immune function; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = muscular/skeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Occup = occupational; OR = odds ratio; OW = organ weight; Resp = respiratory; SLOAEL = serious LOAEL; UR = urinalysis

Figure 2-2. Levels of Significant Exposure to Beryllium–Inhalation

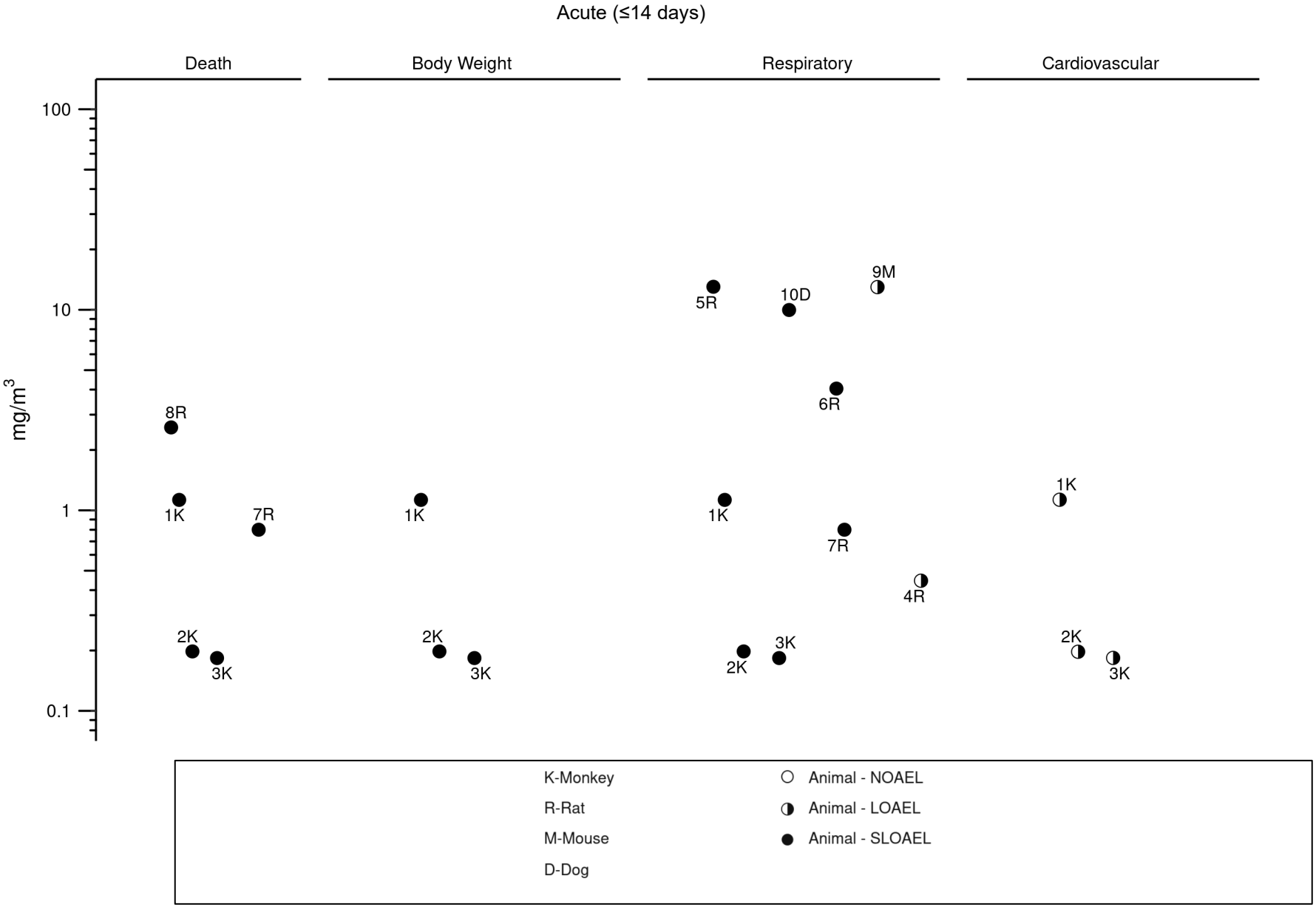


Figure 2-2. Levels of Significant Exposure to Beryllium–Inhalation

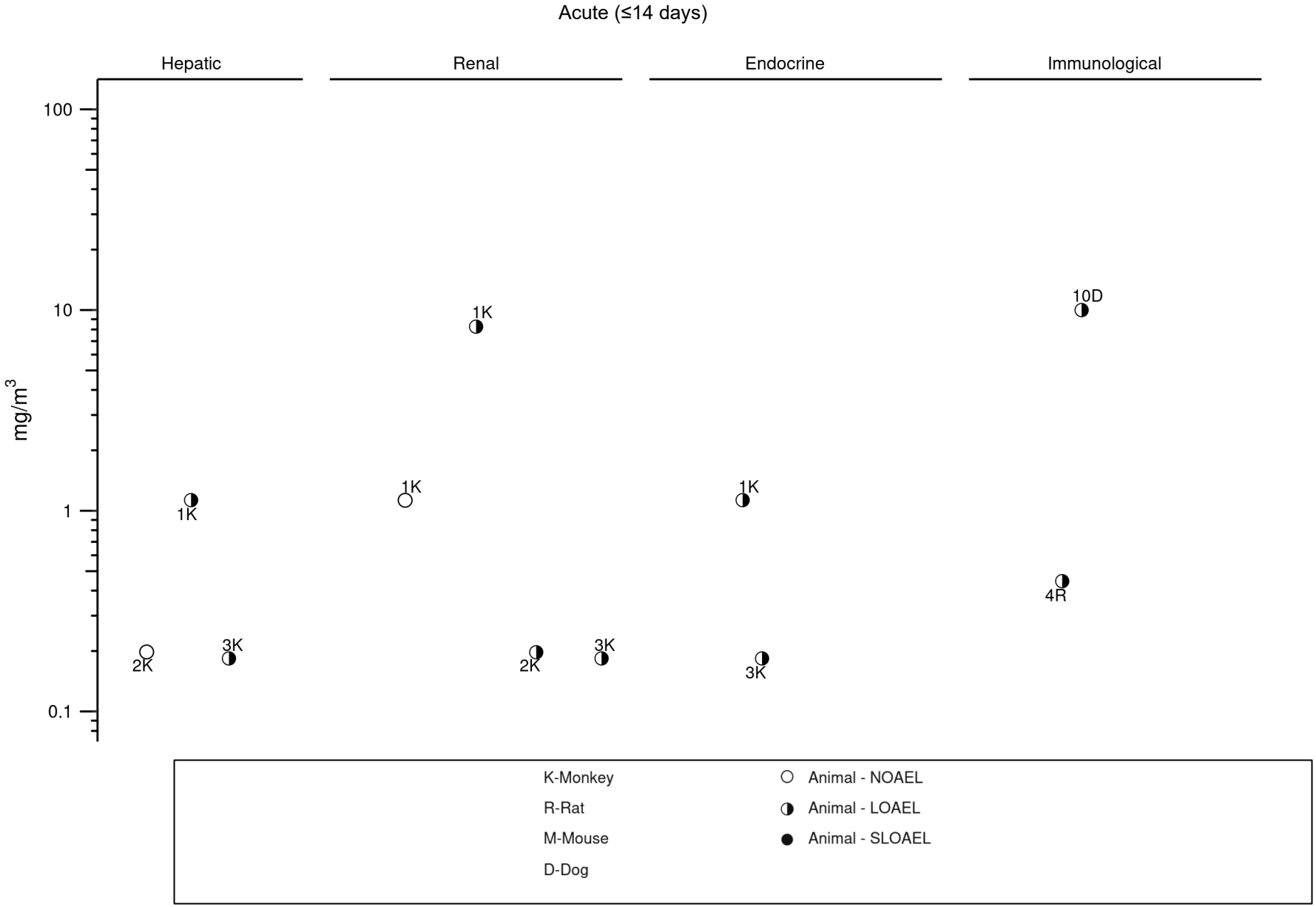


Figure 2-2. Levels of Significant Exposure to Beryllium–Inhalation

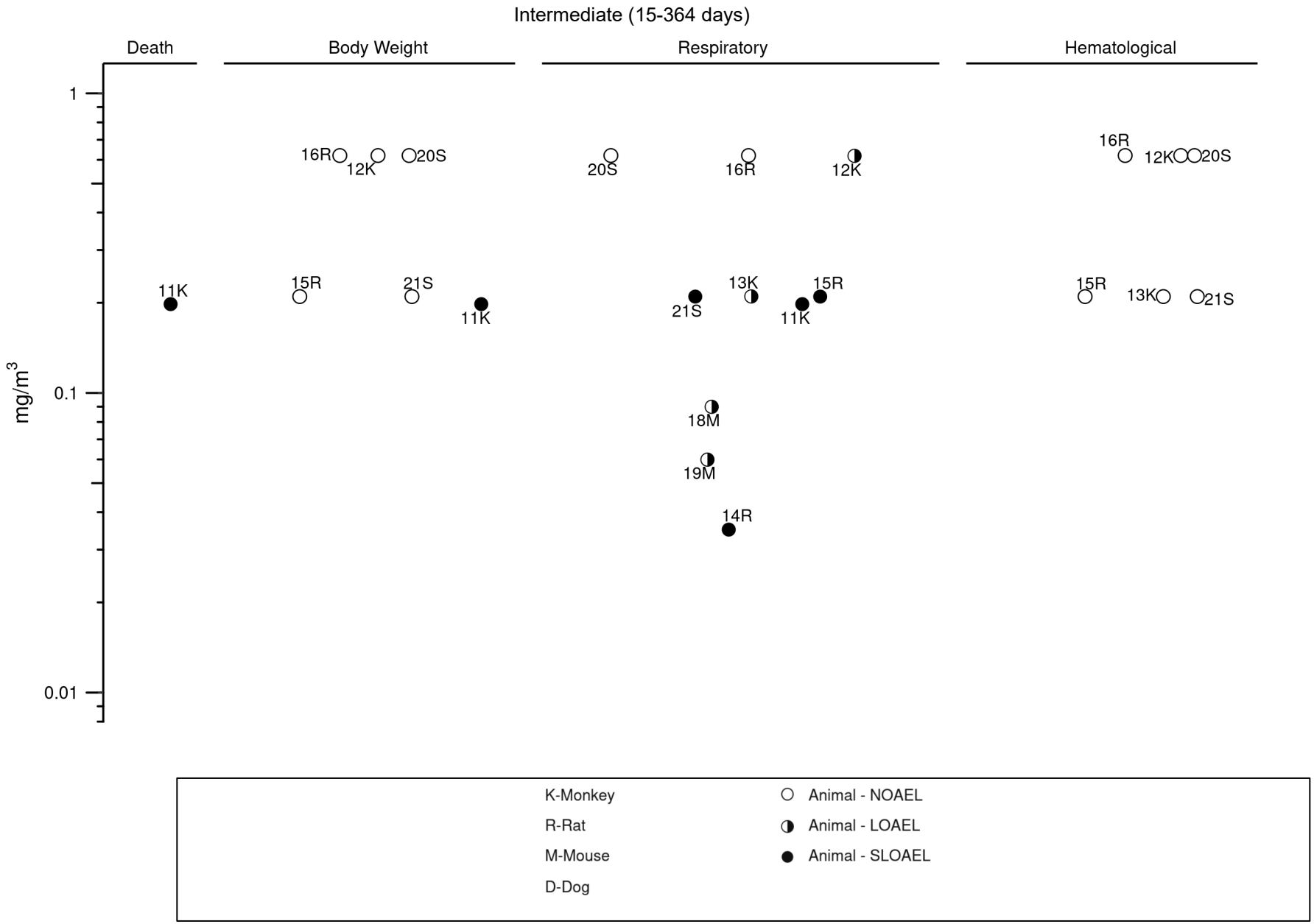


Figure 2-2. Levels of Significant Exposure to Beryllium–Inhalation

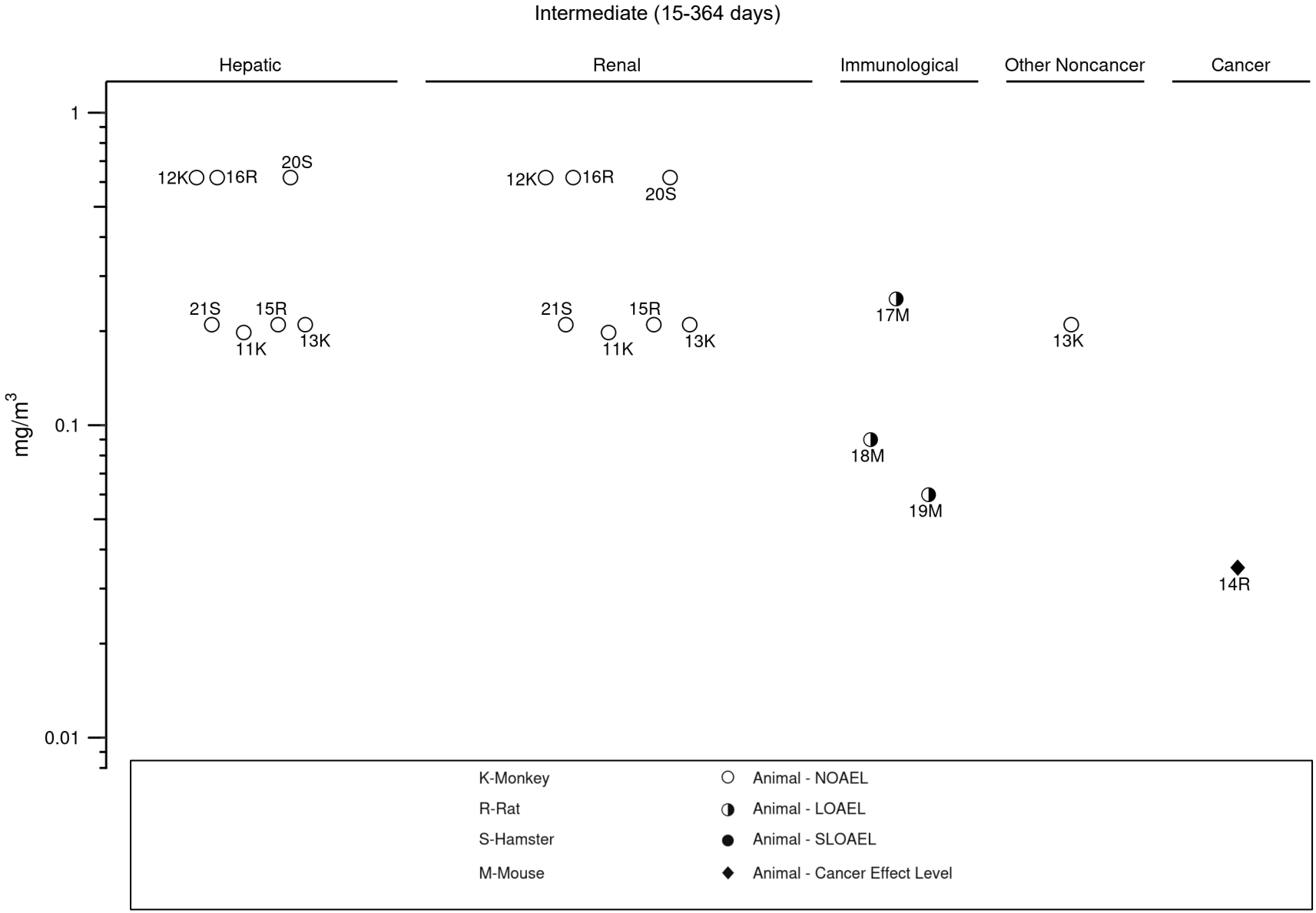


Figure 2-2. Levels of Significant Exposure to Beryllium–Inhalation

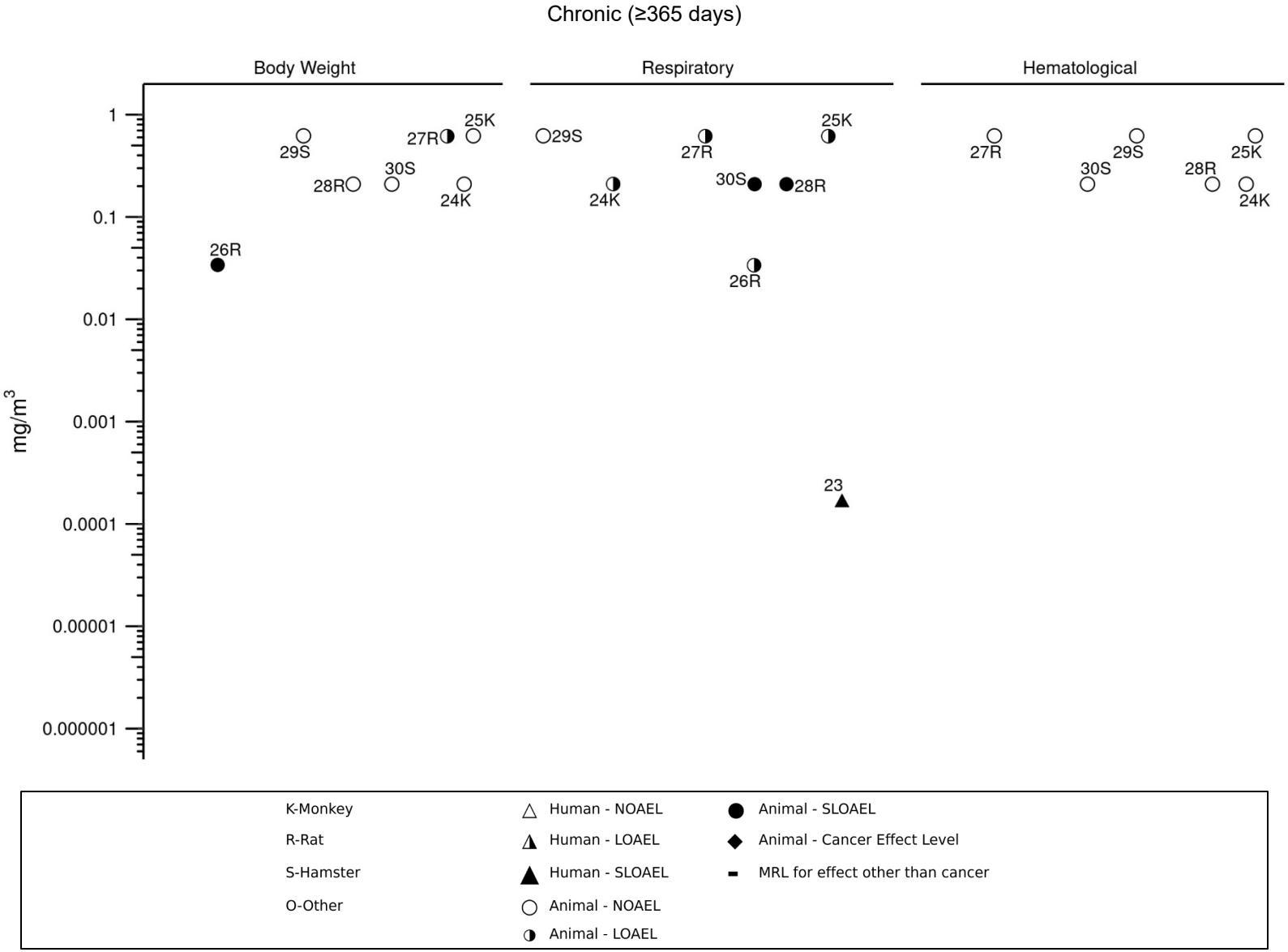


Figure 2-2. Levels of Significant Exposure to Beryllium–Inhalation

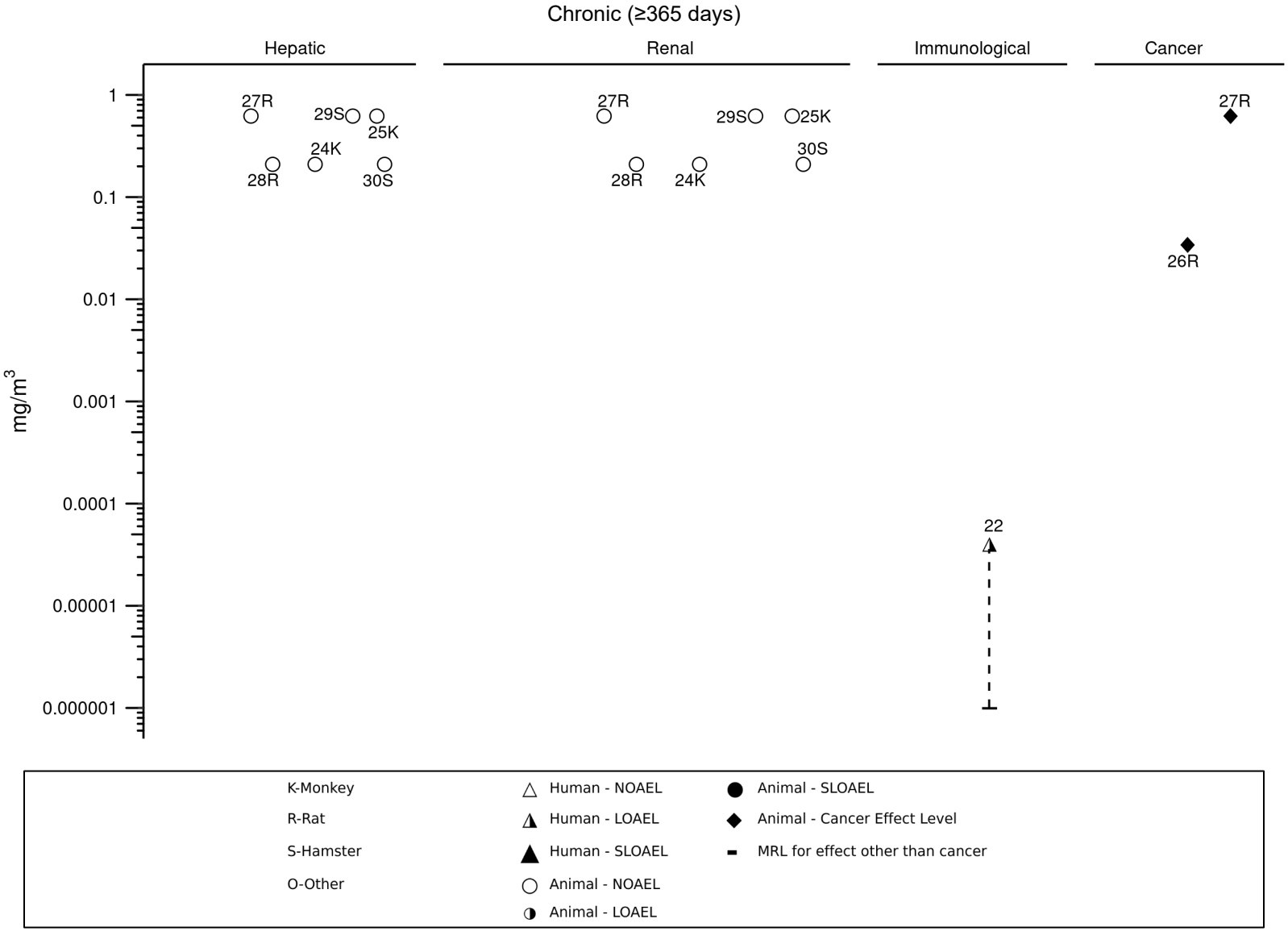


Table 2-2. Levels of Significant Exposure to Beryllium–Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
ACUTE EXPOSURE									
1	RAT (Wistar) 8 M	5 days (W)	0, 9.8	BI HE	Hepatic		9.8 M		87% LDH increase, 76% protein carbonyl content increase, 38% increase malondialdehyde (MDA), 52% GSH decline; 35% CAT decrease, 40% SOD decrease with concomitant decrease in messenger RNA levels
					Neuro		9.8 M		Brain: 23% CAT decrease, 30% SOD decrease with concomitant decrease in messenger RNA levels; 96 – 133% increase in protein carbonyl content, MDA, and LDH
Beryllium Chloride									
El-Beshbishy et al. 2012									
2	RAT (RccHAN:WIST) 6 F	Once (GO)	0, 2000	BW CS LE	Bd wt	2000			
Beryllium									
Strupp 2011a									
3	MOUSE (CBA) 5 M	1 d (GW)	0, 7.5, 25, 50, 70, 115, 140, 250		Death			140	(LD50)
Beryllium Sulfate									
Ashby et al. 1990									

Table 2-2. Levels of Significant Exposure to Beryllium–Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
INTERMEDIATE EXPOSURE									
4	RAT (Wistar) 4 NS	13-42 days (F)	0, 345	BW FI HP	Bd wt	345			
					Musc/skel			345	Rickets
Beryllium Carbonate Jacobson 1933									
5	RAT (NS) 8 NR	21-22 days (F)	0, 70	BI DX	Musc/skel			70	Severe rickets
					Other noncancer		70		58% decrease blood phosphate levels
Beryllium Carbonate Kay and Skill 1934									
6	RAT (Wistar) 10 M	4 weeks (F)	0, 480	BI BW	Bd wt		480		18% decrease in body weight gain
					Other noncancer		480		25% decreased serum phosphate
Beryllium Carbonate Matsumoto et al. 1991									
7	RAT (Sprague-Dawley) 5 F	91d (W)	0, 0.7	BW FI WI	Bd wt	0.7			
Beryllium Sulfate Freundt and Ibrahim 1990									
8	RAT (NS) NS	24-28 days (F)	0, 35, 70, 140, 280, 840	HP	Musc/skel			35	Rickets
Beryllium Carbonate Guyatt et al. 1933									

Table 2-2. Levels of Significant Exposure to Beryllium–Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
9	DOG (Beagle) 5 M, 5 F	26-33 weeks (F)	M: 0, 12; F: 0, 17	HE LE GN RX	Death			12	2/10 deaths
					Resp	12 M			
					Cardio	12 M			
					Gastro			12 M 17F	Ulceration in intestines
					Hemato		12 M		Hypoplasia in bone marrow
							17 F		Hypoplasia in bone marrow
					Musc/skel	12 M			
					Hepatic	12 M			
					Renal	12 M			
					Dermal	12 M			
					Ocular	12 M			
					Endocr	12 M			
					Repro			12 M	Testicular atrophy, testicular degeneration
Beryllium Sulfate **Morgareidge et al. 1976**									

Table 2-2. Levels of Significant Exposure to Beryllium–Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
CHRONIC EXPOSURE									
10	RAT (Wistar) 50 M, 50 F	2 years (F)	0, 0.30, 2.8, 31.0	BW OW FI HP	Bd wt	31			
					Resp	31			
					Cardio	31			
					Gastro	31			
					Hemato	31			
					Musc/skel	31			
					Hepatic	31			
					Renal	31			
					Ocular	31			
					Endocr	31			
Beryllium Sulfate Morgareidge et al. 1975									
11	RAT (Long- Evans) 52 M, 52 F	3.2 years (W)	M: 0, 0.6; F: 0, 0.7	BW HP BC UR	Bd wt	0.7			
					Resp	0.7			
					Cardio	0.7			
					Hepatic	0.7			
					Renal	0.7			
					Other noncancer	0.7			
Beryllium Sulfate Schroeder and Mitchener 1975a									

Table 2-2. Levels of Significant Exposure to Beryllium–Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
12	MOUSE (Swiss) 54 M, 54 F	898 days (W)	0, 1	BW HP	Bd wt	1			
					Resp	1			
					Cardio	1			
					Hemato	1			
					Hepatic	1			
					Renal	1			
Beryllium Sulfate Schroeder and Mitchener 1975b									
13	DOG (Beagle) 5 M, 5 F	143-172 weeks (F)	M: 0, 0.02, 0.1, 1; F: 0, 0.03, 0.2, 1	BI BC BW CS HP GN OW RX DX	Bd wt	1			
					Resp	1			
					Cardio	1			
					Gastro	1			
					Hemato	1			
					Musc/skel	1			
					Hepatic	1			
					Renal	1			
					Dermal	1			
					Ocular	1			
					Endocr	1			
					Repro	1			
					Develop	1			
Beryllium Sulfate Morgareidge et al. 1976									

Table 2-2. Levels of Significant Exposure to Beryllium–Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects

[a] The number corresponds to entries in Figure 2-3; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

BC = blood chemistry; Bd wt or BW = body weight; BI = biochemical changes; CAT = catalase enzyme; Cardio = cardiovascular; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; (F) = feed; F = female(s); FI = food intake; Gastro = gastrointestinal; GN = gross necropsy; (GO) = gavage in oil vehicle; GSH = glutathione; (GW) = gavage with aqueous vehicle; HE = hematology; Hemato = hematological; HP = histopathological; LE = lethality; LOAEL = lowest-observed-adverse-effect level; LD50 = lethal dose, 50% kill; LDH = lactate dehydrogenase; M = male(s); MDA = malondialdehyde; Musc/skel = muscular/skeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OW = organ weight; RBC = red blood cell; Repro = reproductive; Resp = respiratory; RNA = ribonucleic acid; RX = reproductive function; SOD = superoxide dismutase; UR = urinalysis; (W) = drinking water; WI = water intake

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

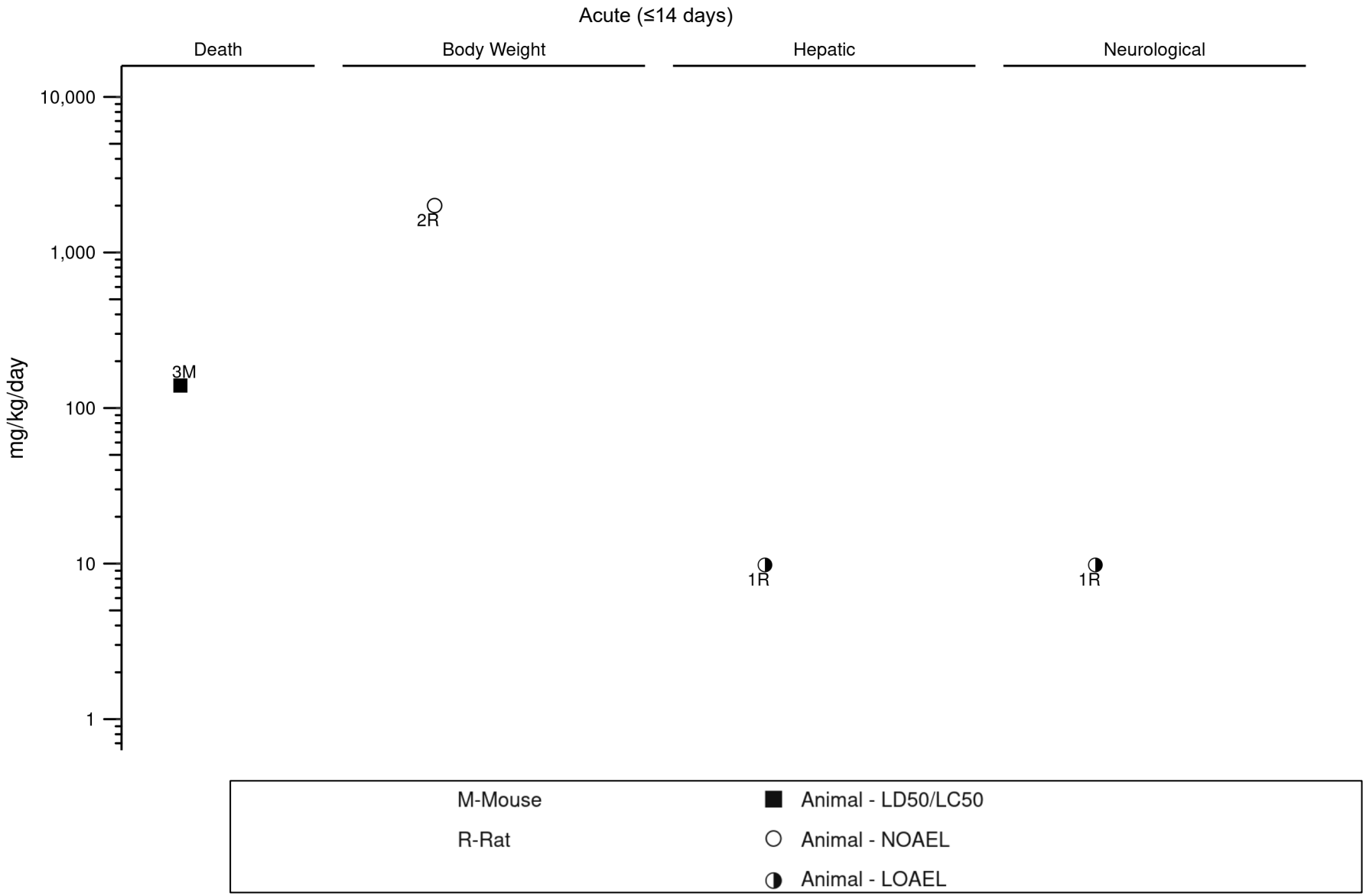


Figure 2-3. Levels of Significant Exposure to Beryllium–Oral

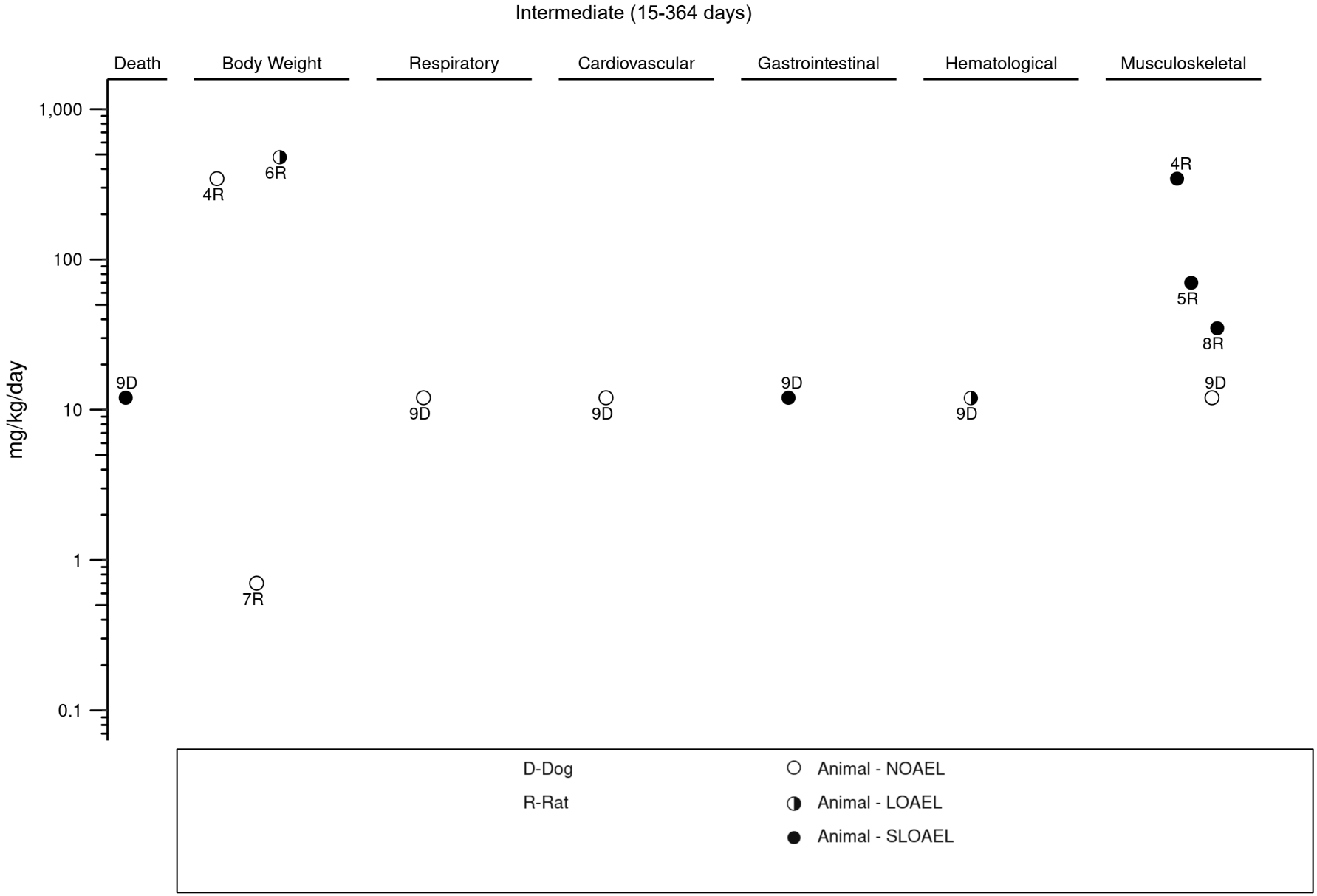


Figure 2-3. Levels of Significant Exposure to Beryllium–Oral

Intermediate (15-364 days)

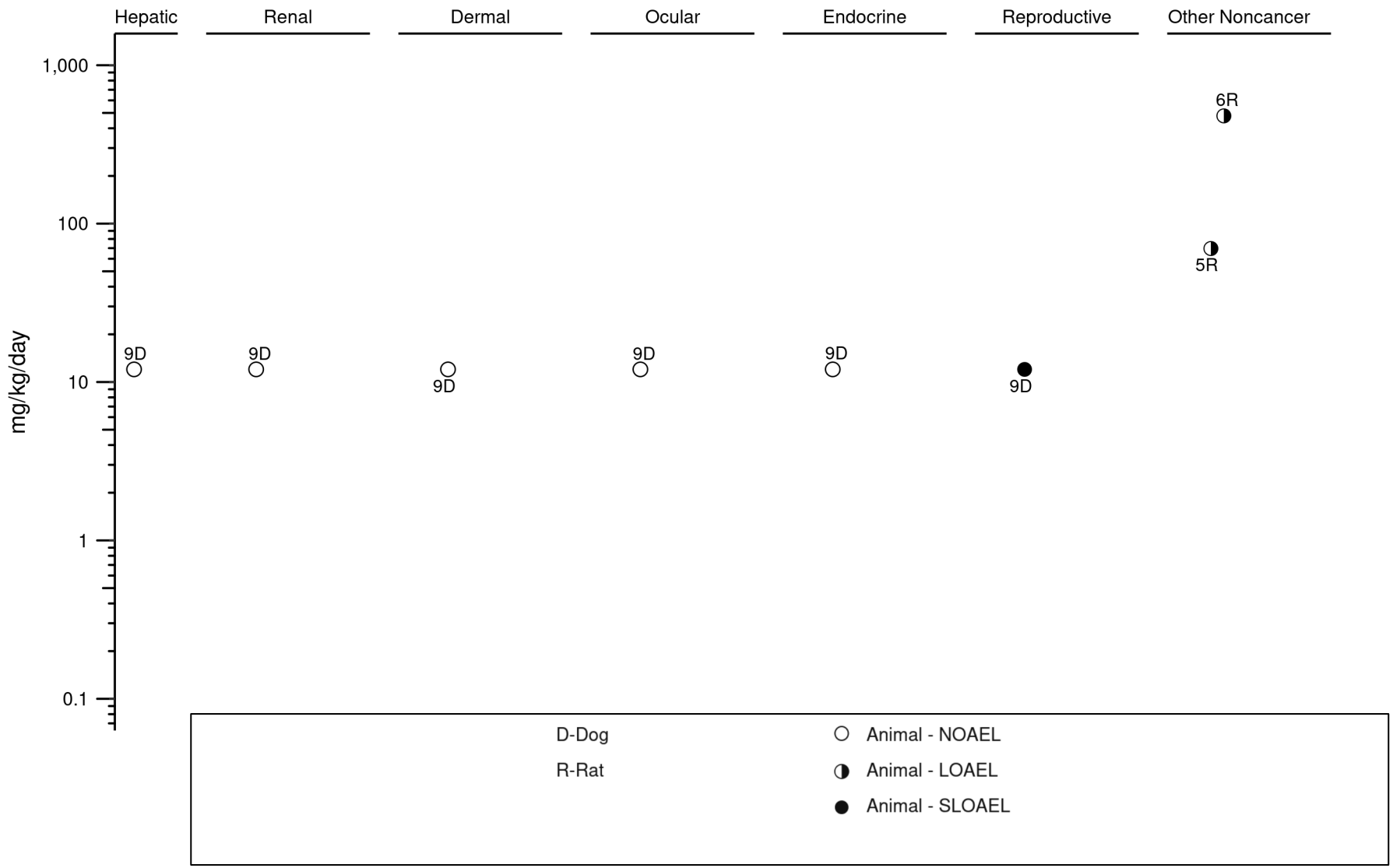


Figure 2-3. Levels of Significant Exposure to Beryllium–Oral

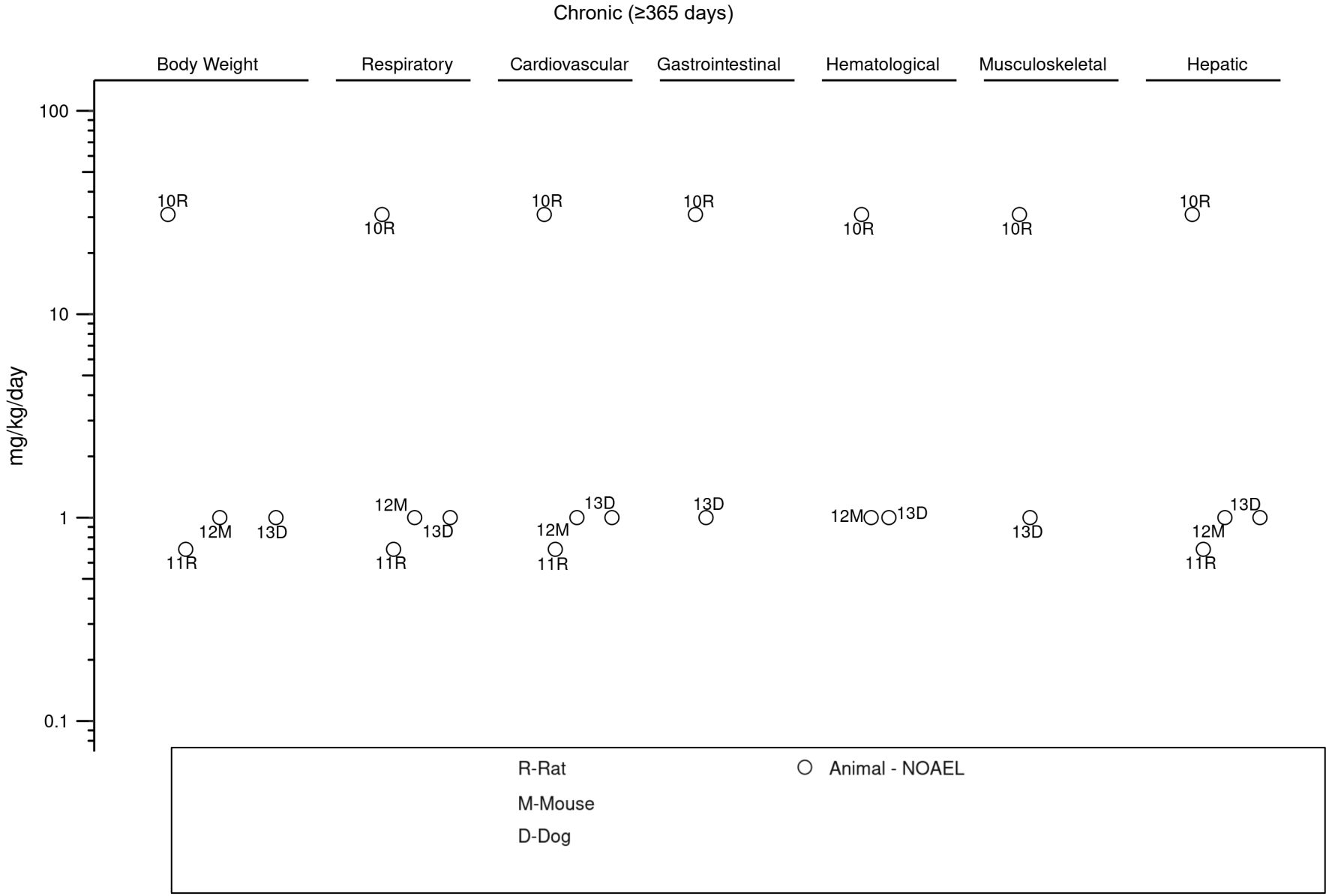


Figure 2-3. Levels of Significant Exposure to Beryllium–Oral

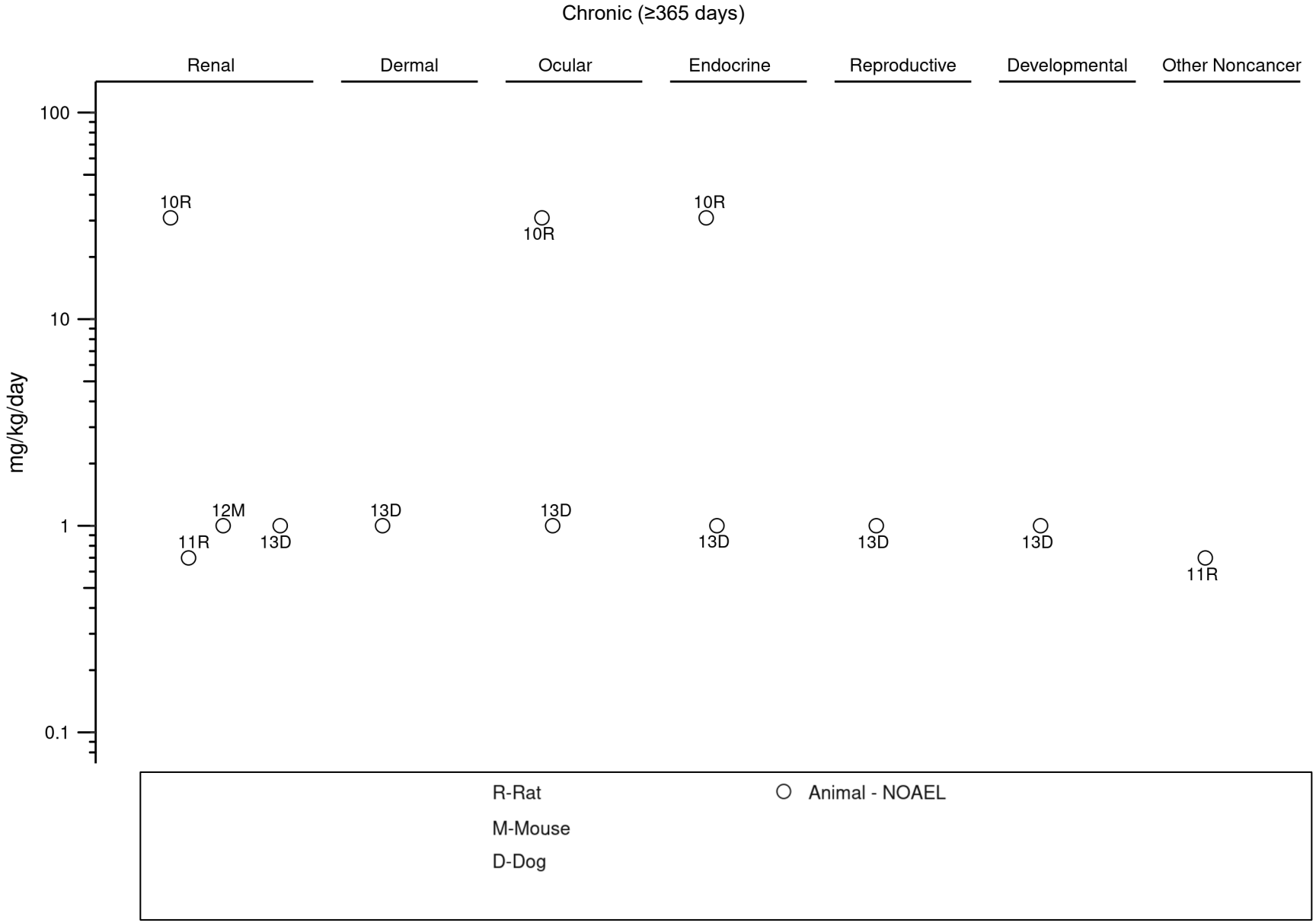


Table 2-3. Levels of Significant Exposure to Beryllium–Dermal

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
1	Mice C3H/HeJ or C3H/HeOuJ 10 NS	2 weeks 3 days/week	0, 0.5 M	IX	Immuno		0.5 M		>30-fold increase in beryllium-stimulated cell proliferation was observed in the auricular lymph node cells and blood
Beryllium Sulfate Tinkle et al. 2003									
2	Mice C3H/HeJ or C3H/HeOuJ NS	Once	0, 0.5 M	IX	Immuno		0.5 M		25-30% increase in ear thickness at 24 hr.
Beryllium Sulfate; BeO and $BeSO_4$ pre-sensitized Tinkle et al. 2003									
3	HUMAN 7-10 M	48 hours	0, 0.19, 1.9, 3.8 mg/mL	CS	Dermal		0.19 mg/mL		3/10 with allergic dermatitis
Beryllium Sulfate; pre-sensitized Curtis 1951									
4	HUMAN 10-13 M	48 hours	0, 0.019, 0.19, 1.9, 3.8 mg/mL	CS	Dermal		0.019 mg/mL		5/13 with allergic dermatitis
Beryllium Fluoride; pre-sensitized Curtis 1951									
5	HUMAN 8-9 M	48 hours	0, 0.19, 1.9, 3.8 mg/mL	CS	Dermal		1.9 mg/mL		4/9 with allergic dermatitis
Beryllium Nitrate; pre-sensitized Curtis 1951									

Table 2-3. Levels of Significant Exposure to Beryllium–Dermal

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
6	HUMAN 16	48 hours	0, 0.019, 0.19, 0.38 mg/mL	CS	Dermal		0.38 mg/mL		8/16 with dermatitis
Beryllium Fluoride Curtis 1951									
7	HUMAN 16	48 hours	0, 0.019, 0.19, 0.38 mg/mL	CS	Dermal		0.38 mg/mL		2/16 with dermatitis
Beryllium Chloride Curtis 1951									
8	GN PIG (albino) 5 M	Once	0, 0.02 M, 0.1 M	CS	Dermal		0.02 M		Delayed type hypersensitivity reaction
Beryllium Fluoride Belman 1969									
9	GN PIG (albino) 5 M	Once	0, 0.1 M	CS	Dermal		0.1 M		Delayed type hypersensitivity reaction
Beryllium Chloride Belman 1969									
10	GN PIG (Hartley) 4-11 NS	Once	0, 0.43 µg, 0.43 mg	HP	Resp		0.43 µg		Lung inflammation
					Dermal		0.43 µg		Delayed type hypersensitivity reaction
					Immuno		0.43 µg		Splenic hyperplasia
Beryllium Sulfate Marx and Burrell 1973									
11	GN PIG (Dunkin Hartley) 10-20 F	24 hours	0, 3%	CS HP	Dermal		3%		Delayed type hypersensitivity reaction, erythema, edema
Beryllium Sulfate Zissu et al. 1996									

Table 2-3. Levels of Significant Exposure to Beryllium–Dermal

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
12	GN PIG (Dunkin-Hartley) 10-20 F	24 hours	0, 50%	CS HP	Dermal		50%		Delayed type hypersensitivity reaction, erythema, edema
Beryllium Aluminum Zissu et al. 1996									
13	GN PIG (Hartley) 2- 4 NS	Once	0, 1.8 µg, 1.8 mg	HP	Dermal		1.8 µg		Delayed type hypersensitivity reaction
Beryllium Oxide Marx and Burrell 1973									
14	GN PIG (Hartley) 2 NS	Once	0, 1.8 mg	HP	Dermal	1.8 mg			
Beryllium Oxide Marx and Burrell 1973									
15	GN PIG (Hartley) 2 NS	Once	0, 0.48 µg, 1.9 mg	HP	Dermal		0.48 µg		Delayed type hypersensitivity reaction
Beryllium Fluoride Marx and Burrell 1973									
16	RABBIT (New Zealand) 1 M, 2 F	4 hours	0, 500 mg	CS	Dermal	500 mg			
Beryllium Strupp 2011a									

Table 2-3. Levels of Significant Exposure to Beryllium–Dermal

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
17	RABBIT (New Zealand) 1 M, 2 F	Once	0, 100 mg	CS	Ocular	100 mg			
Beryllium Carbonate Strupp 2011a									
INTERMEDIATE EXPOSURE									
18	GN PIG (Hartley) 4-11 NS	24 weeks Once/2 weeks	0, 0.86 µg		Dermal		0.86 µg		Increased macrophage inhibition factor and T-cell activity
Beryllium Sulfate Marx and Burrell 1973									

CS = clinical signs; F = female(s); HP = histopathological; hr = hour; Immuno = immunological; IX = immune function; LOAEL = lowest-observed-adverse-effect level; M = male(s) (when part of species column, molar when listed as a dose or an effect level); NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory

2.2 DEATH

Several retrospective cohort studies evaluating death have been conducted; these studies are summarized in Table 2-4. Retrospective mortality studies associating exposure to beryllium with death from cancer are discussed in Section 2.19. As discussed in Section 2.4 under Respiratory Effects, exposure to beryllium can result in two types of nonneoplastic respiratory disease, acute beryllium disease (ABD) and chronic beryllium disease (CBD). Both forms can be fatal. Many human studies indicate an increase in mortality after inhalation exposure. Furthermore, an increase in mortality is observed in animal studies after inhalation exposure. In animal studies after oral exposure, mortality was observed but was contingent on the compound being tested.

Several studies have found the pulmonary disease mortality rate among beryllium workers to be higher than the national average (Infante et al. 1980; Schubauer-Berigan et al. 2011a; Wagoner et al. 1980). In the Wagoner et al. (1980) study, the incidence of death due to nonneoplastic respiratory disease was higher among employees who remained in the industry for <5 years after initial exposure and were exposed prior to 1950 before strict exposure controls were initiated. Infante et al. (1980) found that the incidence of death due to nonneoplastic respiratory disease was higher in workers exposed 15 years prior and who initially developed acute respiratory disease. However, in workers classified as having chronic respiratory disease, the excess number of deaths was not related to the number of years since exposure.

Wagoner et al. (1980) also found the mortality rate due to heart disease to be higher among an occupationally exposed population when compared to the national average. Figgs et al. (2011) assessed the association between beryllium exposure and suicide among a cohort of nuclear workers and found that beryllium exposure likelihood was associated with an increased hazard ratio (HR 2.6; 95% CI 0.9-1.2) for suicide.

Multiple retrospective cohort studies have examined all-cause mortality rates among beryllium workers, with conflicting results (Boffetta et al. 2014, 2016; Infante et al. 1980; Schubauer-Berigan et al. 2011a; Wagoner et al. 1980). Two studies found a higher all-cause mortality rate among beryllium workers than the national average, with standardized mortality ratios (SMRs) ranging from 1.04 (Schubauer-Berigan et al. 2011a) to 2.11 (Infante et al. 1980); Boffetta et al. (2016) did not report such results. The Boffetta et al. (2016) study examined beryllium-exposed workers from 15 different facilities, including eight with primary exposure to insoluble beryllium and seven with exposure to soluble/mixed beryllium compounds; the authors found the all-cause SMR was no different from the U.S. population's national average (SMR 1.00; 95% CI 0.98-1.02). Though all-cause mortality is most widely reported, specific causes previously

mentioned (e.g., respiratory-related fatalities) may have a stronger relationship with beryllium exposure than all-cause mortality, since the respiratory system is the main target of beryllium exposure.

By reviewing the data by beryllium form, Boffetta et al. (2016) found the soluble/mixed beryllium cohort had a higher all-cause SMR of 1.05 (95% CI 1.03-1.08) than the national average, yet it was lower than the national average for workers exposed to insoluble beryllium (SMR 0.90; 95% CI 0.86-0.94). Another study conducted by Boffetta et al. (2014) found similar results among workers from four insoluble beryllium manufacturing facilities (SMR 0.95; 95% CI 0.90-1.00). These studies all compared working populations to national averages rather than other workers, and thus may be biased by the healthy worker effect. Regardless, the difference in mortality rates among workers exposed to soluble/mixed beryllium compared to insoluble beryllium suggests that beryllium solubility may be an effect measure modifier on the beryllium exposure and all-cause mortality relationship.

According to case histories of 3 men and 14 women employed in the beryllium industry for an average of 17 months, 6 of the women died from pulmonary or cardiovascular disease (Hardy and Tabershaw 1946). Most of the workers reported having shortness of breath, general weakness (fatigue), and weight loss. Autopsies revealed granulomatous disease, lung fibrosis, and heart enlargement. These were the first reported cases of CBD.

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

There are several studies regarding death in animals after acute inhalation exposure to beryllium compounds. Exposure to 31 mg beryllium/m^3 as beryllium oxide caused death in 2 of 20 rats (Hall et al. 1950). A 50-minute exposure to an aerosol of beryllium metal at 0.8 mg beryllium/m^3 resulted in the death of 20 of 74 rats 12–15 days after exposure (Haley et al. 1990). Upon necropsy, the rats had hemorrhagic lungs. All rats exposed daily to 4.3 mg beryllium/m^3 as beryllium sulfate tetrahydrate (Stokinger et al. 1950) or 2.59 mg beryllium/m^3 (Sendelbach and Witschi 1987a) as beryllium sulfate died after 14 or 18 days of exposure, respectively. 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/m^3 as beryllium sulfate.

Exposure to 0.43 mg beryllium/m^3 as beryllium sulfate tetrahydrate for 95 days caused death in 23 of 47 rats (Stokinger et al. 1950). Death was reported in 15 of 23 rats exposed to 30 mg beryllium/m^3 as beryllium oxide for 15 days (Hall et al. 1950). When rats, hamsters, and monkeys were exposed to 0.62 mg beryllium/m^3 as beryl or 0.21 mg beryllium/m^3 as bertrandite ore for 6 months, 13, 25, and 11% died, respectively (Wagner et al. 1969). Signs of toxicity included respiratory distress, anemia, and body weight depression. One of five cats and 2 of 34 guinea pigs died when exposed to 0.43 mg beryllium/m^3 as beryllium sulfate tetrahydrate for 95 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 tetrahydrate 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. Deaths observed in the different species of animals is potentially due to the toxicity of the inhaled metal at each duration of exposure.

Oral LD_{50} values in animals vary according to the beryllium compound tested. LD_{50} values for beryllium sulfate were 120 mg beryllium/kg in rats (Lanchow University 1980) and 140 mg beryllium/kg in mice (Ashby et al. 1990). The LD_{50} values for beryllium chloride in rats were 200 mg beryllium/kg (Kimmerle 1966). The LD_{50} values for beryllium fluoride were 18–20 mg beryllium/kg in mice (Kimmerle 1966; Lanchow 1980). The LD_{50} value for beryllium oxyfluoride was 18.3 mg beryllium/kg in rats. The additional toxicity of the fluoride ion accounted for the lower LD_{50} value observed for beryllium fluoride and beryllium oxyfluoride. The difference in the LD_{50} values for the other beryllium compounds is due to differences in solubility and the potential to form insoluble beryllium phosphate in the gastrointestinal tract.

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

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

Table 2-4. Summary of Epidemiological Studies Evaluating Mortality

Reference and study population	Exposure measurement	Death outcomes[a]	Results[b]
Boffetta et al. 2016 Retrospective cohort study; n=16,115 workers in 15 U.S. facilities (8 insoluble beryllium; 7 soluble/mixed beryllium compounds)	Mortality analyses based on national reference rates Full cohort broken into two sub-cohorts: • Insoluble Be workers • Soluble/mixed Be workers	All-cause	Full cohort: SMR 1.00 (0.98 – 1.02) **Insoluble Be: SMR 0.90 (0.86 – 0.94)*** **Soluble/mixed Be: SMR 1.05 (1.03 – 1.08)***
		Other non-malignant respiratory disease	**Full cohort: SMR 1.29 (1.15 – 1.44)*** Insoluble Be: SMR 1.10 (0.85 – 1.40) **Soluble/mixed Be: SMR 1.34 (1.17 – 1.52)***
		COPD	Full cohort: SMR 1.00 (0.88 – 1.13) Insoluble Be: SMR 0.85 (0.65 – 1.09) Soluble/mixed Be: SMR 1.08 (0.93 – 1.25)
Boffetta et al. 2014 Retrospective cohort study; n=4,950 workers (79.8% male) from four U.S. insoluble Be manufacturing facilities	Mortality analyses based on cause-specific standardized mortality ratios using combined county rates (comparing workers to general population within counties where plants are located)	All-cause	**SMR 0.95 (0.90 – 1.00)***
		Nonmalignant respiratory	SMR 0.90 (0.74 – 1.07)
Figgs et al. 2011 Retrospective cohort study; n=6,820; nuclear industry workers	Compared workers with varied history of likely Be exposure to workers with no Be exposure history	Suicide risk	HR 2.6 (0.9 – 7.9)
		Time-dependent model of suicide risk	HR 1.1 (0.9 – 1.2)
Infante et al. 1980 Retrospective cohort study from the BCR; n=421 white male workers	Mortality among cohort compared to the U.S. white male population; no smoking data available for the cohort	All-cause	**SMR 2.11[c]***
		Heart disease	SMR 1.04[c]
		Nonneoplastic respiratory disease	**SMR 16.40[c] ***

Table 2-4. Summary of Epidemiological Studies Evaluating Mortality

Reference and study population	Exposure measurement	Death outcomes[a]	Results[b]
Schubauer-Berigan et al. 2011a Retrospective cohort study; n=9,199 male workers from 7 Be processing plants; 45 to 65 years follow-up time Sub-cohort (SC) from 3 plants with quantitative exposure measurements; n=5,436 male workers	Cumulative Be exposure categories (μg/m^3-day; adjusted for 5-day exposure period/week): • C1: 1 to < 550 • C2: 550 to <2500 • C3: 2500 to <10,300 • C4: ≥10,300	All-cause	**SMR 1.04 (1.02 – 1.07)***
		Categories containing CBD	**SMR 7.80 (6.26 – 9.60)***
		COPD	**SMR 1.23 (1.13 – 1.32)***
		Cor pulmonale	**SMR 1.17 (1.08 – 1.26)***
		Pneumoconiosis & other respiratory disease	**C3: SMR 4.58 (2.99 – 6.71)*** **C4: SMR 2.59 (1.58 – 3.99)*** *Note: C1 and C2 were not significant and thus not reported here.*
Wagoner et al. 1980 Retrospective cohort study; n=3,055 white, male workers from one Be extraction, processing, and fabrication facility	Compared workers to U.S. white male cause-specific mortality rates	All-cause	SMR 1.07 ($p > 0.05$)
		Nonneoplastic respiratory disease (excluding influenza and pneumonia)	**SMR 1.65 ($p < 0.01$)***
		Influenza and pneumonia	SMR 0.80 ($p > 0.05$)
		Heart disease	**SMR 1.13 ($p < 0.05$)***

[a]Many of the studies reported list many more death outcomes than those listed in this table. As beryllium exposure is most closely linked to respiratory effects, deaths related to respiratory disease are listed here, as well as all-cause and any other death outcomes.
[b]Asterisks and bolding indicates a statistically significant ($P < 0.05$) association with Be; unless otherwise specified, values in parenthesis are 95% CIs.
[c]Confidence intervals not reported

BCR = Beryllium Case Registry; CI = confidence interval; CBD = chronic beryllium disease; COD = cause of death; COPD = chronic obstructive pulmonary disease; SMR = standardized mortality ratio; HR = hazard ratio

2.3 BODY WEIGHT

Changes in body weight have been observed in humans and animals after inhalation and oral exposure to beryllium or its compounds. No studies were located regarding body weight effects in humans or animals after dermal exposure to beryllium or its compounds.

Weight loss was common among workers with ABD (VanOrdstrand et al. 1945). Weight loss was also reported in workers with CBD at a fluorescent lamp manufacturing plant (Hardy and Tabershaw 1946). Weight loss, severe at times, has been observed in monkeys, rats, mice, dogs, and cats after acute-, intermediate-, and chronic-duration inhalation exposure to a variety of beryllium compounds. Due to impaired food consumption and "metabolic changes" (no additional information was provided), monkeys exposed for acute durations to 13 mg beryllium/m^3 as beryllium hydrogen phosphate for 8–10 days, 0.184 mg beryllium/m^3 as beryllium fluoride for 7–18 days, or 0.198 mg beryllium/m^3 as beryllium sulfate for 7 days lost 8–34, 19–23, or 24%, respectively, of their original body weight (Schepers 1964). Mice exposed to 4.3 mg beryllium/m^3 as beryllium sulfate tetrahydrate for 14 days had a 13% decrease in body weight (Stokinger et al. 1950). Dogs exposed only once to 115 mg beryllium/m^3 in a single dose as beryllium fluoride, beryllium oxide, and beryllium chloride for 20 minutes had transient weight loss the first 7 days after exposure (Robinson et al. 1968). No effect on body weight was observed in rabbits exposed to 31 mg beryllium/m^3 as beryllium oxide for 10 days (Hall et al. 1950).

Most of the available information on the effect of beryllium on body weight following intermediate-duration exposure comes from three studies that tested a variety of animal species. In monkeys, weight loss was seen following exposure to 0.198 mg beryllium/m^3 as beryllium phosphate for 30 days (Schepers 1964), 30 mg beryllium/m^3 as beryllium oxide for 15 days (Hall et al. 1950), or 0.43 mg beryllium/m^3 as beryllium sulfate for 95 days (Stokinger et al. 1950); but not in monkeys exposed to 0.620 mg beryllium/m^3 as beryllium oxide for 6 months (Wagner et al. 1969). The magnitude of weight loss ranged from 15 to 39%. A 3–9% weight loss was observed in rats exposed to 30 mg beryllium/m^3 as beryllium oxide for 15 days (Hall et al. 1950); however, a series of studies by Wagner et al. (1969) did not find any alterations in body weight gain in rats exposed to 0.210 or 0.620 mg beryllium/m^3 as beryllium oxide. This study also did not find body weight alterations in hamsters exposed to the same concentrations of beryllium oxide. Weight loss was also observed in dogs exposed to 3.6 or 30 mg beryllium/m^3 as beryllium oxide for 40 or 15 days, respectively (Hall et al. 1950), or 0.4 mg beryllium/m^3 as beryllium sulfate for 51–100 days (Stokinger et al. 1950). Weight loss was also observed in cats exposed to 0.04 mg beryllium/m^3 as beryllium sulfate tetrahydrate for 51–100 days (Stokinger et al. 1950) or 30 mg

beryllium/m^3 as beryllium oxide for 15 days (Hall et al. 1950). No effect was observed in rabbits exposed to 4.3 mg beryllium/m^3 as beryllium sulfate tetrahydrate for 14 days (Stokinger et al. 1950).

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

Pregnant dams exposed to beryllium nitrate (50 mg/kg) at day 13 of gestation experienced a nearly 41% decrease in body weight compared to controls (Sharma et al. 2002).

2.4 RESPIRATORY

Human and animal studies indicate that the respiratory tract is the primary target of beryllium toxicity following inhalation exposure. Beryllium exposed people may present with acute beryllium disease (ABD) or chronic beryllium disease (CBD) after inhalation exposures. These diseases are caused by immune system reactions targeting the lungs. Epidemiological evidence in human studies are summarized in Table 2-5.

Studies that examine epidemiological evidence in humans are summarized in Table 2-5. No studies were located regarding respiratory effects in humans after oral or dermal exposure to beryllium or its compounds. In general, noncancerous respiratory effects can be divided into two categories: ABD and CBD, also referred to as berylliosis or chronic berylliosis. ABD is primarily characterized by severe inflammation of the lungs and typically includes an abrupt onset of coughing and/or difficulty breathing. ABD is typically believed to be an irritative response associated with exposure to high concentrations of soluble beryllium compounds. However, new evidence resulting from a detailed review by Cummings et al. (2009) of case reports in workers exposed to beryllium suggests that ABD may be an immunological response to beryllium, rather than irritative. As such ABD may be part of the continuum of CBD and may occur at exposure levels lower than previously reported; however, this theory is not completely accepted in the field.

CBD is a beryllium-specific immune response with primary manifestations in the lung, characterized by the formation of granulomas with varying degrees of interstitial fibrosis. The symptoms associated with CBD include chest pain, cough, and/or dyspnea from relatively mild exertion. Lung function testing in individuals with CBD has shown reduced vital capacity and total lung capacity, increased alveolar-arterial oxygen tension difference, arterial hypoxemia, and decreased carbon monoxide diffusion capacity (Andrews et al. 1969; Johnson 1983; Rossman et al. 1988). Newman et al. (1989) provided diagnostic

criteria for diseases occurring from beryllium exposure. Newman et al. (1989) identified beryllium sensitization (BeS) criteria as consistent abnormal results for blood and/or lung beryllium lymphocyte proliferation test (BeLPT). Subclinical CBD criteria involved sensitized individuals with histopathological evidence of beryllium exposure but no clinical signs. A diagnosis of clinical CBD involved sensitized individuals with histopathological evidence, respiratory symptoms, changes on chest radiographs, or altered pulmonary physiology (Newman et al. 1989). Due to the overlap of methodology in epidemiological studies that look at both beryllium sensitization and CBD, these endpoints are summarized together in Table 2-5. The epidemiologic studies examining beryllium sensitization are summarized in the Immunological section (Section 2.14). Although ABD and CDB have an immune component, they are discussed in this respiratory section because the primary organ affected is the lungs.

Historically, several criteria were used for the diagnosis of CBD: evidence of beryllium exposure, evidence of lower respiratory tract disease and clinical course consistent with CBD, reticulonodular infiltrates on chest x-ray, obstructive or restrictive deficits in lung function or a low diffusing capacity for carbon monoxide, and pathological evidence of non-caseating granulomas and/or mononuclear cell interstitial infiltrates (Newman et al. 1989). Screening technologies (e.g., fiber optic bronchoscopy and transbronchial biopsy methods, development of the BeLPT) allow for the detection of subclinical cases of CBD and beryllium sensitization in the absence of CBD.

Acute Beryllium Disease (ABD). Studies have described cases of ABD associated with high exposures to beryllium. VanOrdstrand et al. (1945) describe several cases among beryllium production workers exposed to beryllium sulfate, beryllium oxide, beryllium fluoride, and beryllium oxyfluoride. Signs and symptoms observed in the affected workers included irritation of the nasal and pharyngeal mucous membranes, sore nose and throat, weight loss, labored breathing, decreased vital capacity, anorexia, and increased fatigue. Eisenbud et al. (1948) observed occupational ABD at concentrations >0.1 mg beryllium/m^3 as beryllium sulfate or beryllium fluoride. A more recent study identified cases of ABD that occurred at lower beryllium exposures. Cummings et al. (2009) identified two cases of ABD in metal production workers where most air samples contained <0.01 mg/ m^3 beryllium and none exceeded 0.1 mg/ m^3. The workers complained of shortness of breath, chest pain, and nonproductive cough. Pulmonary function tests showed decreases in forced vital capacity (FVC) and carbon monoxide diffusing capacity (DL_{CO}), and chest radiographs were normal.

Chronic Beryllium Disease (CBD). The clinical syndrome of CBD was first described by Hardy and Tabershaw (1946) in fluorescent lamp workers. Seventeen chronically exposed workers developed anorexia, dyspnea, cough, easy fatigue, and weakness. An autopsy on one of the workers revealed increased lung weight, diffuse fibrosis, granulomas, abnormal epithelial lining of the bronchioles, and

abnormal alveoli and vasculature. Other case studies of CBD have described similar respiratory effects (Cullen et al. 1987).

Studies at several types of beryllium facilities have also reported cases of CBD; see Table 2-5 for summaries of the studies. In these studies, CBD was generally defined as beryllium sensitization with granulomas (or similar lesions) in the lungs and/or abnormal bronchoalveolar lavage (BAL) BeLPT results. Differences in the prevalence of sensitized workers with CBD have been found between different types of beryllium facilities, which is likely due to the differences in beryllium exposure conditions. In studies of beryllium oxide workers (ceramics and metal refineries), CBD was diagnosed in 4.4-13.0% of all workers (Cullen et al. 1987; Kreiss et al. 1996, 1997; Schuler et al. 2008). Henneberger et al. (2001) observed a higher prevalence of CBD among long-term beryllium oxide ceramics workers (9.1%) compared to short-term workers (1.4%), which may be attributed to the higher median and mean exposure levels experienced among long-term workers (0.39 and 14.9 $\mu g/m^3$, respectively) compared to short-term workers (0.28 and 6.1 $\mu g/m^3$, respectively). Sawyer et al. (2005) also studied beryllium oxide ceramics workers and noted that beryllium levels detected in lungs were increased within the granulomas of patients with CBD compared with beryllium levels outside the granulomas. In workers at nuclear facilities, 10.5–66.7% of the beryllium-sensitized workers were diagnosed with CBD (Arjomandi et al. 2010; Kreiss et al. 1993; Sackett et al. 2004; Stange et al. 1996b, 2001; Welch et al. 2004, 2013). The prevalence of CBD was highest among beryllium production workers, particularly among machinists. The prevalence ranged from 4 to 11% (Cotes et al. 1983; Duggal et al. 2010; Newman et al. 2001; Rosenman et al. 2005; Schuler et al. 2005, 2008). Among beryllium production workers, CBD was diagnosed in 25–64.3% of the workers with beryllium sensitization (Newman et al. 2001; Rosenman et al. 2005; Schuler et al. 2005, 2008, 2012).

Studies by Newman et al. (2005a) and Mroz et al. (2009) followed beryllium-sensitized and CBD subjects over time. In the Newman et al. (2005a) study, approximately 40% of the 76 beryllium-sensitized subjects were still employed and exposed to beryllium. During an average follow-up period of 4.5 years, 30.9% of the subjects developed CBD; these workers were more likely to be employed as machinists. A continual decline in lung function was observed after the initial CBD diagnosis. The investigators modeled the rate of progression from beryllium sensitization to CBD. They estimated that 13% of the subjects would progress from sensitization to CBD at 2 years of follow-up, 19% at 4 years of follow-up, and 37% at 6 years of follow-up. In a follow-up study, Mroz et al. (2009) examined the progression of beryllium sensitization to CBD among 229 subjects diagnosed with beryllium sensitization and 171 subjects with CBD between 1982 and 2002. There was a greater decline in lung function and higher levels of BAL fluid markers in the never-smoker CBD subjects compared to the never-smoker, beryllium-sensitized subjects

30 years after the initial beryllium exposure. Twenty-two subjects with beryllium sensitization developed CBD (12.6% never-smokers and 6.4% ever-smokers). CBD subjects were more likely to have machined beryllium. Among the CBD subjects, 19.3% progressed to needing oral immunosuppressive therapy.

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Nuclear facilities			
Kreiss et al. 1993	895 current workers at a nuclear weapons assembly site	BeS criteria 1 CBD diagnosis criteria 1	1.9% confirmed sensitized Beryllium sensitization was higher for machinists (4.7%) and for persons reporting measured overexposure (7.4%, OR 5.1 (95% CI 1.8, 15.0)); exposure beginning before 1970 (3.6% OR 2.7 (95% CI 1.1, 7.0)); consistent beryllium exposure (3.4%); and sawing (4.7%) or band sawing (6.0%) 50% of beryllium-sensitized workers were diagnosed with CBD Several cases had minimal exposure to Be (employed in administrative functions)
Mikulski et al. 2011a	1,004 former workers at a nuclear weapons assembly site; mean employment duration was 11.2 years Workers divided into three exposure categories: • Virtually no exposure; lowest exposures at this facility; • Rare exposures; can include bystander or indirect exposure; • Occasional exposures; can include bystander or indirect exposures	BeS criteria 1; initial abnormal or borderline results were repeated within 12 months with a split test Lung function testing (FVC)	2.3% were confirmed sensitized Increased risk of sensitization in occasional exposure group (OR 4.58; 95% CI 1.09–18.13) compared to no exposure group; OR 3.83 (95% CI 1.04–14.03) after adjusting for age and smoking No associations between beryllium sensitization and lung function

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Mikulski et al. 2011b	524 former workers at a nuclear weapons assembly site Workers divided into the same three exposure categories as Mikulski et al. (2011a)	BeS criteria 1; repeat samples to confirm one abnormal result or borderline or uninterpretable results Lung function testing (FVC, FEV_1)	1.5% were confirmed sensitized Increase in sensitization in workers in occasional exposure group (OR 2.64; 95% CI 0.23–29.94)
Rodrigues et al. 2008	1,786 former workers at Nevada Test Site Sub-cohort of 1,503 former workers, excludes females and participants with missing data Exposure potential classified by job histories and job tasks	BeS criteria 1; repeat sampling to confirm abnormal or borderline response with a split test Chest radiography with B-reading (used to classify a dust-related abnormality), and high-resolution computer tomography; lung function test	1.3% were confirmed sensitized In sub-cohort, sensitized workers had higher employment duration; 3% increased risk for developing sensitization for each additional year worked Higher risk of sensitization in workers involved in clean-up and working in building where beryllium was machined—OR 2.68 (95% CI 1.10–6.56) and 2.52 (95% CI 1.02–6.19) No difference between sensitized and non-sensitized workers (after adjusting for smoking) in lung function or chest radiographs

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Sackett et al. 2004	2,381 workers involved in the cleanup (deactivation, decontamination, decommissioning, dismantling, and disposal) of beryllium-contaminated buildings and equipment at a nuclear weapons production facility Respiratory protection, protective clothing, and skin protection were required; not required of workers preparing the plant for decontamination and decommissioning unless they had a legacy of known beryllium use	BeS criteria 2; repeat sampling to confirm abnormal response CBD diagnosis criteria 1 Chest radiographs were also performed; in participants categorized as beryllium sensitized, lung function, transbronchial lung biopsies, and BAL were conducted	0.8% were confirmed beryllium sensitized Beryllium-sensitized workers were older, but there were no differences for sex, race, or smoking status 1.2% of workers hired during production had abnormal BeLPT results; 0.9% of workers hired after production ceased had abnormal BeLPT results 10.5% of the beryllium-sensitized workers were diagnosed with CBD Limitations: though 2/19 BeS workers were diagnosed with CBD, only 8/19 workers underwent full clinical evaluation (i.e., 2/8 evaluated workers with BeS were diagnosed with CBD)
Takaro and Firestone 2009	Cross-sectional study 2,773 former workers at a nuclear weapons production site (average age 63 years, 80% male) employed between 1943 to1997 Exposure**:** Workers exposed to beryllium (self-report or work history) were medically screened for berylliosis (also called CBD)	Medical screen included chest x-ray, spirometry and BeLPT; study does not detail specific criteria for berylliosis	3.5% of former workers had abnormal BeLPTs 75 workers showed evidence for CBD Limitations: Incomplete site roster and databases prevented complete ascertainment of workers

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Stange et al. 1996b	4,397 current and former workers at a nuclear weapons assembly site Fixed airhead sample mean concentration (for 1970-1988) 0.016 micrograms/m^3 Personal air monitoring mean concentration (for 1984-1987) 1.04 micrograms/m^3 personal air monitoring devices Questionnaire and interview administered to obtain detailed work and health histories	BeS diagnosis criteria 5; repeat sampling to confirm CBD diagnosis criteria 4	Overall, 2.43% prevalence rate of BeS and CBD 1.8% confirmed beryllium sensitization; sensitization rate was similar in current (1.2%) and former (1.9%) employees 29 confirmed CBD cases (37% of beryllium-sensitized workers) Several cases had minimal exposure to Be (employed in administrative functions)
Stange et al. 2001	Cross-sectional study of 6,614 former and current workers (86.1% male, 86.5% White) at nuclear facility in Colorado	BeS diagnosis criteria 5 CBD diagnosis criteria 1	Overall, 4.54% prevalence rate of BeS and CBD BeS rate (11.4%) highest among machinists (OR: 3.04, 95% CI: 1.48-3.97) BeS found in workers employed for < 5 years
Welch et al. 2004	3,842 former construction workers at three nuclear weapons facilities	BeS diagnosis criteria 3; repeat sampling to confirm abnormal or borderline response with a split test CBD testing (chest radiograph, chest CT scan, lung function tests, pulmonary exercise study, and bronchoscopy with lavage and/or biopsy) in beryllium-sensitized workers	1.4% confirmed beryllium sensitization with two abnormal tests of BeLPT Five confirmed CBD cases (15% of beryllium-sensitized workers)

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Welch et al. 2013	13,810 former construction workers at nuclear weapons facilities	BeS criteria 1; repeat sampling to confirm abnormal or borderline response with a split test only for samples collected prior to 2007 CBD testing (chest radiograph, chest CT scan, lung function tests, pulmonary exercise study, and bronchoscopy with lavage and/or biopsy) in beryllium-sensitized workers CBD diagnosis criteria 2	1.4% confirmed beryllium sensitization 15% of sensitized workers diagnosed with CBD
Arjomandi et al. 2010	50 current and former workers with beryllium sensitization working at a nuclear weapons research and development facility	CBD testing including physical examination, chest imaging (typically radiograph and HRCT), lung function testing, and fiberoptic bronchoscopy with BAL and transbronchial biopsies CBD diagnosis criteria 3	12.5% diagnosed with CBD

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Viet et al. 2000	Case-control study of 248 workers at a nuclear weapon facility. Cases: 124 workers (n=50 CBD, n=74 BeS) Controls: Negative blood lymphocyte proliferation test results and matched to controls by age (± 3yrs) smoking status, gender, and race. Exposure: Mean and cumulative exposure estimates based on job history data, job titles, and fixed airhead exposure data Average employment: 13.2 years (BeS), 19.1 years (CBD) and 14.5 years (controls)	BeS diagnosis criteria 4 and clinical evaluation determined no CBD CBD diagnosis criteria 2 – Positive and lung LPT, and noncaseating granulomas on lung biopsy	CBD cases had higher exposure levels than control (mean: 0.070 vs 0.025 µg/m3; cumulative: 1.35 vs 0.38 µg-years/m3) BeS cases had higher mean exposure levels than controls (0.036 vs 0.026 µg/m3); no difference in cumulative exposure levels compared to controls (0.54 vs 0.40 µg-years/m3) Strong association between the probability of CBD with increasing average exposure (OR: 7.2, 95% CI: 2.2-23.5) and cumulative exposure (OR: 6.9 95% CI: 2.3 -20.6) modeling 10-fold increase in exposure Limitations**:** Fixed airhead samples may not be representative of beryllium levels in personal breathing zones
Beryllium oxide ceramics and metal refinery			
Henneberger et al. 2001	151 beryllium ceramics plant workers Exposure estimated from work history Time since first Be exposure: 0.25 to 40.1 years Median exposure: 0.55 µg/m^3 (0.2 – 1.1 µg/m^3) among BeS workers	BeS diagnosis criteria 1 CBD diagnosis criteria 1	5.3% (8/151) overall prevalence of BeS of which 53% (8/15) had CBD 9.1% (7/77) CBD detected among long term workers and 1.4% (1/74) among short term workers 7 out of 8 BeS were machinists and sensitization rate 14.3% among machinists vs. 12.1% for other workers

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Cullen et al. 1987	Cross-sectional study of 45 workers exposed to beryllium oxide fumes at a precious metal refinery Time weighted-average personal air samples mean throughout refinery: 1.2 µg/m^3; mean in furnace area: 0.52 µg/m^3	Clinical assessment by questionnaire and review of prior radiographs and spirometry results CBD diagnosis criteria 2	40% (18/45) reported lower respiratory tract symptoms (cough, dyspnea, wheezing); 15.6% (7/45) had abnormal x-rays 4 out of 5 workers with CBD worked in the furnace area
Kreiss et al. 1996	Cross-sectional study of 136 workers at a ceramics plant (62.5% males, average age 40.6 years) Exposure estimated from industrial hygiene measurements Cumulative DWA, median: 591.7 pg/m^3-days Breathing zone, median: 0.3 µg/m^3; with machinist area the highest at 63.7 µg Be/m^3 General area: < detection limit (NS) Personal lapels, median: 0.20 µg/m^3	BeS diagnosis criteria 4, or small opacity profusion of ≥1/0 for a B-reading CBD diagnosis criteria 5	5.9% (8/136) Be sensitized; 50% (4/8) BeS workers report exposure to beryllium dust or mist in an accident or unusual incident 4.4% (6/136) CBD 14.3% BeS rate among machinists vs. 1.2% employees involved with other processes at ceramics plant Median DWA higher for machinist (0.9 µg/m^3) than all other jobs (0.3 µg/m^3)
Sawyer et al. 2005	33 current or former beryllium oxide ceramics workers Exposure mostly in the form of either fired or unfired dust	Transbronchial biopsy Secondary Ion Mass Spectroscopy CBD diagnosis criteria 1	Be levels detected in lungs were increased within the granulomas of patients with CBD compared with Be levels outside the granulomas Be detectable in the lungs of patients with CBD who had ceased exposure to Be an average of 9 years previously

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Schuler et al. 2008	136 beryllium oxide ceramics workers employed in 1992; 115 workers followed through 2003 (includes current and former workers)	BeS criteria 4; repeat samples to confirm one abnormal result or borderline or uninterpretable results CBD diagnosis criteria 4	The crude prevalence of beryllium sensitization was 16% (19% if workers lost to follow-up are excluded); highest rate of sensitization was found in workers involved in machining (14%); 73% of the sensitized workers ever worked in machining The crude prevalence of CBD was 11% (13% if workers lost to follow-up are excluded); the overall mean time between hire and CBD diagnosis was 11 years
Beryllium extraction and production			
Cotes et al. 1983	130 male workers (employed : ≥ 6 months) at a beryllium products manufacturing factory between 1952-1963; 30-year follow-up Exposure estimates based on historical facility records	CBD diagnosis criteria 2	4 cases confirmed CBD and one probable; workers exposed to beryllium oxide or hydroxide. Two confirmed cases worked in areas with exposures 0.04 and 0.18 µg/m^3 in 1952 and 1960 Limitations: exposure levels based on general air samples may not be representative of breathing zone levels
Duggal et al. 2010	72 current and former beryllium plant workers; 50 BeS and 22 CBD diagnosed Average exposure: 15.1 years -18.7	BeS diagnosis criteria 4, and no evidence of granulomas and/or mononuclear cell infiltrates on lung biopsy CBD diagnosis criteria 1 Clinical evaluation: lung function (volume and flow rate), chest x-rays	No changes in respiratory flow rates and lung volume observed Diffusing capacity of the lungs for carbon monoxide reduced by 17.4% 11.1% (8/72) demonstrated one or more symptoms typical of CBD

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Deubner et al. 2001b	Cross-sectional study of 75 current workers at a beryllium ore mining and milling facility in Utah Exposure: beryl ore, bertrandite and beryllium hydroxide; average employment: 14.9 – 27.7 years Estimates based on historical data: General area mean: 0.3 µg/m^3 to 1.1 µg/m^3 Breathing zone mean: 1.1 µg/m^3 to 8.1 µg/m^3 Personal lapel mean: 0.05 µg/m^3 to 6.9 µg/m^3 DWA mean: 0.1 µg/m^3 to 0.4 µg/m^3	BeS diagnosis criteria 4 Workers with abnormal results examined by pulmonologist for BAL, BAL LPT and trans bronchial biopsies CBD diagnosis criteria 5	BeS and CBD prevalence rate of 4.0% (3/75) and 1.3% (1/75), respectively; employees with BeS worked in production area Cumulative incidence of CBD among all 360 workers employed between the years 1969 – 1996 was 0.3%; individual with CBD worked 27.7 years at the Utah plant and an additional 10 years at another facility involved in beryllium metal and beryllium oxide production No cases of beryllium sensitization or chronic beryllium disease found in workers who only worked in the mines; form of beryllium may influence the risk for developing beryllium sensitization or chronic beryllium disease
Kelleher et al. 2001	Case-control study of 235 workers in a machining facility (90% male, average age 39 years); 20 cases (13 CBD and 7 BeS) and 206 negative BeS Median employment duration: 14.2 years (16.9 years, adjusted for machinist work-day) cases, 10.5 years (12.5 years adjusted) controls Exposure: estimates based on job history, historical data, and personal samples Median personal samples: 0.13 µg/m^3 Cumulative, median, 2.93 µg/m^3-years (cases) vs. 1.2 µg/m^3-years (controls)	BeS diagnosis criteria 4 Individuals further evaluated (bronchoscopy with BAL and trans bronchial lung biopsy) for CBD	Higher portion of cases worked as machinists (OR=4.4 95% CI: 1.1-17.6) Prevalence of 11.5% of BeS or CBD among machinist vs. 2.9% non-machinist controls 60% (12/20) cases had LTW exposures >0.20 µg/m^3 Increased risk of BeS and CBD among workers compared to controls

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Kreiss et al. 1997	Cross-sectional screening study of 627 workers in a beryllium metal and alloy production plant (85% male, average age 43.9 years) Exposure: historical environmental Be measurements between 1984-1993 Full shift and continuous area samples median (max): 0.6 (1290) µg/m^3; general area samples median (max): 0.4 (2615) µg/m^3; breathing zone samples median (max): 1.4 (3750) µg/m^3; personal lapel samples median (range): 1.0 (0.1-52.6) µg/m^3	BeS diagnosis criteria 6 CBD diagnosis criteria 3	9.4% (59/627) had abnormal BeLPT Overall CBD prevalence: 4.6% (29/627); highest CBD prevalence among ceramics workers exposed to beryllium oxide: 9.0%
Madl et al. 2007	Retrospective study of 27 workers at a beryllium machining facility diagnosed with BeS (n=9), sCBD (n=16) or cCBD (n=2); engineering controls implemented 1996-1999 Average employment: 17. 6 years among CBD cases Employment duration prior to diagnosis: 0.2-22.1 years (BeS), 0.2 -27.5 years (sCBD), 19.8 - 36.1 years (cCBD) Exposure: historical air sampling, employment year, job titles, personal lapel, and general area	BeS: two positive blood BeLPT; further testing of bronchoscopy with BAL and trans bronchial lung biopsy for CBD diagnosis sCBD: (1) two positive blood or one BAL BeLPT, pulmonary granulomas on lung biopsy and no physical symptoms or (2) detection of X-ray or pulmonary function changes associated with cCBD pathology cCBD: beryllium sensitized and have histological evidence of lung granulomas, respiratory symptoms, changes on chest radiographs, and/or altered lung function	BeS and CBD workers exposed to >0.2 µg/m^3 (95% percentile time-weighted average, TWA) based on highest exposed year worked adjusting for engineering controls 90% of BeS and CBD workers exposed to ≥0.4 µg/m^3 (upper bound, 95% percentile) within a year of employment adjusting for engineering controls 22 out of 27 worked machining operation during employment tenure

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Mroz et al. 2009	Prospective cohort study of 229 BeS and 171 cases CBD identified from workplace medical surveillance Comparison group: BeS diagnosed but no pathological evidence of CBD	BeS diagnosis criteria 4 CBD diagnosis criteria 1	22 BeS subjects progressed to CBD (12.6% never-smokers and 6.4% ever-smokers); conversion of BeS to CBD estimated to be 8.8% CBD subjects more likely to be beryllium machinist compared to subjects with BeS (12.7%)
Newman et al. 2001	Cross-sectional study of 235 workers at beryllium machining plant (90% males, average age 39 years Employment duration:1-29 years, 11.7 years average	BeS diagnosis criteria 2, and no evidence of granulomas and/or mononuclear cell infiltrates CBD diagnosis criteria 1	9.4% (22/235) overall rate of BeS and CBD after three rounds of screening between 1995-1999 6.7% (4/60) new employees (<1-year employment) had abnormal blood test, three underwent clinical evaluation; two workers diagnosed with CBD and one with probable CBD; new workers reported no previous exposure to beryllium
Newman et al. 2005a	Prospective cohort study of 55 BeS mostly nuclear weapons industry workers (80%); average age 52.9 years Average employment: 24.2 years (3.6-49.5 years)	BeS diagnosis criteria 4 CBD diagnosis criteria 1	31% (17/55) developed CBD within follow-up period of 3.8 years (range, 1.0–9.5 years) 69% (38/55) BeS did not progress into CBD after 4.8 years average follow-up time (range, 1.7–11.6 years) BeS to CBD more likely to have worked as machinists Conversion rate of BeS to CBD at rate of 6 - 8%/year after initial diagnosis

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Schuler et al. 2012	264 workers at a beryllium production facility with ≤6 years of employment and hired after 1993; full-shift personal air samples were used to generate a job exposure matrix	BeS criteria 4; repeat samples to confirm one abnormal result or borderline or uninterpretable results CBD diagnosis criteria 4	9.8% sensitized 10.3% of workers employed for <1 year were sensitized; 16.7 and 15.0% were employed for <4 or 4–8 months, respectively A trend for increased beryllium sensitization prevalence and exposure levels was found; no cases of beryllium sensitization were found in workers exposed to average respirable beryllium levels of <0.04 µg/m^3 or exposed to the highest concentration of <0.04 µg/m^3; ORs 1.37 (95% CI 1.03–1.66) for log-transformed respirable average beryllium concentration and 1.18 (95% CI 0.95–1.49) for log-transformed cumulative respirable beryllium Clinical evaluation for CBD was done for 22/26 BeS workers; 27% (6/22) of sensitized workers were diagnosed with CBD (2.3% of all workers diagnosed with CBD) No cases of CBD were found in workers exposed to average respirable beryllium concentrations of <0.05 µg/m^3; ORs 1.56 (95% CI 0.86–3.49) for log-transformed average respirable beryllium concentration and 1.68 (95% CI 1.02–3.28) for log-transformed cumulative respirable beryllium concentration

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Rosenman et al. 2005, 2006	577 former employees at a beryllium processing facility in Pennsylvania operating from 1957 to 1978	BeS criteria 5; repeat sampling to confirm initial abnormal result; if the results were negative on repeat test, test was repeated 1 year later Definite/probable CBD testing (chest radiograph, BeLPT, EKG, and bronchoscopy with bronchial biopsy and BAL sampling) in participants with two positive BeLPT results and/or consensus chest radiograph B reading of ≥1/0 for profusion CBD diagnosis criteria 5; probable CBD diagnosis was defined as beryllium sensitization and upper lobe fibrosis	16.6% confirmed beryllium sensitized; 6.9% beryllium sensitized without CBD 5.5% definite CBD and 2.1% probable CBD (7.6% probable or definite CBD); 52.4% of sensitized workers had probable or definite CBD Estimated cumulative exposures were 100 and 181 μg-year/m^3; in the remaining workers, the cumulative exposures were 209 μg-year/m^3; exposures were estimated using a daily weighted average for a specific job and the amount of time spent at that job
Bailey et al. 2010	258 workers at a beryllium processing facility employed between 1993 and 1999 (preprogram group) and 290 starting employment in 2000 or later after exposure controls were put into place (program group)	BeS criteria 6; repeat sampling to confirm initial abnormal, borderline, or uninterpretable results	8.9% confirmed beryllium sensitization in preprogram group and 2.1% confirmed beryllium sensitization in the program group

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Donovan et al. 2007	Approximately 2400 workers at four Brush Wellman facilities involved in mining, manufacturing, and processing Analysis included >10,000 BeLPT results collected from 1992 to 2004	BeS criteria 4; split analyzed at two of four laboratories; follow-up samples to confirm initial abnormal, borderline, or difficult to interpret results	Greatest positive results in workers employed for <1 year (13% in Tucson survey, 13% in Elmore survey, 15% in Reading survey); peak prevalence between 4 and 8 months (19% in Tucson survey, 19% in Elmore survey, and 38% in Reading survey); combined prevalence of 22%; the rates in workers employed >1 year—7.4 and 11% in Tucson and Reading; combined prevalence 8.8%; rate 54% greater in workers employed <1 year than for workers employed >1 year After first year, no relationship between time of employment and prevalence of beryllium sensitization In new employees, 2.4% had at least one abnormal BeLPT and 1.7% confirmed positive during subsequent testing; 1.1% when excluded previous occupational or take-home exposures Reversions were noted (abnormal BeLPT followed by normal results several years later)

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Beryllium alloy			
Schuler et al. 2005	153 workers at a copper-beryllium alloy facility received BeLPT Plant-wide median personal samples were 0.02 µg/m^3 and short-duration high-volume median level was 0.44 µg/m^3; in the rod and wire production area, the median level was 0.06 µg/m^3 and short-term-high volume level was 0.46 µg/m^3	BeS criteria 4; split analyzed at two laboratories; follow-up samples to confirm initial abnormal, borderline, or uninterpretable results CBD diagnosis criteria 4	10/153 (7%) of workers diagnosed with BeS; workers were more likely to report incidents that may have resulted in high beryllium exposures 6/153 (4%) diagnosed with CBD; prevalence of CBD higher among workers in the rod and wire production area No increases in respiratory symptoms in beryllium-sensitized workers
Stanton et al. 2006	88 workers processing copper-beryllium alloy distribution centers Overall mean concentration was 0.05 µg/m^3 (45% below the LOD)	BeS criteria 4; split samples with repeat samples to confirm one abnormal result or indeterminate result Sensitized participants underwent CBD testing of BAL and transbronchial biopsies CBD diagnosis criteria 4	1.1% workers (1/88) were confirmed beryllium sensitized 1.1% confirmed CBD Worker with BeS and CBD may have had unrecognized exposures that occurred during loading and unloading beryllium-contaminated trailer vans or from handling dusty aluminum-beryllium ingots

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Beryllium General Exposure			
Pappas and Newman 1993	15 clinically-identified subjects with beryllium disease; 22 surveillance-identified subjects with beryllium disease Clinically-identified cases included 5 nuclear weapons plant workers, 7 ceramics workers, 1 metal reclamation worker, 1 secretary from a fluorescent lamp manufacturing plant, 1 wife of a Be-extraction plant worker Surveillance-identified cases were identified through two workplace screening projects: 14 nuclear weapons plant workers and 7 ceramics workers	Lung function testing (spirometry, lung volumes, diffusing capacity for carbon monoxide, arterial blood gases, maximal exercise capacity) CBD diagnosis criteria 1	93% of clinically-identified beryllium disease patients had one or more abnormalities, compared to 57% of surveillance-identified patients Clinically-identified patients performed less work, had more severe gas exchange abnormalities, and had higher dead space to tidal volume ratio at maximal exercise than surveillance-identified patients

[a]Beryllium sensitization criteria (all tests were conducted using BeLPT with peripheral blood):
Criteria 1—beryllium sensitization defined as two abnormal BeLPTs or one abnormal and one borderline test result with repeat samples to confirm abnormal or borderline results.
Criteria 2—beryllium sensitization defined as abnormal BeLPT result on first test and abnormal or borderline result on second test.
Criteria 3—beryllium sensitization defined as abnormal BeLPT result on first test and abnormal or borderline result on second test or borderline on first test and abnormal on second test.
Criteria 4—beryllium sensitization defined as two abnormal BeLPT results.
Criteria 5—beryllium sensitization defined as two abnormal BeLPT results or abnormal BAL BeLPT result.
Criteria 6—beryllium sensitization defined as two non-normal (abnormal, borderline, or uninterpretable) BeLPT results.

[b]CBD diagnosis criteria:
Criteria 1—beryllium sensitization with mononuclear cell infiltrates and/or noncaseating granulomas or BAL lymphocytosis and abnormal BAL BeLPT.
Criteria 2—beryllium sensitization or abnormal beryllium lymphocyte transformation test on blood or lung lavage cells; lung pathology consistent with CBD and lung biopsy showing granulomas or lymphocytic process consistent with CBD, CT scan showing changes consistent with CBD, or pulmonary function study or exercise tolerance test showing pulmonary deficits consistent with CBD.
Criteria 3—beryllium sensitization and presence of granulomas or positive BAL BeLPT, and HRCT evidence of pulmonary nodules.
Criteria 4—beryllium sensitization with granulomas or other pathologic abnormalities consistent with CBD.
Criteria 5—beryllium sensitization with granulomas.

BAL = bronchoalveolar lavage; BeLPT = beryllium lymphocyte proliferation test; BeS = beryllium sensitization; CBD = chronic beryllium disease; cCBD = clinical chronic beryllium disease; CI = confidence interval; CT = computed tomography; DWA = daily weighted average; EKG = electrocardiogram; FVC = forced vital capacity; FEV_1 = forced expiratory volume at 1 second; HRCT = high-resolution computed tomographic scanning; LOD = level of detection; LTW = lifetime weighted; OR = odds ratio; sCBD = subclinical chronic beryllium disease; TWA = time-weighted average

Several investigators have examined exposure-response relationships for CBD. Madl et al. (2007) examined exposure-response relationships for cases (workers with BeS and CBD, combined) among workers from a beryllium machining facility. Workers with BeS and CBD were exposed to >0.2 μg/m^3 (95th percentile TWA), and 90% were exposed to concentrations >0.4 μg/m^3 (95th percentile TWA) within a given year of work history based on highest exposed year worked adjusting for engineering controls. The authors concluded that the upper bound of worker exposures were better represented by using shorter averaging times (i.e., year vs. complete work history) (Madl et al. 2007). Viet et al. (2000) assessed exposure-response relationships in a case control study of workers at the Rocky Flats nuclear production facility. Fifty workers with CBD were matched by age, smoking status, gender, and race to an equal number of controls. For the CBD cases, the mean exposure level (0.070 versus 0.025 μg/m^3), cumulative exposure level (1.35 versus 0.38 μg-years/m^3), and duration of employment (19.1 versus 14.4 years) were higher than controls. Comparisons between the CBD cases and BeS cases revealed differences in mean exposure level (0.070 versus 0.036 μg/m^3), cumulative exposure level (1.35 versus 0.54 μg-years/m^3), duration of employment (19.1 versus 13.2 years), and employment start date (1964.9 versus 1970.2).

Pappas and Newman (1993) investigated whether early beryllium disease was also associated with impaired lung function. Twenty-one "surveillance-identified" subjects (individuals with abnormal BeLPT results who did not seek medical attention prior to the diagnosis of BeS) were compared with the results in 15 "clinically-identified" subjects (individuals who sought medical attention because of respiratory problems or abnormal x-rays). Lung function tests included spirometry, lung volumes, diffusing capacity for carbon monoxide, arterial blood gases, and maximal exercise capacity. Physiological abnormalities in lung function were observed in 57% of the surveillance-identified subjects compared to 93% of the clinically identified subjects.

Chronic Beryllium Disease (CBD) in Settings Other than Manufacturing. Although CBD is usually associated with occupational exposure to beryllium at manufacturing facilities, it has also been reported in dental technicians (Brancaleone et al. 1998; Fireman et al. 2001; Kotloff et al. 1993); in glassblowers, jewelry makers, and other artisans (Jamoussi et al. 2018; Naccache et al. 2003); in individuals living within 1.5 miles of beryllium manufacturing facilities (Maier et al. 2008); and in families of beryllium workers who wore contaminated clothing at home (Chesner 1950; Dattoli et al. 1964; Eisenbud et al. 1949; Lieben and Metzner, 1959; Lieben and Williams 1969). Eisenbud et al. (1949) examined 10,000 residents living within 1 mile of a beryllium manufacturing facility. Ten cases of CBD (based on radiological evidence) were detected, excluding para-occupationally and occupationally exposed residents. The length of exposure varied from 5 to 49 years in the residents. Three more cases were detected in a follow-up study (Sterner and Eisenbud 1951). Affected residents lived within 0.75 miles of

the facility and study authors report that air concentrations "probably ranged between 0.01–0.1 µg beryllium/m^3". There is insufficient information about the beryllium concentrations in this study to be useful for establishing whether a health effect will occur at those levels.

Reversible Respiratory Effects. Reversible respiratory effects have been observed in several studies. Cummings et al. (2009) described two cases with ABD who had experienced decreases in forced vital capacity (FVC) and carbon monoxide diffusing capacity (DL_{CO}) with continued exposure. Several weeks after removal from beryllium exposure, no respiratory symptoms were noted, and pulmonary function was improved. One of the workers returned to work in the area of the facility that involved exposure to soluble beryllium compounds and redeveloped respiratory symptoms and impaired lung function within several months. The second worker returned to work in different areas of the facility that involved exposure to less soluble and insoluble beryllium compounds; the investigators did not note whether respiratory symptoms redeveloped in this worker.

Sprince et al. (1978) conducted health surveys (including measurement of lung function and x-rays) in 1971 and 1974 in beryllium workers without a diagnosis of beryllium disease. When lung function test results and arterial blood gas results were compared to the 1971 values, a slight decrease in peak expiratory flow rate, increase in alveolar-arterial O_2 tension, and decrease in alveolar-arterial CO_2 tension were observed in a group of 111 workers. When workers with radiological abnormalities suggestive of interstitial disease were re-examined in 1974, nine workers had normal radiographs, and nine had radiographs suggestive of interstitial disease; it should be noted that some of these workers had previous exposure to asbestos, silica, or soft coal. Improvements in hypoxia and decreased alveolar-arterial O_2 tension were observed among 13 workers diagnosed with hypoxia in 1971; no change in lung function was observed in this group. Additionally, therapy that controls the immune response (i.e., corticosteroids) can improve pulmonary function (Aronchick et al. 1987).

Donovan et al. (2007) showed a reversion of BeS; 10 of the 18 beryllium-sensitized workers who continued to work in beryllium operations had normal beryllium lymphocyte proliferation test (BeLPT) results (sent to two laboratories) 6 years later. False positive and false negative results may contribute to these "apparent" reversions (Newman et al. 2001; Stange et al. 2001, 2004; Newman et al. 2005; Middleton 2006). However due to methodological changes, the reliability of the BeLPT has improved throughout the years. Splitting samples, increasing the number of indices with proliferative responses, and repeat sampling have increased the sensitivity (correctly identifies people with disease) and specificity (correctly identifies people without disease) of the BeLPT. With these changes, the BeLPT has sensitivity estimated at 88% with a 96% specificity (Balmes et al. 2014). Test result variability may also occur because of intra-individual differences in lymphocytes or other physiological variations (Donovan et al.

2007; Fontenot et al. 2005). While Donovan et al. (2007) noted an improvement in respiratory effects corresponding to a dramatic decrease in beryllium exposure, it cannot be ruled out that previous methodology, physiological variations, or intra-individual differences may have influenced BeLPT results.

Respiratory Effects in Animals from Acute Inhalation Exposure to Beryllium. In animals, the respiratory system is also the primary target for inhalation exposure to beryllium. Sanders et al. (1975) studied the respiratory effects in both rats and hamsters to concentrations of 1–100 mg beryllium/m^3 as beryllium oxide (calcined at 1,000 C) (exact concentrations were not clearly specified). Rats, exposed for 30–180 minutes, had initial alveolar deposition of 1–63 µg beryllium in the lungs and, depending on the amount of alveolar deposition, developed slight to moderate granulomatous lesions in the lungs. Dust-laden or degenerative macrophages and a moderate infiltration of lymphocytes were also noted in the lungs of rats. Hamsters exposed until an initial lung burden of 16–17 µg beryllium was achieved developed only a few small areas of granuloma formation and degenerating macrophages. Hart et al. (1984) also studied rats exposed to beryllium in the form of beryllium oxide (0.447 mg beryllium/m^3, calcined at 560°C, for 1 hour). Pulmonary lavage fluid from rats was examined at various intervals for 21 days after exposure for cell populations; acid and alkaline phosphatase enzyme activity of lysozyme and lactic dehydrogenase; and biochemical analysis of protein, lipid, phosphorus, phosphatidylcholine, and sialic acid (Hart et al. 1984). Microscopic examination of the cell populations revealed inflammation characterized by increased interstitial mononuclear cells and a thickening of the alveolar septa. Increases in the lipids and proteins and levels of acid and alkaline phosphatase, lysozyme, and lactic dehydrogenase indicated cellular damage to the type II cells or the alveolar epithelium. 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). Rats exposed to 3.3 mg beryllium/m^3 and mice exposed to 7.2 mg beryllium/m^3 as beryllium sulfate for 1 hour and examined for 12 months indicated the occurrence of pneumonitis with thickening of the alveolar walls and inflammation of the lung (Sendelbach et al. 1986, 1989; Sendelbach and Witschi 1987b). Increased levels of acid and alkaline phosphatase, and lactic dehydrogenase in the lavage fluid of the lungs of treated rats and mice indicated damage to the cellular populations; the increase in protein indicated alveolar damage. These studies demonstrate the ability of soluble beryllium compounds to damage the lung long after exposure ceases.

Dogs exposed to 10 mg beryllium/m^3 as beryllium oxide calcined at 500 or 1,000°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 beryllium/m^3 as beryllium hydrogen phosphate for 8–10 days and to 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.

Respiratory Effects in Animals from Intermediate Inhalation Exposure to Beryllium. Animals exposed to beryllium compounds for intermediate durations had health effects like those caused by acute exposure. Rats and hamsters exposed to 0.21 mg beryllium/m^3 as bertrandite ore for 6 months developed granulomatous lesions composed of several large, tightly packed, dust-laden macrophages and a few lymphocytes (Wagner et al. 1969). However, when the rats were exposed to 0.620 mg beryllium/m^3 as beryl ore, the lungs were unaffected except for a few small areas of atypical alveolar wall cell proliferation.

Monkeys exposed to 0.210 or 0.620 mg beryllium/m^3 as bertrandite or beryl ore, respectively, had relatively minor changes in the lung (Wagner et al. 1969). The changes observed were aggregates of dust-laden macrophages, lymphocytes, and plasma cells near respiratory bronchioles and small blood vessels. Vascular congestion, emphysema, and pneumonitis were observed during histological examination of the lungs of dogs exposed to 3.6 mg beryllium/m^3 as beryllium oxide for 40 days or to 31 mg beryllium/m^3 as beryllium oxide for 17.5 days (Hall et al. 1950). Epithelialization of the alveoli, focal metaplasia, and granulomas were observed in rats exposed to beryllium sulfate for 6 months (Schepers et al. 1957); however, a nonexposed-related outbreak of pneumonia limits the interpretation of these results. Exposure of rabbits, dogs, cats, and monkeys to 0.04 mg beryllium/m^3 as beryllium sulfate 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, similarly exposed rats experienced respiratory distress (Hall et al. 1950).

Respiratory Effects in Animals from Chronic Inhalation Exposure to Beryllium. Chronic exposure to beryllium and its compounds causes similar health effects to those observed after shorter exposure

durations. Wagner et al. (1969) studied intermittent daily exposure of monkeys, rats, and hamsters for periods up to 23 months to 15 mg/m^3 bertrandite or beryl ore dust (0.210 and 0.620 mg beryllium/m^3, respectively). Fifteen mg ore/m^3 of bertrandite ore or beryl ore was the threshold limit value (TLV) for inert dust. 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. The beryllium ores contained high levels of silica (approximately 64%). It is possible that the high dust and silica exposure levels may have contributed to the observed effects, though silicosis was not observed (Wagner et al. 1969).

Rats exposed chronically to levels as low as 0.006 mg beryllium/m^3 as beryllium oxide or 0.0547 mg beryllium/m^3 as beryllium sulfate had inflamed lungs and fibrosis (Vorwald and Reeves 1959). Rats exposed to 0.034 mg beryllium/m^3 as beryllium sulfate for 72 weeks had inflamed lungs, emphysema, arteriolar wall thickening, granulomas, fibrosis, and proliferative responses within the alveoli (Reeves et al. 1967).

Respiratory Effects in Animals from Oral Exposure to Beryllium. There is limited information on the respiratory system as a target of oral exposure to beryllium or its compounds. Thickening of the alveolar epithelium with areas of necrosis was observed in rats maintained on diets containing beryllium nitrate that provided 2 mg beryllium/kg every 3 days for 40 days (Goel et al. 1980). However, since the beryllium nitrate was mixed with food pellets, it is possible that the lung effects resulted from aspiration of the beryllium nitrate particulates into the lungs during feeding.

No microscopic lung abnormalities were observed in dogs exposed to 12 mg beryllium/kg/day as beryllium sulfate in the diet for up to 40 months (Morgareidge et al. 1976) or in rats exposed to 31 mg beryllium/kg/day as beryllium sulfate in the diet for 2 years (Morgareidge et al. 1975). Furthermore, chronic exposure to 0.7 or 1 mg beryllium/kg/day as beryllium sulfate in drinking water did not cause lung effects in rats and mice (Schroeder and Mitchener 1975a, 1975b).

2.5 CARDIOVASCULAR

The database is not robust enough to make any conclusionary remarks concerning potential cardiovascular effects. A single monkey species and a qualitative human study have suggested heart effects. It is possible that these effects are secondary to the respiratory effects, rather than direct toxicity

to the heart. No studies were located regarding cardiovascular effects in humans after oral exposure to beryllium or its compounds. No studies were located regarding cardiovascular effects in humans or animals after dermal exposure to beryllium or its compounds.

Data regarding the cardiovascular effects of beryllium and its compounds in humans by inhalation exposure are limited. Severe cases of CBD can result in cor pulmonale. “Cor pulmonale can be defined as an alteration in the structure (e.g., hypertrophy or dilatation) and function of the right ventricle (RV) of the heart caused by a primary disorder of the respiratory system resulting in pulmonary hypertension” (Garrison et al. 2020). In a case history study of 17 individuals exposed to beryllium in a plant that manufactured fluorescent lamps, autopsies revealed right atrial and ventricular hypertrophy (Hardy and Tabershaw 1946). An increase in deaths due to heart disease or ischemic heart disease was found in workers at a beryllium manufacturing facility (Ward et al. 1992). The study authors state that it is possible that the cardiac effects are not due to direct toxicity to the heart, but rather are a response to impaired lung function.

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

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

2.6 GASTROINTESTINAL

It is unclear whether gastrointestinal effects result from oral exposure to beryllium, as only two animal species have been tested and have conflicting results. Effects observed in dogs were at a non-

environmentally relevant dose level (a higher level than found in the general environment). No studies were located regarding gastrointestinal effects in humans or animals after inhalation exposure to beryllium or its compounds. No studies were located regarding gastrointestinal effects in humans or animals after dermal exposure to beryllium or its compounds.

In an exposure study, extensive ulcerative and inflammatory lesions were observed at 26-33 weeks in the small intestine, stomach, and large intestine of dogs exposed to 12 mg beryllium/kg/day as beryllium sulfate in the diet; similar; less severe lesions were observed in 1 of 10 dogs exposed to 1 mg beryllium/kg/day (Morgareidge et al. 1976) for 143-172 weeks. No lesions were observed in dogs exposed to 0.1 mg beryllium/kg/day. The only other study that examined gastrointestinal tract tissues was a chronic rat study conducted by the same group. No microscopic abnormalities of the stomach, small intestine, or large intestine were observed in rats exposed to 31 mg beryllium/kg/day as beryllium sulfate in the diet for 2 years (Morgareidge et al. 1975).

2.7 HEMATOLOGICAL

Potential hematological effects from beryllium exposure in humans have not been well studied. Anemia was observed in animals after inhalation and oral exposure. No studies were located regarding hematological effects in humans after oral or dermal exposure to beryllium or its compounds.

No differences in white blood cell counts, hematocrit, or differential white blood cell percentages were observed in a machinist with CBD who worked with beryllium metal (Johnson 1983). A study involving 170 case histories of beryllium workers in the Cleveland area reported normal erythrocyte sedimentation rates, blood counts, and blood chemistry (VanOrdstrand et al. 1945).

Inhalation and oral duration animal studies of beryllium and its compounds suggest hematotoxic potential. Although a few reported studies observed no effect (Hall et al. 1950; Sanders et al. 1975; Wagener et al. 1969), the majority of studies located were consistent with hematological effects; for example, hemoglobin, blood count, and hematocrit levels were altered due to beryllium exposure (El-Beshbishy et al. 2012; Hall et al. 1950; Mathur et al. 1987; Nirala et al. 2008; Sharma and Shukla 2000).

Acute exposure of animals to beryllium and its compounds had little effect on hematological parameters in some studies; however, other reports have shown that intermediate-duration exposures caused anemia in several species. However, 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. 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).

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 for the duration of exposure. Rabbits exposed to 307 mg beryllium/m^3 as beryllium oxide for 60 days developed macrocytic anemia (Hall et al. 1950). The erythrocyte counts decreased over time, and there was a tendency to develop hypochromia, indicated by transient decreases in the average mean corpuscular hemoglobin concentration.

Dogs exposed to 30 mg beryllium/m^3 as beryllium oxide for 15 days exhibited a moderate, progressive leukocytosis, while dogs exposed to 3.6 mg beryllium/m^3 for 40 days developed macrocytic anemia manifested as an increased mean corpuscular volume and decreased erythrocyte count. The bone marrow was almost exhausted. Differential counting of the bone marrow smears indicated a decrease in erythroblasts and an increase in normoblasts. Exposure to the more soluble compounds of beryllium caused effects like 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 95 and 100 days, respectively (Stokinger 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 increasing exposure durations, dogs exposed to 0.04 mg beryllium/m^3 as beryllium sulfate had decreased phospholipid and cholesterol content of the red blood cells. The changes in the biochemical constituents of the red blood cells may reflect a toxic effect on erythropoietic processes in the bone marrow.

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

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

Male Wistar rats exposed to beryllium orally as 86 mg/kg-bw of beryllium chloride (equivalent to experimental LD_{50}) for five days elicited significant decreases in red blood count, hemoglobin levels, and hematocrit percentages compared to controls. In an *in-vitro* study, beryllium chloride at concentrations of 2.5, 5.0, and 10.0 µg/ml resulted in increased platelet reactivity leading to thromboxane production and platelet aggregation (Togna et al. 1997).

Following intermediate exposure to beryllium parenterally administered to rats as 1.0 mg/kg of beryllium nitrate for 6 days/week for three weeks, hemoglobin was reduced by 12%, and zinc protoporphyrin (ZPP) increased by 82%, suggesting anemia. Further, blood ALAD activity (that produces heme) was inhibited by 18%, and urinary ALA (coenzyme in energy production) excretion increased but only transiently (Mathur et al. 1993). Exposure to beryllium as 1.0 mg/kg of beryllium nitrate for 28 days intraperitoneally caused significant depletion of hemoglobin by 20% and serum albumin by 41% (Nirala et al. 2008). Rats exposed once intramuscularly to beryllium as 50 mg/kg beryllium nitrate were characterized as having macrocytic anemia and exhibited significant decreases in hemoglobin percentage over the observed days (Sharma and Shukla 2000).

2.8 MUSCULOSKELETAL

Irregularities in bone morphologies were observed in rats after oral exposure to beryllium carbonate (30-345 mg/kg/day). However, dog and rat studies using beryllium sulfate (1-31 mg/kg/day) did not find any musculoskeletal effects. No effects were observed in humans. No studies were located regarding musculoskeletal effects in humans or animals after inhalation or dermal exposure to beryllium or its compounds.

Early studies indicate that rats fed large amounts of beryllium carbonate in the diet developed rickets. Rats exposed to 35–840 mg beryllium/kg/day as beryllium carbonate for an intermediate duration developed rickets (Guyatt et al. 1933; Jacobson 1933; Kay and Skill 1934). The fragility of the bones increased with increasing concentrations of beryllium. Although there are several methodological deficiencies in these studies (e.g., small numbers of animals per group and lack of statistical analysis), collectively, the studies suggest a relationship between beryllium carbonate ingestion and the occurrence of rickets.

Beryllium rickets are thought to be secondary to phosphorus deficiency rather than a direct effect on the bone. Beryllium in the gut can bind to soluble phosphorus compounds to form insoluble beryllium phosphate, thus decreasing the amount of soluble phosphorus compounds available for absorption (Kay and Skill 1934).

No bone effects were observed in dogs chronically exposed to 12 mg beryllium/kg/day as beryllium sulfate in the diet (Morgareidge et al. 1976). Chronic exposure to 31 or 12 mg beryllium/kg/day as beryllium sulfate did not cause morphological abnormalities in the muscle tissue of rats (Morgareidge et al. 1975) or dogs (Morgareidge et al. 1976), respectively. However, Drolet-Vives et al. (2009) nose-only exposed groups of C3H/HeJ mice to filtered air (n=7) or 250 μg/m^3 beryllium metal with a fine (MMAD 1.5 μm; n=40) or large (MMAD 4.1 μm; n=35) particle size for 6 hours/day, 5 days/week for 3 weeks, resulted in beryllium accumulation in bone. Those exposed to finer particles and those exposed for longer time periods had more accumulation in bone.

2.9 HEPATIC

Limited human studies and conflicting results in animal studies for hepatic effects from beryllium exposure preclude conclusive remarks regarding hepatic effects. No studies were located regarding hepatic effects in humans after oral exposure to beryllium or its compounds. No studies were located regarding hepatic effects in humans or animals after dermal exposure to beryllium or its compounds.

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 via serum glutamic oxaloacetic transaminase (also called aspartate aminotransferase or AST), or serum glutamic pyruvic transaminase (also called alanine aminotransferase or ALT). 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).

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

Intermediate-duration exposure of rats, monkeys, and hamsters to 0.210 and 0.620 mg beryllium/m^3 as bertrandite or beryl ore did not result in histological evidence of hepatic damage (Wagner et al. 1969). However, decreases in serum protein concentration and the albumin/globulin ratio in the blood indicated that some liver damage occurred in dogs exposed to 3.6 mg beryllium/m^3 as beryllium oxide (Hall et al.

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

No adverse hepatic effects were revealed by histological examination or liver enzyme analysis of rats, hamsters, and monkeys chronically exposed to beryllium oxide as bertrandite or beryl ore (Wagner et al. 1969). Evidence of hepatic effects from oral exposure to beryllium compounds is mixed. A few studies indicate beryllium exposure has few, if any, effects on the liver, while other studies report observations to the contrary.

Biochemical analysis of the lipid and protein contents of liver homogenates from rats exposed to 0.2 mg beryllium/kg/day as beryllium sulfate for 6 to 24 weeks did not reveal any hepatic damage (Reeves 1965); however, histological examination was not performed. Other studies suggest intermediate exposure to beryllium alters hepatic enzymes. Oral exposure of beryllium as 1 mg/2ml/kg of beryllium nitrate daily for 28 days caused significant increases in AST, ALT, lactate dehydrogenase (LDH) and gamma-glutamyl transpeptidase levels after beryllium administration; however, serum alkaline phosphatase (ALP) was decreased. Substantial alteration of the ultra-morphology of the liver was observed as well (Nirala and Bhadauria 2008).

Similar observations were reported by Sharma and Shukla (2000). Beryllium administered once as 50 mg/kg of beryllium nitrate intramuscularly induced changes in AST and ALT levels, as much as 51% and 62%, respectively and in combination with severe lesions in the liver. Histopathology examination revealed hypertrophy of hepatocytes including vacuolization, swollen Kupffer cells, deformed nuclei, and increased chromatin (Sharma and Shukla 2000).

Acute exposure to beryllium as 86 mg/kg of beryllium chloride administered orally increased AST and ALT serum levels 1.9 and 1.5 times greater than controls, respectively, indicating liver damage. Liver LDH enzyme levels were also elevated 1.9 times as much as controls and the measurement of the reaction of carbonyl groups with dinitrophenylhydrazine suggest oxidative damage to liver proteins, which may lead to functional damage (El-Beshbishy et al. 2012). Dogs fed 12 mg beryllium/kg/day as beryllium sulfate for 143-172 weeks (Morgareidge et al. 1976) and rats fed 31 mg beryllium/kg/day as beryllium sulfate for 2 years (Morgareidge et al. 1975) did not develop morphological abnormalities of the liver or changes in liver weight. Rats given 0.7 mg beryllium/kg/day as beryllium sulfate in drinking water for 3.2 years had transient increases in serum cholesterol (Schroeder and Mitchener 1975a). Histological examination of the livers of the exposed rats did not provide evidence of morphological alterations. In mice exposed to beryllium sulfate via a similar regimen, no changes in serum cholesterol or morphological abnormalities were observed (Schroeder and Mitchener 1975b).

Other available animal studies where beryllium was administered intraperitoneally, intravenously, or intramuscularly suggest beryllium has hepatotoxic potential.

Rats exposed to beryllium as 1.0 mg/kg beryllium nitrate daily for 28 days had AST and ALT levels elevated by 77% and 90%, respectively, marking damage to the liver (Nirala et al. 2008). Other hepatic enzymes, including ALP have been observed to decrease between 28% and 68%, indicating damage to the liver (Mathur et al. 1993, 2004). With altered enzymatic levels, Mathur et al. (1993) also observed severe lesions and hepatocytes exhibiting cytoplasmic granulation and debris accumulation. Sharma et al. (2000) reported in an intermuscular injection study similar ALP activity where decreases between 29% and 48% were observed 3 and 7 days post exposure, respectively.

IV injection studies have shown a correlation between the rise in acid phosphatase and beryllium concentration in the liver (Witschi and Aldridge 1968 via Mathur et al. 1987). Acid phosphatase levels of rats acutely exposed to beryllium as 50 mg/kg of beryllium nitrate increased on days 2 - 30 after exposure (Mathur et al. 1987, Sharma et al. 2000). Changes in levels of acid phosphatase may indicate the initial start of damage or disease processes in the liver.

Levels of hepatic glutathione (GSH) (Mathur et al. 1993, Nirala and Bhadauria 2008) and lipid peroxidation (Mathur et al. 1993) were reported to increase; however, other studies such as Nirala et al. (2008) showed increases in hepatic lipid peroxidation but decreased levels in reduced GSH. The rise in levels of lipid peroxidation indicate cell injury leading to the generation of cytotoxic products, which can induce structural and functional changes in the cell (Nirala et al. 2008). GSH is an antioxidant that aids in preventing cell damage caused by reactive oxygen species including heavy metals. Altered GSH levels after beryllium administration indicate severe oxidative stress on the target organ.

The liver is responsible for the synthesis and metabolism of cholesterol. Acute exposure to beryllium as beryllium nitrate disturbed lipid profiles, elevating triglycerides and cholesterols in the liver significantly, pointing to alterations in the metabolism function of the liver (Mathur et al. 1987; Nirala and Bhadauria 2008; Nirala et al. 2008). Beryllium was noted to cause hypoalbuminemia (Nirala et al. 2008).

2.10 RENAL

Monkeys that were acutely exposed had renal effects from high amounts of inhaled beryllium (≥8.3 mg/m^3) or from the combination of pre-sensitization and lower dose exposure (≥0.184 mg/m^3). Intermediate and chronic exposure at doses up to 0.62 mg beryllium/m^3 did not result in renal effects for monkeys, rats, or hamsters. Limited human studies showed potential renal effects. No studies were located regarding renal effects in humans after oral exposure to beryllium or its compounds. No studies

were located regarding renal effects in humans or animals after dermal exposure to beryllium or its compounds.

Kidney stones were observed in 10% of the cases of CBD collected by the Beryllium Case Registry up to 1959 (Hall et al. 1959). In a cohort mortality study of workers employed at beryllium manufacturing facilities, an increased risk of death from chronic and unspecified nephritis, renal failure, and other renal sclerosis was observed (Ward et al. 1992).

Renal effects in animals after inhalation exposure to beryllium and its compounds have been studied. No adverse renal effects were detected by urinalysis, kidney weight measurement, or histological examination in rats, rabbits, hamsters, and guinea pigs exposed to beryllium oxide for acute durations (Hall et al. 1950; Sanders et al. 1975). Guinea pigs, mice, hamsters, and rats exposed to 4.3 mg beryllium/m^3 as beryllium sulfate had protein in the urine; however, there was no protein in the urine of similarly exposed rabbits (Stokinger et al. 1950). No other measures of renal integrity were conducted in this study. Histological examination revealed glomerular degeneration in the kidneys of monkeys exposed to beryllium sulfate or beryllium fluoride at very low levels (0.198 or 0.184 mg beryllium/m^3, respectively) for 6 hours/day with durations of 7 to 16 days. Schepers (1964) also observed monkeys with glomerular degeneration when exposed to 13 mg beryllium/m^3 as beryllium hydrogen phosphate for 6 hours/day and 8-30 days. These concentrations were lethal to the monkeys. No histological evidence of renal damage was observed in rats exposed up to 6 days/week for 8 hours/day and 180 days to 0.035 mg beryllium/m^3 as beryllium sulfate (Schepers et al. 1957).

Intermediate-duration exposure (6 months) of rats, hamsters, and monkeys to 0.210 or 0.620 mg beryllium/m^3 as bertrandite or beryl ore, respectively, did not result in evidence of renal effects during histological examination or enzyme analysis (Wagner et al. 1969). No renal effects were observed in dogs exposed to 31 mg beryllium/m^3 as beryllium oxide for 40 days. Urinary protein increased in dogs exposed to 0.43 mg beryllium/m^3 and rats exposed to 2.0 mg beryllium/m^3 as beryllium sulfate for 51–100 days (Stokinger et al. 1950). No renal effects were identified by histological examination or enzyme analysis in rats, hamsters, and monkeys exposed for 12–17 months to 0.21 or 0.62 mg beryllium/m^3 as bertrandite or beryl ore (Wagner et al. 1969).

Few renal effects have been observed after oral exposure to beryllium. Histological examination of rats fed 31 mg beryllium/kg/day as beryllium sulfate for 2 years established no evidence of morphological damage to kidney tissue; however, kidney weight increased slightly (Morgareidge et al. 1975). No significant alterations in kidney weight or histological examinations were observed in dogs exposed to 12 mg beryllium/kg/day as beryllium sulfate in the diet for 143- 172 weeks (Morgareidge et al. 1976).

Morphological alterations of the kidney were not observed in either sex of rats exposed to 0.6 mg beryllium/kg/day as beryllium sulfate daily for 3.2 years or of mice exposed to 1 mg beryllium/kg/day as beryllium sulfate daily for 898 days, respectively (Schroeder and Mitchener 1975a, 1975b). Female rats, however, developed a transient glucosuria (Schroeder and Mitchener 1975a).

Other available animal studies where beryllium was administered intraperitoneally or intramuscularly reported altered biochemical indices. Observed effects include acid phosphatase, ALP, and lipid peroxidation and decreased protein and glycogen levels in the kidney (Sharma et al. 2000; Sharma et al. 2002; Mathur et al. 2004; Nirala et al. 2008; Nirala and Bhadauria 2008). These may be indicative of damage and oxidative stress induced by beryllium at the cellular level. Histopathology examination by Nirala and Bhadauria (2008) releveled renal damage characterized by deformed ultrastructural integrity (loosely arranged mitochondria, cytoplasmic condensation, and vacuolation). It should be noted these studies did not examine other renal endpoints aside from biochemical indices.

2.11 DERMAL

Occupational studies indicate dermal eruptions from beryllium exposure; however, the studies often have multiple exposure routes (e.g., inhalation, dermal) and therefore cannot be attributed to just one route. No studies were located regarding dermal effects in humans after oral exposure to beryllium or its compounds. Skin lesions were observed in humans and animals after dermal exposures (Table 2-3).

Several case studies involving dermal occupational exposure to beryllium have documented dermal effects. Two studies conducted skin biopsies among beryllium workers and have documented granulomas containing beryllium (McConnochie et al. 1988; Williams et al. 1987). In the Williams et al. (1987) study, 26 beryllium workers had documented skin lesions resulting from cuts and abrasions sustained at work. 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).

Dermatological abnormalities (i.e., contact dermatitis and skin ulcers) due to beryllium exposure were also reported in the case histories of 42 workers exposed to beryllium sulfate, beryllium fluoride, or beryllium oxyfluoride (VanOrdstrand et al. 1945). The contact dermatitis cases were characterized as an edematous, papulovesicular dermatitis. Conjunctivitis occurred only as a splash burn or in association with contact dermatitis of the face. Ulceration occurred only after the skin was accidentally abraded and was predominantly seen in beryllium sulfate workers. These ulcers began as small, indurated papules surrounded by an area of erythema which later underwent necrosis.

Schuler et al. (2005) also found that beryllium oxide ceramics workers with CBD were more likely to report ulcers or small craters in the skim, compared to employees without CBD. Specifically, workers with CBD were among the five who reported ulcers or small craters, compared to four employees with CBD among 135 with no reported ulcers or craters. An allergic contact dermatitis can also occur and is most frequently caused by beryllium fluoride (Curtis 1951) (see Section 2.14). Cummings et al. (2009) reviewed cases through a survey of workers at a beryllium manufacturing plant; two workers reported dermal and respiratory symptoms and a significant decline in pulmonary function. One reported a rash and skin ulcers on their wrists and forearms within 2 weeks of beginning work in the metal production operation, and the other complained of a rash within a year of being hired—both improved upon cessation of exposure. In both cases the rash and skin ulcers were associated with exposure to soluble beryllium compounds, particularly beryllium fluoride. Haberman et al. (1998) examined the use of beryllium dental materials which may cause allergic contact dermatitis in some patients. Signs and symptoms consistent with gingivitis, oral lichen planus, leukoplakia, aphthous ulcers, and pemphigus were observed with exposure to beryllium in dental alloys (Haberman et al. 1998).

Information regarding dermal effects in animals after oral exposure to beryllium or compounds is limited. Histological examination of the skin of rats exposed to 31 mg beryllium/kg/day as beryllium sulfate in the diet for 2 years (Morgareidge et al. 1975) or in dogs exposed to 12 mg beryllium/kg/day as beryllium sulfate in the diet for 26-33 weeks (Morgareidge et al. 1976) did not indicate morphological changes.

Strupp (2011a) examined the effects of beryllium metal particle size on skin sensitization in guinea pigs and skin irritation in rabbits. No skin sensitization was observed in guinea pigs exposed intradermally to beryllium metal powder suspended in Freund’s complete adjuvant. No skin irritation was observed in rabbits exposed dermally to 0.5 g of beryllium metal powder for four hours (Strupp 2011a). Delayed hypersensitivity reactions, as described under Immunological Effects, were observed in beryllium-sensitized guinea pigs dermally exposed to beryllium sulfate, beryllium fluoride, beryllium oxide, or beryllium chloride (Belman 1969; Marx and Burrell 1973). Rats and guinea pigs also had delayed hypersensitivity reactions upon airborne exposure with information provided in the Immunological Effects section.

2.12 OCULAR

There is limited information on ocular effects in humans and animals. Conjunctivitis has been noted to occur after a splash burn or in association with contact dermatitis of the face (VanOrdstrand et al. 1945). No studies were located regarding ocular effects in humans after oral exposure to beryllium or its

compounds. According to a case history, twins occupationally exposed to beryllium had reduced tear secretions (McConnochie et al. 1988).

No studies were located regarding ocular effects in animals after inhalation or dermal exposure to beryllium or its compounds. Two studies examined the eyes of animals repeatedly exposed to beryllium sulfate in the diet. No ocular effects were observed in rats exposed to 31 mg beryllium/kg/day for 2 years (Morgareidge et al. 1975) or dogs exposed to ≤1 mg beryllium/kg/day for 143-172 weeks (Morgareidge et al. 1976). One study evaluated the effects of beryllium exposure in rabbits. Rabbits exposed to beryllium as 0.1 g of beryllium metal powder applied to the conjunctival sac of the eye showed slight redness, but after 7 days no signs of irritation were present (Strupp 2011a).

2.13 ENDOCRINE

There are limited studies on the potential endocrine effects from beryllium exposure. A single occupational study and monkey studies observed adrenal gland changes after beryllium inhalation exposure. No effects were observed in the endocrine system after oral exposure in human and animals. No studies were located regarding endocrine effects in humans or animals after dermal exposure to beryllium or its compounds.

One out of 17 workers exposed to beryllium in a fluorescent lamp manufacturing plant died from CBD (Hardy and Tabershaw 1946). Histological examination of the adrenal glands revealed marked hyperemia and vacuolization of cortical cells. Examination of the pancreas revealed marked hyperemia. Another worker exhibited bilateral enlargement of the thyroid which contained a cystic mass the size of a silver dollar.

Effects on the adrenal glands have also been observed in animals exposed to beryllium compounds. Histological examination of monkeys acutely exposed to 1.13 mg beryllium/m^3 as beryllium hydrogen phosphate or 0.184 mg beryllium/m^3 as beryllium fluoride revealed hypoplasia and hypotrophy of the adrenal glands (Schepers 1964). However, the adrenal glands of monkeys exposed to 0.196 mg beryllium/m^3 as beryllium sulfate were normal. Rats and hamsters exposed to 1–100 mg beryllium/m^3 as beryllium oxide for 30–180 minutes had increased adrenal weights (Sanders et al. 1975). The exact exposure concentrations were not specified. There were no studies available for intermediate or chronic duration inhalation exposures.

There is limited information on potential endocrine effects following oral exposure to beryllium. No adverse effects were observed in the adrenal glands, thyroid, pituitary, or pancreas of dogs exposed to 12 mg beryllium/kg/day as beryllium sulfate in the diet for 26 to 33 weeks (Morgareidge et al. 1976) or in

rats exposed to 31 mg beryllium/kg/day as beryllium sulfate in the diet for 2 years (Morgareidge et al. 1975).

2.14 IMMUNOLOGICAL

Alterations in lymphocytes and inflammatory responses were consistently observed in humans and animals after inhalation exposure to beryllium and its compounds. Potential immune effects from oral beryllium exposure have not been addressed. Dermal beryllium studies also indicate immune responses for humans and animals (Table 2-3).

Beryllium-sensitized cells accumulate at sites of CBD, 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 CBD (Williams and Kelland 1986). Virtually all patients with CBD 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 and improve pulmonary function (Aronchick et al. 1987; Marchand-Adam et al. 2008; Sood 2009). A retrospective cohort study of 48 subjects observed that inhalation of corticosteroids in workers with CBD showed improvements in symptoms of coughing by 58% (compared to 17% in controls), and dyspnea improved in 26% of the workers (Mroz et al. 2018).

CBD and beryllium sensitization have similar etiologies so epidemiological studies tend to look at both endpoints, and these are therefore discussed under Respiratory Effects in Section 2.4, Table 2-5. However, the findings are highlighted in this section. Studies specifically looking at patch testing are also covered in this section. Patch testing indicates beryllium hypersensitivity, though using soluble beryllium compounds may be sensitizing and may exacerbate the condition in patients with CBD (Cotes et al. 1983; Epstein 1983; Stoeckle et al. 1969; Tepper and VanOrdstrand 1972), contraindicating the use of patch testing in humans. The BeLPT is now the preferred test.

Beryllium Sensitization . A number of epidemiological studies have evaluated the prevalence of beryllium sensitization among workers at several types of facilities (see Table 2-5); a common limitation of most of these studies is a lack of exposure monitoring data, although some studies attempted to estimate average and/or cumulative exposure levels based on work histories and monitoring data. Newman et al. (2005b) describe beryllium sensitization as a beryllium-specific cell-mediated immune response. T lymphocytes recognize beryllium as an antigen triggering cell proliferation, release of inflammatory mediators, and accumulation of inflammatory cells in the target organ. Beryllium sensitization can occur in the absence of CBD and in the absence of symptoms (Kreiss et al. 1989). Studies have found that the rates of beryllium sensitization vary by the type of beryllium exposure (discussed further in the CANCER section).

The highest rates of beryllium sensitization were found in beryllium production workers; rates ranged from 7 to 19% (Bailey et al. 2010; Donovan et al. 2007; Rosenman et al. 2005; Henneberger 2001; Kreiss et al. 1996, 1997; Newman et al. 2001; Schuler et al. 2005, 2008, 2012). Several studies have found that beryllium sensitization and disease can occur within the first year of exposure or less (Donovan et al. 2007; Newman et al. 2001; Schuler et al. 2005, 2012). Newman et al. (2001) found that 6.7% of new employees (worked in the plant for <1 year) were sensitized; all had worked for less than 3 months when tested and reported no previous beryllium exposure. Donovan et al. (2007) found the prevalence in workers from three facilities ranged from 13 to 15% in workers employed <1 year compared to 7.4–11% in workers employed for >1 year. Within the first year of exposure, the prevalence peaked between 4 and 8 months; the overall prevalence in workers employed for 4–8 months was 22%. No relationship between prevalence and duration of employment was found after the first year of employment. As with the Donovan et al. (2007) study, a study of rod and wire production workers found the highest prevalence of beryllium sensitization among workers with ≤1 year of exposure (13% compared to 7% overall) (Schuler et al. 2005). A study of beryllium production workers found higher prevalence in workers exposed for <4 months (16.7%) or 4–8 months (15.0%) compared to 9.8% overall (Schuler et al. 2012). Duggal et al. (2010) followed the same population as Donovan et al. (2007) for 7.4 ±3.1 years.; no significant changes in flow rates and lung volumes were observed from baseline among the 72 current and former beryllium-sensitized workers, but diffusing capacity of the lungs for carbon monoxide dropped to 17.4% of predicted capacity. Eight subjects (11.1%) developed symptoms typical of CBD at follow-up after 7.4 ±3.1 years.

Several studies provided some estimates of exposure levels associated with beryllium sensitization. Kelleher et al. (2001) expanded the results of Newman et al. (2001). The respective mean and median cumulative exposures were 6.09 and 2.93 μg/m^3-years for the cases (beryllium sensitization or CBD) and 2.27 and 1.24 μg/m^3-years for the controls. None of the cases had estimated lifetime-weighted average beryllium exposure levels of <0.02 μg/m^3; 60% of the cases had lifetime-weighted averages of >0.20 μg/m^3. In the control group, 11% of the workers were exposed to <0.02 μg/m^3, and 48% were exposed to >0.20 μg/m^3.

Kreiss et al. (1996) found the highest beryllium sensitization rate among the machinists at the Rocky Flats Technology site (14.3% versus 1.2% for all other workers), where beryllium exposure levels were higher (median daily weighted average for machinists was 0.9 μg/m^3 versus 0.3 μg/m^3 for all other jobs). Viet et al. (2000) studied the same population at the Rocky Flats facility and found that exposure to beryllium was significantly higher among the beryllium sensitization cases compared to controls (0.036 versus

0.026 μg/m^3), but there were no significant differences for cumulative exposure level (0.54 versus 0.40 μg-years/m^3) or duration of employment (13.2 versus 14.5 years).

Schuler et al. (2005) showed that the highest prevalence of beryllium sensitization was in workers in the rod and wire production area, where beryllium levels were more likely to exceed 0.2 μg/m^3. Rosenman et al. (2005, 2006) created a task exposure (amount of time spent at a task) and job exposure (daily weighted average exposure) matrix and estimated that the mean average exposure for workers at a beryllium processing facility with beryllium sensitization was 1.6 μg/m^3. Using personal air sampling data, Schuler et al. (2012) found no incidences of beryllium sensitization in workers exposed to average or peak exposure respirable beryllium levels of <0.04 μg/m^3 and that the prevalence of beryllium sensitization increased with increasing beryllium levels.

A relationship between beryllium exposure level and beryllium sensitization is supported by a study of workers at a beryllium processing facility that initiated a program to control beryllium exposure (Bailey et al. 2010). Beryllium sensitization was confirmed in 8.9% of the workers employed between 1993 and 1999 compared to 3.1% of workers employed after exposure controls were put into place in 2000.

Deubner et al. (2001b) examined beryllium mine and milling workers at a beryllium extraction facility and found the prevalence of BeS to be 4%. General area, breathing zone, and personal lapel samples were used to estimate historical beryllium exposure. The mean general area, breathing zone, and personal lapel samples ranges were 0.3–1.1, 1.1–8.1, and 0.05–6.9 μg/m^3, respectively.

A relatively low prevalence (1.3 to 3.3%) of beryllium sensitization was found among workers in nuclear facilities (a weapons assembly site and at the Nevada Test Site) or construction workers at nuclear weapons facilities who were exposed to beryllium while on the job (Kreiss et al. 1993; Mikulski et al. 2011a, 2011b; Rodrigues et al. 2008; Sackett et al. 2004; Stange et al. 1996b, 2001; Welch et al. 2004, 2013). A study by Rodrigues et al. (2008) found an association between employment duration and increased risk of beryllium sensitization. Although none of the studies provided exposure monitoring data, Mikulski et al. 2011a, Rodrigues et al. 2008, and Stange et al. 2001 noted that the risk of sensitization was significantly higher in workers involved in beryllium machining (OR 3.83; 95% CI 1.04-14.03 [adjusted for age and smoking], OR 2.52; 95% CI 1.02–6.19 and OR 3.04; I95% CI 1.95-4.77, respectively) compared to workers who were not involved in beryllium machining. A similar rate of beryllium sensitization (1.1%) was found in beryllium alloy workers (Stanton et al. 2006).

Thirteen individuals with dermatitis because of occupational dermal contact with beryllium fluoride, inhalation of 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 test results were reported for pre-sensitized individuals following exposure to beryllium fluoride (5 out of 13 individuals), beryllium nitrate (4 out 9 individuals), beryllium sulfate (3 out of 10 individuals), or beryllium chloride (3 out of 10 individuals) at a dose of 0.19 mg beryllium/ml. Non-sensitized individuals exposed to either beryllium fluoride (8 of 16 individuals) or beryllium chloride (2 of 16 individuals) developed dermatitis when exposed to 0.38 mg beryllium/ml (Curtis 1959). This demonstrated that patch testing could potentially sensitize individuals to beryllium.

Yoshifuku et al. (2012) reported that beryllium patch testing may result in an active sensitization. The authors report that in two cases initial patch testing results were negative for beryllium. However, on day 10, skin reactions in the form of an erythematous lesion appeared in the area where a 1% aqueous beryllium nitrate solution had been applied. Six months later the skin patch testing was repeated, using concentrations of 0.01%, 0.1%, and 1% beryllium nitrate. Both cases had positive reactions appear for the 1% solution but not the 0.01% or 0.1% solutions. Due to the potential for an active sensitization, the authors recommend that beryllium patch testing be performed only when previous exposure is strongly suspected.

Bircher et al. (2011) used skin patch testing to test for allergic responses to a series of metals, including $BeSO_4$. Three of the 87 people from a clinic in Switzerland had a positive response to beryllium, and only one of the three had an occupational exposure. One person who had a negative initial patch test was retested two years later and had a positive patch test for beryllium, despite not having additional exposure to beryllium during the 2-year period. Bircher et al. (2011) suggests this person was sensitized to beryllium during the initial patch test and does not recommend use of skin patch testing for beryllium, as there is the potential for inadvertent sensitization from the patch test.

Skin patch testing in three individuals with CBD resulted in strongly positive reactions that were characterized by erythema, induration (tissue hardening), and vesicles (Fontenot et al. 2002). Mild to moderate spongiosis involving the lower layers of the epidermis and focal edema of the papillary epidermis were observed in skin biopsy samples obtained 96 hours post-exposure. A second skin biopsy taken from the three individuals 2–5 weeks post exposure showed the presence of a noncaseating granuloma; the spongiosis and edema had resolved.

Toledo et al. (2011) reported 12 cases of positive results of skin patch testing with beryllium chloride, all of which were delayed response. The authors suggested that due to the delayed reaction, readings should be taken on day 7 or later, in order to ensure accurate results (Toledo et al. 2011). Chaudhry et al. (2017) subjected 87 individuals to skin patch test with an aqueous solution of 1% beryllium sulfate tetrahydrate

and noted that three of the 87 individuals had no reaction at day 5 but did react by day 7 or later; one had a strong reaction and two had weak reactions. The results reported by Toledo et al. (2011) and Chaudhry et al. (2017) suggest that delayed readings may help to identify reactions to beryllium that may be missed by earlier readings.

In a study by Tinkle et al. (2003), 0.5 M beryllium sulfate (10 mice) or acetone olive oil mixture (control group; also 10 mice) was placed on the dorsal side of the ears of C3H/HeJ or C3H/HeOuJ mice for 3 days/week for 2 weeks. Greater than 30-fold increases in beryllium-stimulated cell proliferation were observed in the auricular lymph node cells and peripheral blood mononuclear cells of the beryllium-exposed mice. In another experiment, beryllium oxide in petrolatum was applied to the backs of mice for 24–30 hours; 6 days later, all mice were challenged with a single application of beryllium sulfate applied to the ear. The challenge test resulted in increased murine ear thickness, as compared to the control group.

Studies have quantified the levels of T cells in lungs of patients exposed to beryllium and have observed that beryllium induces an immune response in the lungs and suggests a high degree of compartmentalization of lymphocytes in the lungs (Rossman et al. 1988; Saltini et al. 1989; Fontenot et al. 2002). No histopathological lesions were observed in the spleen, lymph nodes, or thymus of rats chronically exposed to 131 mg beryllium/kg/day as beryllium sulfate in the diet (Morgareidge et al. 1975) or in dogs exposed to 12 mg beryllium/kg/day as beryllium sulfate in the diet for up to 33 weeks (Morgareidge et al. 1976).

Kim et al. (2013) evaluate the effects of short-term exposure to beryllium on the immune system of workers in a Korean manufacturing plant. T lymphocytes, B cells, and TNFα levels were measured in serum samples collected from 43 exposed workers. The exposure time for the workers was less than 3 months, and the mean ambient beryllium levels varied depending on type of work: molding (3.4 $\mu g/m^3$, grinding (112.3 $\mu g/m^3$), and sorting (2.3 $\mu g/m^3$). After a process change, ambient levels were less than 0.1 $\mu g/m^3$. Multiple logistic regression showed that CD95 (a T lymphocyte) was not affected by exposure to beryllium, whereas the T-lymphocyte population was affected by beryllium exposure. Limitations of this study including the small sample size and a relatively small range of beryllium exposures potentially precluded finding a correlation between exposure and immune response. The authors suggest that short-term exposure to beryllium may not result in an immune response.

Immunological effects have also been observed in animals after inhalation exposure to beryllium. Beagle dogs were exposed to beryllium oxide (BeO) calcined at either 500°C or 1000°C to achieve either high or low initial lung burdens. There were 14 dogs at each calcination temperature for the low initial lung burden and eight dogs in the high initial lung burden for each calcination temperature. There were also

four controls. 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 1.13 mg beryllium/m^3 or for 30 days to 0.198 mg beryllium/m^3 as beryllium hydrogen phosphate revealed hypoplasia of the lymph nodes (Schepers 1964). The hypoplasia may be a result of the nutritional status of the animal since most of the monkeys lost body weight and were anorexic. Histological examination of monkeys exposed for 7–13 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.

Similar *in vivo* and *in vitro* immunological effects have been observed in other animals exposed to beryllium. 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 BeLPTs (Stiefel et al. 1980). When lymphocytes from naïve controls and Be-exposed animals were exposed *in vitro* to beryllium salts, they showed increased proliferation rates greater than those of the controls (Stiefel et al. 1980). 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).

Salehi et al. (2009) reported significantly higher CD4 and CD8 counts in splenic mononuclear cells in exposed mice than in the control group, a lower percentage of CD19 (a marker for B cells), increased in expression of cytotoxic $CD8^+$ T cells and $CD4^+$ T helper cells, and an increase in IFN-γ in mice exposed for three weeks to fine (285 ± 32 μg/m3) or inhalable (253.3 ± 31 μg/m3) beryllium metal particles. However, the statistical significance of these results is questionable, as the number of mice sacrificed does not match with the number of mice reported in the results, and the authors did not provide an explanation for the discrepancy in the number of reported mice. Therefore, this study is not included in the LSE tables. Although significant differences in the results of BeLPT testing were found between the beryllium-exposed mice and controls, the concentration (100 μmol) of beryllium sulfate used in the BeLPT test proved toxic to most of the murine cell cultures, indicating that murine cell cultures may not be a good model for human toxicity.

Both IRSST (2012) and Muller et al. (2011) reported significant increases in the expression of IFN-γ, $CD4^+$, and $CD8^+$ and a decrease in CD19 expression in splenic mononuclear cells in mice exposed, nose only, to beryllium metal, beryllium oxide, or beryllium aluminum for three weeks. Except for IFN-γ, which was greater in beryllium-oxide-exposed mice compared to beryllium-metal-exposed mice, there were no differences between the beryllium groups. Significantly higher percentages of $CD4^+$ and $CD8^+$ lymphocytes were observed in mice exposed to fine beryllium aluminum particles compared to mice exposed to larger beryllium aluminum particles. This study is not included in the LSE tables due to discrepancies in the total reported number of tissue samples.

Muller et al. (2010b) also nose-only exposed groups of 30 C3H/HeJ mice to HEPA filtered air (same control group as fine particle study described above), beryllium metal (MMAD of 1.50±0.12 μm), beryllium oxide (MMAD of 0.41±0.03 μm), or beryllium aluminum (MMAD 4.40±1.64 μm) intermittently for 3 weeks. The study also involved exposure to fine particles. The measured beryllium concentration was 252 $\mu g/m^3$. The mice (30/group) were sacrificed 1 week after exposure termination, and histological examinations of the lungs were conducted. Lung inflammation was observed in all three beryllium groups (see Table 2-6). Comparing these results to those obtained in mice exposed to fine particles (Muller et al. 2010b) suggests that exposure to fine particles resulted in more severe lung damage than exposure to larger particles. This is potentially due to dosimetric differences in delivery versus an inherent difference between the toxicity of the two types of particles.

Table 2-6. Lung Inflammation Severity Scores in Mice Exposed to Beryllium Metal, Beryllium Oxide, or Beryllium Aluminum

Sacrificed 1 week post-exposure	No inflammation	Mild inflammation	Moderate inflammation
Controls	95.5%	4.5%	0%
Beryllium metal	0%	54.5%	45.5%
Beryllium oxide	22.7%	63.6%	13.6%
Beryllium aluminum	44.4%	55.6%	0%
Sacrificed 3 weeks post-exposure	**No inflammation**	**Mild inflammation**	**Moderate inflammation**
Beryllium metal	0%	29.4%	70.6%
Beryllium oxide	0%	75.0%	25.0%
Beryllium aluminum	0%	77.8%	22.2%

Source: Muller et al. 2010b, 2011

2.15 NEUROLOGICAL

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

No changes in brain weight and no histopathological lesions were observed in the brain, nerve, or spinal cord of rats chronically exposed to 31 mg beryllium/kg/day as beryllium sulfate in the diet (Morgareidge et al. 1975) or in dogs exposed to ≤1 mg beryllium/kg/day as beryllium sulfate in the diet for 143-172 weeks (Morgareidge et al. 1976). This information is insufficient to conclude that beryllium does not cause neurological effects because more sensitive neurological or neurobehavioral tests were not performed.

2.16 REPRODUCTIVE

No studies were located regarding reproductive effects in humans after inhalation, oral, or dermal exposure to beryllium or its compounds. No studies were located regarding reproductive effects in animals after dermal or inhalation exposure to beryllium or its compounds. Available animal studies are unclear and inconsistent on the effects of oral beryllium exposure on reproduction.

Pregnant rats acutely exposed to beryllium as beryllium nitrate (50 mg/kg) on day 13 of gestation were found to have a 71% decrease in live fetuses per litter, reduced fetal weight by 33%, and nearly three times more post-implementation losses than the control groups (Sharma et al. 2002). In a study where female albino rats were exposed to beryllium as 0.031 mg/kg beryllium nitrate once on days 14, 16, 18, and 20 post coitum, fetus and placenta mean weight were reduced by half. Dams were found to have decreased body weight (Mathur and Mathur 1994). The study authors postulated that beryllium disrupts enzymes responsible for energy metabolism.

Two rodent studies evaluated the effects of beryllium on male reproductive organs. Groups of five male mice were administered 0, 93, 75, 188, or 375 mg/kg beryllium chloride via gavage for 5 days and were sacrificed (Fahmy et al. 2008). At all doses tested, there were significant increases in the percentage of abnormal sperm. 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 epididymides 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.

Testicular atrophy was observed in male dogs exposed to beryllium sulfate doses of 12 mg/kg/day for 26-33 weeks (Morgareidge et al. 1976). Dogs exposed to lower doses (≤ 1 mg/kg/day) for a longer duration (>365 days) were mated, and the pups were weaned; the study authors reported that there were no significant alterations in the number of pregnancies, number of pups, or number of live pups observed at doses of 1 mg beryllium/kg/day as beryllium sulfate in the diet. This was conducted in a small sample of animals (5 per sex per dose group).

2.17 DEVELOPMENTAL

Developmental effects of beryllium in humans are limited to cross-sectional studies or case studies after occupational exposure to beryllium or its compounds. A single oral study in dogs looked for developmental effects and found none. No studies were located regarding developmental effects in animals after inhalation or dermal exposure to beryllium or its compounds.

An infant was clinically diagnosed with Bartter syndrome, and a fecal test revealed elevated levels of beryllium among other heavy metals. His mother was occupationally exposed to beryllium-copper alloy through lead soldering for 14 years. This case study suggests beryllium may be transferred to the infant in-utero or through lactation (Crinnion and Tran 2010). This observation is supported by findings from Sharma et al. (2002), who observed offspring with beryllium accumulation when pregnant rats were exposed to a single dose of beryllium as 50 mg/kg beryllium nitrate.

Shirai et al. (2010) investigated the association between maternal exposure to heavy metals during pregnancy and birth size including birth weight, length, and head circumference. Single spot urine samples were collected from seventy-eight pregnant females. The geometric mean of beryllium was measured at 0.031 µg/g creatinine. No association was determined between beryllium and birth size; however, this absence of evidence should be interpreted cautiously. This was a cross-sectional study and limited by small sample size.

There is limited information on beryllium's potential to induce developmental effects in animals following oral exposure. As discussed under Reproductive Effects, the Morgareidge et al. (1976) chronic dog study co-housed males and females and allowed them to mate and wean their pups. Pups in the first litter were examined for gross and skeletal malformations. No significant alterations in the occurrence of gross or skeletal malformations, number of live pups, pup body weights, or pup survival were observed at

1 mg beryllium/kg/day; however, stillborn, or cannibalized pups dying within the first few postnatal days were not examined.

2.18 OTHER NONCANCER

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

Changes in metabolic activity including energy metabolism and enzyme activity due to beryllium exposure have been reported. Mathur et al. (1987) observed substantial decrease in blood sugar level in rats 2 to 10 days post-exposure to beryllium as 0.316 mg/kg beryllium nitrate. Changes in glucose and enzyme activity responsible for energy metabolism were observed for glucose-6-phosphatase, adenosine triphosphatase, and succinic dehydrogenase in pregnant and non-pregnant rats when exposed to between 0.031 mg/kg and 50 mg/kg of beryllium as beryllium nitrate (Mathur and Mathur 1994; Sharma et al. 2000; Sharma et al. 2002). Messer et al. (2000) reported beryllium ions at 0.75 to 12 ppm increase mitochondrial NADH reductase activity *in vitro*. This increase in mitochondrial function may be a compensatory response to maintain normal cellular function. No changes in succinate dehydrogenase activity were reported.

Various measures of cellular damage including lipid peroxidation and oxidative stress have been observed by El-Beshbishy et al. (2012). Catalase, responsible for the breakdown of hydrogen peroxide and the antioxidant superoxide dismutase (SOD), were found to significantly decrease in both liver and brain tissue after exposure to beryllium. Significant increases in malondialdehyde (MDA), a measure of lipid peroxidation, were observed as well.

An *in vitro* study by Dobis et al. (2008) supports the oxidative damages caused by beryllium. Comparing blood mononuclear cells from subjects with CBD, subjects with beryllium sensitization, and non-beryllium exposed individuals, Dobis et al. (2008) found beryllium to significantly increase levels of oxidative stress by depleting available thiol antioxidants and generating reactive oxygen species (ROS).

2.19 CANCER

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

2.19.1 Cancer in Humans

Numerous retrospective cohort mortality studies examining workers at beryllium processing facilities have been conducted and are summarized in Table 2-7. The populations studied all have some degree of overlap, as described in Table 2-8, and many were reevaluations of earlier studies.

Bayliss et al. (1971) examined 6,818 male workers at several beryllium processing facilities in Ohio and Pennsylvania. There was a slight increase in deaths due to lung cancer in the beryllium workers (SMR=1.06). Limitations of this study include lack of analysis for potential effect of latency, elimination of over 2,000 workers due to incomplete records (e.g., date of birth), and the combining of populations from several different plants into one cohort (EPA 1987; MacMahon 1994).

A subsequent study (Wagoner et al. 1980) examined 3,055 white male beryllium workers at one facility in Reading, Pennsylvania. An increase in lung cancer deaths was observed (47 versus 34.29 expected) in the beryllium workers. Increases in lung cancer deaths were found in workers with a latency period of at least 25 years (20 observed versus 10.79 expected). Increases in lung cancer deaths were also observed (17 versus 9.07 expected) in workers employed for <5 years and a latency period of at least 25 years.

Table 2-7. Beryllium Facilities Included in Studies Evaluating Cancer Endpoints

Reference	Lorain, OH	Reading, PA	Luckey, OH	Perkins (Cleveland, OH)[b]	St. Claire (Cleveland, OH)[b]	Elmore, OH	Hazelton, PA	Shoemakersville, PA	Tucson, AZ	Chester, PA	Delta, UT	4 Distribution Centers
Bayliss et al. 1971	✓	✓	✓	✓	✓	✓	✓					
Boffetta et al. 2014		✓		✓	✓			✓	✓			
Boffetta et al. 2016	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Levy et al. 2002, 2009	✓	✓	✓	✓	✓	✓	✓					
Mosquin and Rothman 2017		✓				✓	✓					
Sanderson et al. 2001a,b		✓										
Schubauer-Berigan et al. 2008		✓										
Schubauer-Berigan et al. 2011a	✓	✓[a]	✓	✓	✓	✓[a]	✓[a]					
Schubauer-Berigan et al. 2011b, 2017		✓				✓[a]	✓[a]					
Wagoner et al. 1980		✓										
Ward et al. 1992	✓	✓	✓	✓	✓	✓	✓					

✓ Facility was included in the cohort for the study listed in the left-hand column
[a]Facility/facilities were included in a separate/sub-analysis.
[b]Perkins and St. Claire facilities are often combined into one “Cleveland” cohort.

Table 2-8. Summary of Epidemiological Studies Evaluating Cancer Endpoints

Reference and study population	Exposure or comparison population information	Cancer outcomes	Effects
Bayliss et al. 1971[c] Retrospective cohort study; n=6,818 male workers; employed during 1942-1967	Cause-specific mortality among workers compared to mortality rates for the U.S.	Lung cancer Digestive cancer	SMR 1.06 SMR 0.75
Boffetta et al. 2016 Retrospective cohort study from 15 facilities (8 insoluble Be; 7 soluble/mixed Be); n=16,115; employed during 1925-2008; followed until 2011	Cause-specific mortality among workers compared to mortality rates for the U.S.	All cancer Lung cancer	SMR • **Whole cohort: 0.93 (0.89 to 0.98)**[a] • Insoluble Be: 0.94 (0.86 to 1.02) • **Soluble/Mixed Be: 0.94 (0.89 to 0.99)**[a] SMR • Whole cohort: 1.02 (0.94 to 1.10) • Insoluble Be: 0.88 (0.75 to 1.03) • Soluble/Mixed Be: 1.09 (0.99 to 1.19)
Boffetta et al. 2014 Retrospective cohort study from 4 U.S. insoluble Be manufacturing facilities; n=4,950 workers (3,912 men; 1,038 women); followed through 2009	Cause-specific mortality among workers compared to mortality rates for the U.S. (all facilities combined) or regional mortality rates	All cancer Lung cancer Uterine cancer (females only)	SMR 1.00 (0.90 to 1.10) SMR: 0.96 (0.80 to 1.14) **SMR: 3.02 (1.22 to 6.23)** [a]
Levy et al. 2002, 2009 Retrospective cohort study from 7 beryllium production facilities; n=9,225 male workers; employed during 1940 – 1969; vital status ascertained as of 12/31/1988 (Re-analyses of Ward et al. 1992)	2002: Lung cancer mortality among workers compared to mortality rates from the city within which each plant is located, county rates, and U.S. rates 2009: Calculated univariate and multivariate lung cancer hazard ratios to adjust for smoking in a different way than original study (Ward et al. 1992)	Lung cancer	SMR – Lorain plant • **Compared to U.S.: 1.69 (1.28 to 2.19)**[a] • **Compared to county: 1.60 (1.21 to 2.07)**[a] • Compared to city: 1.14 (0.86 to 1.48) SMR – Reading plant • **Compared to U.S.: 1.24 (1.03 to 1.48)**[a] • **Compared to county: 1.42 (1.18 to 1.70)**[a] • Compared to city: 1.07 (0.89 to 1.28) HR – Lorain plant • Univariate: 1.36 (0.92 to 2.02) • Multivariate: 1.26 (0.80 to 1.99)

Table 2-8. Summary of Epidemiological Studies Evaluating Cancer Endpoints

Reference and study population	Exposure or comparison population information	Cancer outcomes	Effects
			HR – Reading plant • Univariate: 0.98 (0.69 to 1.38) • Multivariate: 1.00 (0.69 to 1.48)
Levy et al. 2007 Case-control study; n=142 cases; 200 matched controls within 3 years of age (Re-analyses of Sanderson et al. 2001a,b)	See Sanderson et al. 2001a,b	Lung cancer	OR • Cumulative: 0.99 (0.91 to 1.08) • Average: 1.11 (0.95 to 1.31) • Max: 1.06 (0.92 to 1.22)
Infante 1980 Retrospective cohort study from the BCR; n=421 white male workers Sub-cohorts: S_{ABD}=Workers entered into BCR with a diagnosis of ABD S_{CBD}=Workers entered into BCR with a diagnosis of CBD	Lung cancer mortality among cohort compared to the U.S. white male population; no smoking data available for the cohort	All cancer Lung cancer	**SMR 1.53[a,c]** SMR[c] • All: 2.12 • **S_{ABD}: 3.14[a]** • S_{CBD}: 0.72
Mosquin and Rothman 2017 Retrospective cohort study from 3 Be processing plants in Ohio and Pennsylvania; n=5,436 male workers (A re-analysis of Schubauer-Berigan et al. 2011a)	Be exposure quartiles (µg/m^3-day [cumulative] and µg/m^3 [maximum]; adjusted for 5-day exposure period/week) Cumulative Be exposure: • C1 (referent): 1 to < 550 • C2: 550 to <2500 • C3: 2500 to <10,300 • C4: ≥10,300 Maximum Be exposure: • M1 (referent): <10 • M2: 10 to <25 • M3: 25 to <70	Lung cancer	SRR for cumulative exposure (No lag)[c] C2 / C3 / C4 All workers: 0.90 / 0.94 / 1.13 Tenure <1 yr: 0.98 / 0.90 / 1.16 Tenure ≥1 yr: 1.16 / 1.68 / 1.97 SRR for cumulative exposure (lagged 10 years)[c] C2 / C3 / C4 All workers: 0.98 / 0.94 / 1.17 Tenure <1 yr: 1.01 / 0.94 / 1.18 Tenure ≥1 yr: 1.58 / 1.70 / 2.16 SRR for maximum exposure (No lag)[c] M2 / M3 / M4 All workers: 1.87 / 1.91 / 1.59

Table 2-8. Summary of Epidemiological Studies Evaluating Cancer Endpoints

Reference and study population	Exposure or comparison population information	Cancer outcomes	Effects
	• M4: ≥70 SRR compared to C1 or M1		Tenure <1 yr: 1.63 / 2.24 / 1.56 Tenure ≥1 yr: 2.18 / 1.39 / 1.72 SRR for maximum exposure (lagged 10 years)[c] M2 / M3 / M4 All workers: 1.89 / 1.92 / 1.57 Tenure <1 yr: 1.64 / 2.28 / 1.57 Tenure ≥1 yr: 2.17 / 1.39 / 1.68
Sanderson et al. 2001a, 2001b Case control study; n=142 lung cancer cases; 710 age-race-matched controls; follow-up through 1992	Be exposure quartiles (μg/m^3-day [cumulative] and μg/m^3 [mean and maximum]; adjusted for 5-day exposure period/week) Cumulative Be exposure: • $Q1_{Cumu}$ (referent): ≤1,425 • $Q2_{Cumu}$: 1,426 to 5,600 • $Q3_{Cumu}$: 5,601 to 28,123 • $Q4_{Cumu}$: >28,123 Lag / Cases / Controls No lag: 4,606 / 6,328 **10 yrs[a]: 4,057 / 2,036** **20 yrs[a]: 844 / 305** Mean Be exposure: • $Q1_{Mean}$ (referent): ≤11.2 • $Q2_{Mean}$: 11.3 to 24.9 • $Q3_{Mean}$: 25.0 to 34.0 • $Q4_{Mean}$: >34.0 Lag / Cases / Controls No lag: 22.8 / 19.3 **10 yrs[b]: 22.6 / 12.3** **20 yrs[b]: 10.2 / 5.3**	Lung cancer	**SMR: 1.22 (1.03 to 1.43)[a]** OR for cumulative (μg/m^3-days) exposures (quartiles): Lag / Q2 / Q3 / Q4 No lag / $Q2_{Cumu}$ / $Q3_{Cumu}$ / $Q4_{Cumu}$ OR: 0.73 / 0.85 / **0.57[a]** 10 yrs: 809-3,970 / 3,971-20,996 / >20,996 OR: 1.38 / 1.38 / 0.92 20 yrs: 21-2,195 / 2,196-12,376 / >12,376 OR: **2.18[b]** / **1.89[a]** / **1.89[a]** OR for mean (μg/m^3) exposures (quartiles): Lag / Q2 / Q3 / Q4 No lag / $Q2_{Mean}$ / $Q3_{Mean}$ / $Q4_{Mean}$ OR: 1.61 / **1.75[a]** / 1.27 10 yrs: 9.6-23.6 / 23.7-32.8 / >32.8 OR: **2.39**** / **2.71**** / **1.83[a]** 20 yrs: 1.1-19.3 / 19.4-25.5 / >25.5 OR: **1.92[a]** / **3.06**** / 1.70 OR for mean (μg/m^3) exposures (three categories): <2 / >2-20 / >20 No lag: 1.00 / 2.10 / 2.23 10 yrs: 1.00 / **4.07[b]** / **4.17[b]** 20 yrs: 1.00 / **2.30[b]** / **2.19[b]**

Table 2-8. Summary of Epidemiological Studies Evaluating Cancer Endpoints

Reference and study population	Exposure or comparison population information	Cancer outcomes	Effects
	Max Be exposure: • $Q1_{Max}$ (referent): ≤17.0 • $Q2_{Max}$: 17.1 to 25.0 • $Q3_{Max}$: 25.1 to 71.5 • $Q4_{Max}$: >71.5 Lag / Cases / Controls: No lag: 32.4 / 27.1 **10 yrs[b]: 30.8 / 16.1** **20 yrs[b]: 13.1 / 6.5**		OR for maximum (μg/m³) exposures (quartiles): Lag: No lag; $Q2_{Max}$: OR **1.82[a]**; $Q3_{Max}$: OR 1.08; $Q4_{Max}$: OR 1.14 10 yrs: $Q2_{Max}$: 10.1-25.0, OR **3.34[b]**; $Q3_{Max}$: 25.1-70.0, OR **2.19[a]**; $Q4_{Max}$: >70.0, OR **1.92[a]** 20 yrs: $Q2_{Max}$: 1.1-23.0, OR **1.95[a]**; $Q3_{Max}$: 23.1-56.0, OR **2.89[b]**; $Q4_{Max}$: >56.0, OR 1.67 OR for maximum (μg/m³) exposures (three categories): No lag: <2: 1.00; >2-20: 1.85; >20: 2.22 10 yrs: <2: 1.00; >2-20: **3.89[b]**; >20: **4.58[b]** 20 yrs: <2: 1.00; >2-20: **2.09[a]**; >20: **2.34[b]**
Schubauer-Berigan et al. 2008 Case control study; n=142 lung cancer cases; 710 age-race-matched controls; follow-up through 1992 (Re-analyses of Sanderson et al. 2001a,b)	See Sanderson et al. 2001a,b ORs adjusted by birth year (BY) and by age-at-hire (AH) BY categories: <1899, 1900-1910, 1911-1920, >1921 AH categories: <24.99, 25.0-34.99, 35.0-44.99, >45.0	Lung cancer	OR for cumulative (μg/m³-days) exposures (quartiles): Lag: No lag; $Q2_{Cumu}$; $Q3_{Cumu}$; $Q4_{Cumu}$ OR (BY-adjusted): 0.77; 0.89; 0.61 OR (AH-adjusted): 0.75; 0.85; **0.56[a]** 10 yrs: 809-3,970; 3,971-20,996; >20,996 OR (BY-adjusted): 1.27; 1.23; 0.83 OR (AH-adjusted): 1.24; 1.18; 0.78 20 yrs: 21-2,195; 2,196-12,376; >12,376 OR (BY-adjusted): 1.46; 1.29; 1.30 OR (AH-adjusted): 1.37; 1.21; 1.18 OR for mean (μg/m³) exposures (quartiles): Lag: No lag; $Q2_{Mean}$; $Q3_{Mean}$; $Q4_{Mean}$ OR (BY-adjusted): 1.68; **2.02[a]**; 1.33 OR (AH-adjusted): 1.55; **1.80[a]**; 1.21 10 yrs: 9.6-23.6; 23.7-32.8; >32.8 OR (BY-adjusted): **2.04[a]**; **2.47[a]**; 1.59 OR (AH-adjusted): **2.05[a]**; **2.38[a]**; 1.54

Table 2-8. Summary of Epidemiological Studies Evaluating Cancer Endpoints

Reference and study population	Exposure or comparison population information	Cancer outcomes	Effects			
			OR (BY-adjusted) OR (AH-adjusted)	1.29 1.24	**2.14[a]** 2.05	1.19 1.11
Schubauer-Berigan et al. 2011a Retrospective cohort study from 7 Be processing plants in Ohio and Pennsylvania; n=9,199 male workers; 45 to 65 years of follow-up time; follow-up through 2005. (Follow-up study to Ward et al. 1992) Sub-cohort from 3 plants with quantitative exposure measurements; n=5,436 male workers	Be exposure quartiles (μg/m^3-day; adjusted for 5-day exposure period/week) Cumulative Be exposure: • C1 (referent): 1 to < 550 • C2: 550 to <2500 • C3: 2500 to <10,300 • C4: ≥10,300 Maximum Be exposure: • M1 (referent): <10 • M2: 10 to <25 • M3: 25 to <70 • M4: ≥70 • M_{all} ≥10 SMR compared to U.S. population	Lung cancer	SMR • **Whole cohort: 1.17 (1.08 - 1.28)[a]** • **Lorain: 1.45 (1.17 to 1.78)[a]** • **Reading: 1.20 (1.04 to 1.37)[a]** SMR of sub-cohort (lagged 10 years): • **C4: 1.31 (1.06 – 1.65)[a]** • C4 (excluding short-term workers): 1.26 (0.97 - 1.61) • **C4 (excluding workers exposed to other occupational carcinogens ≥1 year): 1.48 (1.05 to 2.03)[a]** • **C4 (excluding professional workers): 1.30 (1.02 to 1.64)[a]** SMR of sub-cohort (unlagged 10 years): • M1: 0.83 (0.67 to 1.02) • **M_{all}: 1.40 (1.21 to 1.61)[a]** • **M_{all}: (excluding short-term workers): 1.32 (1.04 to 1.65)[a]** • **M_{all}: (excluding workers exposed to other occupational carcinogens ≥1 year): 1.46 (1.24 to 1.71)[a]** • **M_{all}: (excluding professional workers): 1.39 (1.20 to 1.60)[a]**			
		Nervous system cancer	SMR Whole cohort: 0.87 (0.58 to 1.24)			
Schubauer-Berigan et al. 2011b Retrospective cohort study from 3 plants with quantitative exposure measurements; n=5,436 male	Mean DWA exposure category (μg/m^3): • D1 (referent): < 0.6 • D2: 0.6 to <2.0 • D3: 2.0 to <8.0	Lung cancer	HR for all workers: • **D2: 2.29 (1.29 to 4.30)[a]** • **D3: 2.84 (1.54 to 5.49)[a]** • **D4: 5.68 (2.66 to 12.4)[a]** • **D5: 4.88 (2.64 to 9.62)[a]**			

Table 2-8. Summary of Epidemiological Studies Evaluating Cancer Endpoints

Reference and study population	Exposure or comparison population information	Cancer outcomes	Effects
workers (same population as sub-cohort of Schubauer-Berigan et al. 2011a)	• D4: 8.0 to <12 • D5: 12 to <50 • D6: ≥50 HR compared to D1		• **D6: 4.13 (2.14 to 8.41)[a]** **Exposure-response coefficient: 0.155 (p<0.0001)[a]** HR for workers excluding asbestos-exposed and professionals: • D2: 1.30 (0.59 to 3.11) • **D3: 2.41 (1.06 to 5.82)[a]** • **D4: 7.22 (2.62 to 21.4)[a]** • **D5: 6.68 (2.81 to 18.0)[a]** • **D6: 4.80 (1.74 to 14.2)[a]** **Exposure-response coefficient: 0.231 (p=0.0001)[a]**
Schubauer-Berigan et al. 2017 Retrospective cohort study from 3 plants with quantitative exposure measurements; n=5,436 male workers; Follow-up through 2005 Two-plant cohort (plants 6 & 7) excluded plant 2. Plants 6 & 7 handled higher percentage of soluble Be	Mean Be exposure (μg/m^3 – tertiles of case distribution): • $T1_{Mean}$ (referent): 0 to <0.88 • $T2_{Mean}$: 0.88 to <1.85 • $T3_{Mean}$: ≥1.85 Cumulative Be exposure (μg/m^3-days tertiles of case distribution): • $T1_{Cumu}$ (referent): 0 to 723 • $T2_{Cumu}$: 723 to < 4211 • $T3_{Cumu}$: ≥4211 Two-plant cohort compared to full three-plant cohort described in Schubauer-Berigan et al. 2011b	Lung cancer	HR mean Be exposure: • $T2_{Mean}$: 1.18 (0.63 to 2.19) • $T3_{Mean}$: 1.72 (0.92 to 3.24) Exposure-response coefficient: 0.270 (p=0.61) HR cumulative BE exposure: • $T2_{Cumu}$: 1.34 (0.67 to 2.68) • $T3_{Cumu}$: 1.68 (0.78 to 3.63) **Exposure-response coefficient: 0.170 (p=0.033)[a]**
Steenland & Ward, 1991 Retrospective cohort study from the BCR; n=689; entry into BCR 1952-1980; followed through 1988	Cancer mortality rates compared to U.S. male and female population (all races)	Lung cancer	SMR • **All: 2.00 (1.33 to 2.89)[a]** • **Men: 1.76 (1.02 to 2.67)[a]** • **Women: 4.04 (1.47 to 8.81)[a]** • **S_{AP}: 2.32 (1.35 to 3.72)[a]** • S_{CBD}: 1.57 (0.75 to 2.89)

Table 2-8. Summary of Epidemiological Studies Evaluating Cancer Endpoints

Reference and study population	Exposure or comparison population information	Cancer outcomes	Effects
Sub-cohorts: S_{AP}=Workers entered into BCR with a diagnosis of acute pneumonitis S_{CBD}=Workers entered into BCR with a diagnosis of CBD			
Wagoner et al. 1980[d] Retrospective cohort study; n=3,055 white male workers employed between 1942 and 1967; followed through 1975	Cancer mortality rates compared to the U.S. white male population Lung cancer mortality rates calculated for the cohort overall, by interval since onset of employment, and by duration of employment	All cancer Lung cancer	SMR: 1.05 SMR • **All: 1.37**[a] SMR by onset of employment (years) • <15: 0.95 • 15-24: 1.28 • **≥25: 1.85**[b] SMR by duration of employment (years) • **<5: 1.40**[a] • ≥5: 1.23
		Digestive cancer	SMR: 0.95
Ward et al. 1992 Retrospective cohort study; n=9,225 male workers employed between 1940 and 1969; followed through 1988	No occupational history data, beyond starting and ending dates of employment Lung cancer mortality rates compared to county lung cancer rates	Lung cancer	SMR: • **All: 1.26 (1.12 to 1.42)**[a] • **Lorain: 1.69 (1.28 to 2.19)**[a] • **Reading: 1.24 (1.03 to 1.48)**[a] • Luckey: 0.82 • Cleveland (Perkins & St. Claire): 1.08 • Elmore: 0.99 • Hazelton:1.39 SMR pre-1950 (Lorain, Reading, & Cleveland): • **All: 1.42**[b] • **Lorain: 1.69 (1.28–2.19)**[b] • **Reading: 1.26 (1.02 to 1.56)**[a] • Cleveland: 1.06

Table 2-8. Summary of Epidemiological Studies Evaluating Cancer Endpoints

Reference and study population	Exposure or comparison population information	Cancer outcomes	Effects
			SMR after smoking adjustment factor of 1.1323 (Lorain & Reading): • All: 1.12 • Lorain: 1.49 • Reading: 1.09

ABD = acute beryllium disease; BCR = Beryllium Case Registry; CBD = chronic beryllium disease; DWA = daily weighted average; F = female; HR = hazard ratio; M = male; SMR = standardized mortality ratio; SRR = standardized rate ratio

[a]*P* < 0.05
[b]*P* <0.01
[c]Confidence intervals not reported
[d]Study received criticism for using male mortality data for the period of 1941-1967, which may have resulted in a 10-11% underestimation of expected lung cancer deaths

To assess the influence of lowering beryllium exposure concentrations, lung cancer deaths were segregated by date of initial employment (Wagoner et al. 1980). An increase in lung cancer deaths was observed in workers initially hired before 1950 (before strict beryllium controls were instituted in 1950) and a 25-year or higher latency period (20 observed versus 10.76 expected). A slight increase in lung cancer deaths was also observed in workers initially employed after 1950, across latency periods (7 observed versus 4.60 expected). The study authors note that using national mortality rates probably resulted in a 19% underestimation of cancer risk because Berks County, Pennsylvania (where 87% of the workers resided) has a lower age-adjusted lung cancer rate than the U.S. general population (31.8 per 100,000 versus 38.0 per 100,000). However, EPA (1987) notes that most of the beryllium workers residing in Berks County lived in the city of Reading, Pennsylvania, with a lung cancer mortality rate 12% higher than the national rate. Thus, using the national rates may have resulted in an underestimation of expected deaths.

Wagoner et al. (1980) accounted for the contribution of cigarette smoking to lung cancer deaths by comparing smoking histories of the beryllium cohort (obtained during a 1968 medical survey) with U.S. white male smoking history (obtained by the 1964–1965 Health Interview Survey conducted by the Public Health Service). Using these data, the study authors estimated that the smoking habits of the beryllium workers would result in a 14% higher risk of lung cancer than the comparison population, though it is unlikely that "cigarette smoking per se could account for the increased risk of lung cancer among beryllium-exposed workers in this study."

EPA (1987) and MacMahon (1994) have discussed limitations of the Wagoner et al. (1980) study. Specifically, EPA (1987) notes that using male mortality data for the period of 1941–1967 resulted in a 10–11% underestimation of expected lung cancer deaths because nationwide lung cancer rates were increasing. EPA (1987) and MacMahon (1994) commented that the influence of cigarette smoking may have been underestimated by the study authors, and EPA estimated that differences in cigarette smoking patterns would result in a 4.6–18.8% underestimation of expected deaths. EPA (1987) also asserted that one individual who died of lung cancer but did not work at the beryllium facility because he failed the pre-employment physical should not have been included in analyses. After adjusting for use of outdated mortality data and cigarette smoking, EPA (1987) estimated that the rightful omission of this worker would result in no association between beryllium exposure and lung cancer mortality (46 observed versus 41.90 expected deaths for all workers and 20 observed and 14.67 expected deaths for workers with a 12-year latency period).

Ward et al. (1992) examined mortality data for a cohort of 9,225 male workers employed at seven beryllium processing facilities in Ohio and Pennsylvania. The SMR for trachea, bronchi, and lung cancer was 1.26 (95% CI 1.12–1.42). Analysis of mortality data for each individual plant revealed that increases

in lung cancer deaths were only found in two facilities: Lorain, Ohio (SMR 1.69) and Reading, Pennsylvania (SMR 1.24).

To assess the effect of duration of exposure and latency on lung cancer mortality, the total cohort and the Lorain and Reading cohorts were divided into several latency and duration of employment categories. For the total cohort, duration of employment was not associated with increased lung cancer deaths, but increased latency was associated with increased lung cancer deaths. In the total cohort, increases in lung cancer deaths were observed in the >30-year latency category (SMR 1.46), workers employed for <1 year with a >30-year latency (SMR 1.52), and in the 25–30-year latency period for workers employed for <1 year (Ward et al. 1992).

Among workers at the Lorain and Reading facilities, increases in cancer mortality were also observed in workers employed for <1 year with a 30-year latency (SMRs 1.68 and 1.42, respectively). The decade of hire also influenced lung cancer deaths; this was independent of potential latency. The highest cancer mortality rates were observed among workers hired before 1950. Three of the seven beryllium-processing facilities were open in the 1940s; elevated cancer risks were observed at two of the facilities: Lorain (SMR 1.69; 95% CI 1.28–2.19) and Reading (SMR 1.26; 95% CI 1.02–1.56).

The cancer risk was not elevated in the plants operating during the 1950s or 1960s (the Lorain plant closed in 1948). Ward et al. (1992) also examined the influence of geographic variation in lung cancer mortality by comparing cancer mortality in the cohort with county lung cancer data. This comparison did not change the overall conclusions of the study. As with the Wagoner et al. (1980) study, Ward et al. (1992) used smoking habit data available from a 1968 Public Health Survey (which included approximately 16% of the cohort and four facilities [including the Reading, Pennsylvania facility]) to account for this confounding variable. A smoking adjustment factor of 1.1323 was estimated using the available data on the beryllium cohort and smoking habit data for the U.S. population (obtained from the National Center for Health Statistics, 1965 and Office of Health, Research, Statistics, and Technology, 1970). The smoking adjusted SMRs for the entire cohort, the Reading cohort, and the Lorain cohort are 1.12, 1.09, and 1.49, respectively.

In a study sponsored by Brush Wellman, Levy et al. (2002) used data from the Ward et al. (1992) study to recalculate the SMRs for lung cancer using city mortality rates rather than county or U.S. rates and a different indirect method for adjusting for smoking; the incidence of lung cancer among beryllium workers was not substantially increased. A meta-analysis of the data indicated an increase in lung cancer risk, although the SMRs were lower than those calculated by Ward et al. (1992). IARC (2012) noted that there

are several potential methodological limitations of this reanalysis (e.g., the city mortality rates used for these calculations were not published, whereas Ward et al. (1992) used only published rates.

In a similar study sponsored by industry, Levy et al. (2009) re-evaluated the lung cancer mortality data from the Ward et al. (1992) study by calculating hazard ratios using Cox proportional regression analysis to examine potential confounders. Unlike the Ward et al. (1992) study, Levy et al. (2009) did not find substantial differences in hazard ratios between the exposed cohorts and the reference cohorts. Additionally, no differences in the hazard ratios between the different dates of hires (which are considered a surrogate for exposure concentration) were found.

NIOSH sponsored a study by Schubauer-Berigan et al. (2011a), which extended follow-up from the Ward et al. (1992) study to 2005. Lung cancer mortality was examined among 9,199 workers at seven facilities, and beryllium exposure data were assessed in four of these seven facilities (exposure data were available for 5,436 of the 9,199 workers). Beryllium exposure was assessed by estimating maximum and cumulative daily weighted average exposures for specific job operations and using these data and the amount of time each worker spent in that task to create job-exposure matrices. Elevated SMRs were found for lung cancer in workers at two of the facilities (SMR 1.45; 95% CI 1.17–1.78 at the Lorain facility and SMR 1.20; 95% CI 1.04–1.37 at the Reading facility) and all facilities combined (SMR 1.17; 95% CI 1.08–1.28). At some facilities, the lung cancer mortality rate was 64% higher than the U.S. population.

In the sub-cohort of workers in the facilities with monitoring data (5,436 workers), Schubauer-Berigan et al. (2011a) examined lung cancer rates for both cumulative and maximum beryllium exposure. For cumulative exposure, the lung cancer rates were higher than the U.S. population only for cumulative beryllium exposure of ≥10,300 $\mu g/m^3$-days; however, there was no increase in trend with cumulative exposure observed in the standardized rate. When short-term workers (<1 year) were excluded, the SMR in the lowest exposure group decreased and yielded a positive trend (4.28×10^{-8} lung cancer deaths per $\mu g/m^3$-day·person-year) in the standardized rate with increasing cumulative exposure (p=0.012). Trends for cumulative exposure were stronger when stratified by plant: 6.99×10^{-8} (p<0.0001) at the Reading plant, 3.57×10^{-7} (p<0.0001) at the Elmore plant, and 1.10×10^{-7} (p=0.13) at the Hazelton plant. Adjusting for a smoking bias factor did not substantially alter the results. For maximum exposure, lung cancer SMRs were not elevated for those within the <10 $\mu g/m^3$ exposure group but were elevated for higher exposure groups. For example, all exposure groups combined with 10 $\mu g/m^3$ or higher maximum exposure demonstrated a 40% (CI 21%-61%) increased risk of lung cancer compared to the general population. Maximum daily weighted average exposure ≥10 $\mu g/m^3$ was associated with a 72% increased lung cancer rate (95% CI 32%-124%) compared to receiving <10 $\mu g/m^3$ exposure.

Schubauer-Berigan et al. (2011a) also examined nervous system cancers and urinary tract cancers. Findings related to these two types of cancers excluded workers employed for <1 year. No relationship between nervous system cancer and cumulative or maximum beryllium exposure were found. Associations (increased SMR and standardized rate ratio [SRR] values) between beryllium exposure and urinary tract cancer were observed in workers with maximum beryllium exposures of ≥10 μg/m^3.

Mosquin and Rothman (2017) conducted a reanalysis of the Schubauer-Berigan et al. (2011a) study, with funding provided by Materion Corporation. This reanalysis used standardization and Poisson regression to evaluate the effect of cumulative and maximum exposure, unlagged and lagged 10 years, adjusting for plant, employment tenure, and date of hire. The study authors found a modest increase in risk in the full cohort by duration of tenure, and within most subgroups defined by plant and date of hire. The study authors note that the regression-based point-wise confidence bands do not clearly separate risk for low versus high exposure groups, but the authors do not report any confidence intervals in the paper.

To address criticisms of the Ward et al. (1992) and Schubauer-Berigan et al. (2011a, 2011b) studies, NIOSH funded another study by Schubauer-Berigan et al. (2017) to evaluate whether cohort members who were exposed to lower levels of mainly insoluble forms of beryllium demonstrated an increased risk of lung cancer. The study consisted of employees from three plants (Reading, Elmore, and Hazelton) for which quantitative exposure estimates were available. From these three plants, a two-plant cohort was created (Elmore and Hazelton), which removed the larger and higher exposed plant (Reading). The exposure-years to insoluble-only beryllium were 50%, 64%, and 67% for Reading, Elmore, and Hazelton, respectively. After adjustment for confounders, there was a monotonic increase in lung cancer mortality across exposure categories within the two-plant cohort. The exposure-response coefficients (per ln increase in estimated exposure) were 0.278 for mean exposure and 0.170 for cumulative exposure in the two-plant cohort, compared with 0.155 ($p<0.001$) and 0.094 ($p=0.0017$) in the full cohort, respectively.

As a follow-up to the Ward et al. (1992) study, Sanderson et al. (2001a) conducted a case control study using workers from the Reading, Pennsylvania facility. The study consisted of 142 lung cancer cases and 5 age-race matched controls for each lung cancer case. Three quantitative exposure metrics were used to estimate beryllium exposure levels: cumulative beryllium exposure, average beryllium exposure level, and maximum exposure level.

Cumulative beryllium exposure was calculated by summing the products of the number of days a worker held a particular job times the estimated annual average beryllium exposure for the job on those specific days. Average beryllium exposure was calculated by dividing the cumulative exposure level by the number

of days the worker was employed. The maximum exposure level was the highest TWA exposure of any job the worker held, regardless of duration.

As described in a companion paper (Sanderson et al. 2001b), historical measurements were estimated using actual industrial hygiene measurements and extrapolations from existing measurements over time and across jobs. No industrial hygiene measurements were available before 1947. Data from 1947 to 1960 were used to estimate exposure during the period of 1935 to 1960 based on the assumption that exposure levels remained constant during this time period. When job-specific exposure levels were not available, measurements from other areas of the facility that were expected to have similar types of exposures were used as surrogates.

The overall lung cancer mortality rate for the Reading plant through 1992 was 1.22 (95% CI 1.03–1.43), which is slightly lower than the mortality rate of this cohort through 1988 (see discussion of the Ward et al. 1992 study). Most of the cases and controls (approximately 60%) were hired during the 1940s when beryllium levels were uncontrolled. The average duration of employment was 3.7 years for the cases and 5.5 years for the controls; however, approximately 67 and 50% of the cases and controls, respectively, were employed for <1 year (Sanderson et al. 2001b).

Sanderson et al. (2001a) found that compared to controls, a higher percentage of cases worked as general labor or in maintenance departments, where some of the highest beryllium exposures occurred, particularly; there were differences in lung cancer mortality rate when tenure was lagged 10 or 20 years to discount exposures that may not have contributed to causing cancer because they occurred after cancer induction. Exposure levels were not substantially different between cases and controls, respectively, with cumulative (4,606 μg/m^3 days versus 6,328 μg/m^3 days), average (22.8 μg/m^3 versus 19.3 μg/m^3), and maximum exposure levels (32.4 μg/m^3 versus 27.1 μg/m^3), within the same order of magnitude.

When the exposure was lagged 10 or 20 years, exposure levels were higher among the cases. Cumulative beryllium exposure levels were 4,057 and 2,036 μg/m^3 days for the cases and controls, respectively, when lagged 10 years and 844 and 305 μg/m^3 days, respectively, when lagged 20 years. Average exposure levels for the cases and controls were 22.6 and 12.3 μg/m^3, respectively, when lagged 10 years and 10.2 and 5.3 μg/m^3, respectively, when lagged 20 years. The maximum exposure levels were 30.8 and 16.1 μg/m^3 for the cases and controls, respectively, when lagged 10 years and 13.1 and 6.5 μg/m^3, respectively, when lagged 20 years (Sanderson et al. 2001a; 2001b).

Elevated odds ratios were observed in three highest quartiles (when compared to the first quartile) of average exposure and maximum exposure when exposure was lagged for 10 or 20 years, but not when unadjusted exposure levels were used. The odds ratios were elevated in the three highest quartiles of

maximum exposure when exposure was lagged 20 years and in the highest quartile of unadjusted maximum exposure. Similarly, elevated odds ratios were found when the average and maximum exposure levels were divided into three categories (>2, >2-20, and >20 µg/m^3) and lagged 10 or 20 years (Sanderson et al. 2001a; 2001b). In general, no relationship between duration of employment and cancer risk was found.

Sanderson et al. (2001a) also attempted to address two potential confounding variables: cigarette smoking and exposure to other chemicals. The workers were potentially exposed to several other chemicals including nitric acid aerosols, aluminum, cadmium, copper, fluorides, nickel, and welding fumes. Elevated odds ratios were found for copper and fluorides when exposure was lagged 10 or 20 years. Interpretation of this finding is difficult because there were no workers exposed to fluorides or copper only and exposure to fluorides and copper was highly associated with exposure to several beryllium compounds. Smoking history was only available for a small number of cases and controls. Thus, the study authors used an indirect method for assessing the possible association between smoking status and cancer risk. The authors noted that for smoking to be a confounding variable, there would have to be an association between smoking status and beryllium exposure level; no such association was found.

In another industry sponsored study, Levy et al. (2007) re-analyzed the data from the nested case-control study by Sanderson et al. (2001a) and criticized the log-transformation of the exposure metrics and the use of a value of 0.1 assigned to subjects having no exposure during the latency period. Using untransformed exposure metrics, Levy et al. (2007) did not find associations between lung cancer mortality and any of the exposure metrics. Levy et al. (2007) also noted that the mean ages at death, first employed, and termination were higher in the controls, as compared to the cases.

Following letters and critiques of the Sanderson et al. (2001b) study (Deubner et al. 2001a, 2007; Sanderson et al. 2001c), NIOSH funded a reanalysis of the study (Schubauer-Berigan et al. 2008). This reanalysis evaluated whether adjusting for age-at-hire and birth year (that may account for known differences in smoking rates by birth year) influenced the association between beryllium exposure and lung cancer mortality; the study also evaluated the choice of the exposure value used during the latency period (because exposure metrics were log transformed, a value of zero could not be used to account for no exposure during the latency period). Increases in the risk of lung cancer were associated with average exposure using a 10-year lag; cumulative exposure was not associated with lung cancer mortality when adjusted for birth cohort. Using a small value to avoid taking the log of zero did not reduce the magnitude of the findings.

Boffetta et al. (2014) conducted a retrospective mortality study (funded by Materion Brush, Inc.), which evaluated lung cancer in 4,950 workers (3,912 males, 1,038 females) exposed to insoluble forms of

beryllium at four U.S. manufacturing facilities. Cause-specific mortality among the workers was compared to mortality rates for the United States (all facilities combined) or regional mortality rates. In the whole cohort, there were no increases in deaths from all cancer types (SMR 1.00; 95% CI 0.90–1.10) and lung cancer (SMR 0.96; 95% CI 0.80–1.14), even when the workers were divided by latency and/or start date. An increase in deaths from uterine cancer was found. Seven uterine cancer deaths were observed; two cervical cancers and five corpus cancers; the investigators noted that these cancers have very different molecular and clinical characteristics and do not have overlapping known risk factors.

In a retrospective mortality study sponsored by Materion Brush Inc., Boffetta et al. (2016) evaluated the relationship between the solubility of beryllium exposures and cancer outcomes. The cohort included 16,115 workers employed during 1925-2008 in 15 facilities; eight of the facilities involved exposure to insoluble beryllium, and seven of the facilities involved exposures to soluble/mixed beryllium compounds. There were no increases in deaths from all cancer types and lung cancer.

In addition to these retrospective mortality studies and case control studies of beryllium workers, NIOSH funded two studies (Infante et al. 1980; Steenland and Ward 1991). In the Infante et al. (1980) study, 421 white male workers entered the cohort between July 1952 and December 1975. The cohort included workers in beryllium extraction and smelting, metal production, and fluorescent tube production. Mortality rates were compared to the U.S. white male population for the same period, and lung cancer (which includes trachea and bronchi cancers) was observed (7 observed compared to 2.81 expected). 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 ($p<0.05$). However, Infante et al. (1980) may have underestimated the number of expected U.S. deaths for the 1967 time period. In an analysis of the Wagoner et al. (1980) study (described earlier in Section 2.19) using a similar method, EPA (1987) stated that using male mortality data for the period of 1941–1967 resulted in a 10–11% underestimation of expected lung cancer deaths because nationwide lung cancer rates were increasing. The contribution of cigarette smoking to the observed increase in lung cancer deaths was not adjusted for in the NIOSH studies because no smoking data were available for the cohort. The study authors note that it is unlikely that individuals with acute beryllium illness had smoking habits of sufficient magnitude to account for the excessive lung cancer risk in this group. This hypothesis suggests that an increased acute dose may be more important in whether an individual gets cancer than the length of time a person is exposed, especially to lower doses.

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 1991). The cohort consisted of 689 individuals, 66% of whom were men. Of the entire cohort, 34% had been diagnosed with ABD and 64% with CBD

(2% of the subjects had unknown disease type). The mortality rates were compared with that of the U.S. population after stratification by age, race, sex, and calendar time. Increases in lung cancer mortality were observed among the beryllium workers (SMR 2.00; 95% CI 1.33–2.89). There were 70 deaths from all types of cancer, 28 of which were due to lung cancer. Of these, 22 lung cancer deaths occurred in men (SMR 1.76, 95% CI 1.02–2.67), and 6 occurred in women (SMR 4.04, 95% CI 1.47–8.81). No trend was found for duration of exposure or for time since initial exposure. The lung cancer excess was more pronounced among those with ABD (SMR 2.32; 95% CI 1.35–3.72) than those with CBD (SMR 1.57; 95% CI 0.75–2.89). Data on smoking status were available for 141 men and 82 women, and data on amount smoked were available for 51 men and 16 women. Analysis showed that the cohort smoked less than the U.S. population, and there were more former smokers and fewer current smokers in the cohort than in the U.S. population. Thus, the study authors concluded that the lung cancer excess was probably not due to smoking; the study authors also ruled out selection bias, concluding that excess exposure to beryllium was the causative factor. It is also possible that the beryllium disease process (particularly ABD) contributes to the development of lung cancer.

In general, the early (prior to 1987) studies that associated beryllium exposure with lung cancer have been inadequately controlled for confounding factors such as smoking, improperly calculated expected deaths from lung cancer, included employees in the beryllium industry who were not actually exposed to beryllium (e.g., salesmen, clerks), or used inappropriate controls. Studies by Ward et al. (1992), Steenland and Ward (1991), Sanderson et al. (2001a), and Schubauer-Berigan (2008, 2011a,b) have addressed many of these issues and provide strong data on the carcinogenic potential of beryllium in humans. NTP (2016) and IARC (2012) have concluded that beryllium is a human carcinogen; EPA (IRIS 2002) classified it as a probable human carcinogen (group B1). IARC (2012) noted that several aspects of the Ward et al. (1992), Sanderson et al. (2001b), Steenland and Ward (1991), and Schubauer-Berigan et al. (2008) studies support the conclusion that beryllium is a human carcinogen. In particular, IARC noted (a) the consistency of lung cancer excess in most of the locations, (b) greater excess cancer risk in workers hired prior to 1950 when beryllium levels were much higher than in subsequent decades, and (c) the highest risk of lung cancer in individuals with ABD and at the facility with the greatest proportion of ABD. In addition, the nested case-control studies found evidence for an exposure-response relationship that was strongest when using the 10-year lag average-exposure metric.

2.19.2 Cancer in Animals

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

exposed to 0.035 mg beryllium/m^3 as beryllium sulfate for 180 days had increased lung cancer rates, compared to controls (Schepers et al. 1957).

Cancer incidence was not increased in hamsters exposed to 0.21 or 0.62 mg beryllium/m^3 as bertrandite or beryl ore for chronic durations (Wagner et al. 1969). In addition, rats similarly exposed to bertrandite ore did not have a greater incidence of lung cancer than that observed in the controls. However, 18 of 19 rats exposed to 0.62 mg beryllium/m^3 as beryl ore developed tumors that were classified as bronchial alveolar cell tumors, adenomas, adenocarcinomas, or epidermoid tumors. Primary pulmonary cancer of the bronchiole was observed at 9 months in rats exposed to 0.006 or 0.0547 mg beryllium/m^3 as beryllium oxide (Vorwald and Reeves 1959). The rats were examined for signs of cancer at 6, 9, 12, and18 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. Moreover, there were extensive metastases to the mediastinal lymph nodes and other areas of the body (Vorwald 1968). 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.

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

2.20 GENOTOXICITY

The genotoxicity of beryllium has been studied in *in vivo* animal models, and *in vitro* cultures of microorganisms and mammalian cells. A summary of the genotoxic activities is provided in Table 2-9. The results of genotoxicity assays of soluble beryllium compounds are inconsistent. Negative results were reported for beryllium nitrate using *Salmonella typhimurium* (Arlauskas et al. 1985; Endo et al. 1991; Kuroda et al. 1991). On the other hand, beryllium sulfate was found to be mutagenic using *Bacillus subtilis* (Kanematsu et al. 1980), but results were negative when mutagenicity was evaluated using *Salmonella typhimurium* (Ashby et al. 1990; Rosenkranz and Poirier 1979; Simmon 1979; Yamamoto et al. 2002) and in *Saccharomyces cerevisiae* (Simmon 1979).

Ulitzur and Barak (1988) reported positive results for mutagenicity of beryllium chloride when evaluating *Photobacterium fischeri* using a reverse mutation assay. Furthermore, while beryllium chloride and beryllium sulfate were found to be mutagenic, the dose-response relationship was weak when the compounds were tested with *Escherichia coli* (Taylor-McCabe et al. 2006; Zakour and Glickman 1984).

In mammalian cell culture, beryllium chloride and beryllium chloride induced gene mutation (Hsie et al. 1978; Miyaki et al. 1979) and were found to be weak mutagens by themselves, but strong comutagens when used in conjunction with 1-methyl-3-nitro-1-nitrosoguanidine (MNNG) when tested in *Escherichia coli* (Taylor-McCabe et al. 2006).

Beryllium metal was not found to be mutagenic or clastogenic *in vitro* in bacterial (*S. typhimurium* and *E. coli*) or mammalian gene mutation assays, with and without metabolic activation (Strupp 2011b).

Overall, soluble beryllium compounds appear to be weakly genotoxic. It should be noted that 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. Inconsistent findings may be due to the physical/chemical properties of beryllium.

Chromosome aberration assay of beryllium was evaluated. Beryllium sulfate and chloride were reported to induce chromosomal aberrations in mammalian cells (Larramendy et al. 1981; Talluri and Guiggiani 1967), while other studies of beryllium sulfate gave negative results (Ashby et al. 1990; Brooks et al. 1989; Paton and Allison 1972). A study using Be ions observed chromosome aberrations in mammalian cells *in vitro* (Talluri and Guiggiani 1967), while others saw negative results (Paton and Allison 1972). Beryllium alone does not produce chromosomal aberrations, but in conjunction with X-rays it produces a response in Chinese hamster ovary (CHO) cells (Brooks et al. 1989). In mice administered a single dose

of 2187.5 mg/kg beryllium chloride via gavage, significant increases in chromosomal aberrations were observed in the bone marrow and spermatocytes; no significant alterations were observed at 93.75 mg/kg. Repeated exposure for 1, 2, or 3 weeks resulted in significant increases in chromosomal aberrations in bone marrow and spermatocytes at 293.75 mg/kg/day. The investigators noted that the percentage of induced chromosomal aberrations was dose- and duration-related (Fahmy et al. 2008). Treatment of human primary lymphocytes with beryllium metal extracts in a mammalian cell chromosome aberration assay did not reveal a genotoxic potential, neither in the presence nor in the absence of metabolic activation (Strupp 2011b).

No DNA damage was observed when human T-lymphocyte cells were exposed to 50–5,000 μM beryllium chloride *in vitro* (Caicedo et al. 2008). No significant DNA damages or micronucleus frequencies (MNFs) were observed in a human B lymphoblast cell line exposed to 17.2±5.9 μg/L (17.2±5.9 ppm) beryllium metal extracts of Ni-Cr-Be-based dental alloy (Zhihong et al. 2011); however, dental alloys containing beryllium were found to be cytotoxic (Elshahawy et al. 2009). Significant increases in DNA strand breaks and micronuclei formation were observed in the bone marrow of mice administered >11.5 mg/kg/day beryllium chloride via gavage for 7 days; exposure to 5.75 mg/kg/day did not result in significant alterations (Attia et al. 2013).

Beryllium and its compounds were associated with significant alterations in the ability to repair damaged DNA. An unscheduled DNA synthesis assay did not induce DNA repair synthesis, indicating beryllium metal may not directly damage DNA. A cell-transforming potential and a tendency to inhibit DNA repair when the cell is severely damaged by an external stimulus were observed (Strupp 2011b). Thus, beryllium may inhibit the repair of DNA damage and act in a cooperative manner to enhance the genotoxicity of other agents (Snow 1992). Beryllium sulfate was not found to affect DNA repair in mammalian cells (Williams et al. 1989); however, it increases misincorporation in cell-free DNA synthesis *in vitro* (Sirover, 1975). Additionally, *in vitro* studies of beryllium sulfate induced morphological transformation of mammalian cells in culture (DiPaolo and Casto, 1979; Dunkel et al., 1981; Pienta et al., 1977) and enhanced viral-induced transformation of hamster embryo cells (HEC) (Andersen 1983; Casto 1981; Casto et al. 1979).

Beryllium and its compounds were associated with significant alterations in gene expression associated with DNA damage repair. Beryllium appears to interfere with gene expressions associated with DNA repair. Gene expression analysis on the bone marrow cells from beryllium chloride–exposed mice showed significant alterations in genes associated with DNA damage repair. Therefore, beryllium chloride may cause genetic damage to bone marrow cells due to the oxidative stress. The induced unrepaired DNA

damage is probably due to the downregulation in the expression of DNA repair genes, which may lead to genotoxicity and eventually cause carcinogenicity (Attia et al. 2013).

Mitochondrial RNA expression of catalase and superoxide dismutase genes were found to significantly decline in male Wistar rats treated orally with 86 mg beryllium chloride/kg-bw for five consecutive days. Beryllium induced oxidative stress leads to functional damages in the liver and brain of rats together with hematological abnormalities (El-Beshbishy et al. 2012). The ability of beryllium to interfere with gene expression may be related to its ability to induce genotoxicity (Perry et al. 1982).

Beryllium may induce carcinogenesis by activating or inhibiting cellular enzymes, or by interfering with gene expression by inhibiting protein phosphorylation (Snow 1992). Beryllium may also decrease the reliability of DNA replication by mimicking magnesium and may reduce editing activity of DNA polymerase (Luke et al. 1975). Snow (1992) suggests that beryllium's ability to adversely impact cellular metabolism and DNA repair along with the immune response may be sufficient to result in carcinogenesis.

The differential display reverse transcription polymerase chain reaction (DDRT-PCR) method was used to detect differences in expressed genes in peripheral blood monocytes from berylliosis patients after stimulation with beryllium sulfate. Beryllium sulfate was found to cause mean changes of 32.5-37.4% in the gene sequencing of four berylliosis patients after examining 1663 sequence tags. Alterations associated with BeSO4 were detected at 1.4–4.5%, and an exclusive association with BeSO4 was found in 2.6–5.7% of the analyzed sequence tags (Gaede et al. 2005). The author speculated that monocyte/macrophage lineage in berylliosis patients does not act in a typical beryllium-induced manner, but in a way that might be common for various granuloma inductors.

Gene expression profiling was conducted on human peripheral blood mononuclear cells, and nearly 450 differentially expressed genes were relevant to the immunopathogenesis of CBD. A gene enrichment analysis identified the JAK (Janus kinase) STAT (signal transducer and activator of transcription) set of genes to be overly represented, so they may be associated with CBD. It should be noted that CBD shares similar pathogenic genes/pathway with sarcoidosis. The top shared pathways included cytokine–cytokine receptor interactions, and toll-like receptor, chemokine and JAK–STAT signaling pathways (Li et al. 2016).

Many DNA methylation and gene expression changes associated with CBD and sarcoidosis were tested in lung cells obtained by bronchoalveolar lavage (BAL) from individuals with CBD, beryllium sensitization, sarcoidosis, and additional progressive sarcoidosis and remitting sarcoidosis. There were extensive, genome-wide, significant DNA methylation changes in those with CBD (52,860 CpGs with nominal

P<0.005 and FDR-adjusted q<0.05), but not those with sarcoidosis. Genomic alterations in DNA methylation in CBD were substantial compared with those with beryllium sensitization. DNA methylation and gene expression in sarcoidosis were more genetically variable, perhaps due, at least in part, to disease status and state, such as disease progression versus remission. These data demonstrate that CBD and sarcoidosis have many similarities in DNA methylation. Analysis of progressive versus remitting sarcoidosis demonstrated that DNA methylation markers of disease progression changes are more subtle. CBD-associated epigenetic marks affect gene expression in BAL cells, suggesting the significance of epigenetic markers in lung immune response in granulomatous lung disease (Yang et al. 2019).

The carcinogenicity of beryllium sulfate was evaluated using *in vitro* mammalian cell culture. Keshave et al. (2001) reported that after 72 hours of varying concentrations of beryllium sulfate (50-200 μg), there was a concentration-dependent 9- to 41-fold increase in the frequency of cell morphological changes observed. In this study, beryllium sulfate induced morphological cell transformation in mammalian cells, and those cells are potentially tumorigenic. Cell transformation induced by BeSO4 may be attributed, in part, to the gene amplification of K-ras and c-jun, and some BeSO4-induced transformed cells possess neoplastic potential resulting from genomic instability (Keshava et al. 2001).

Table 2-9. Genotoxicity of Beryllium and Its Compounds *In Vitro*

Species (test system)	End-point	With activation	Without activation	Reference	Compound
Prokaryotic organisms:					
Salmonella typhimurium	Gene mutation	—	—	Arlaukas et al. 1985; Ashby et al. 1990; Endo et al. 1991; Kuroda et al. 1991; Rosenkranz and Poirer 1979; Simmon et al. 1979; Simmon 1979; Yamamoto et al. 2002; Strupp 2011b	Beryllium sulfate Beryllium nitrate Beryllium chloride Beryllium oxide Beryllium metal
S. typhimurium	Gene mutation	No data	—	Tso and Fung 1981; Arlauskas et al. 1985	Beryllium ion Beryllium nitrate
Bacillus subtilis	Gene mutation	No data	+	Kanematsu et al. 1980	Beryllium sulfate
Escherichia coli	Gene mutation	No data	+	Zakour and Glickman 1984 Taylor-McCabe et al. 2006	Beryllium chloride Beryllium sulfate
Photobacterium fischeri	Gene mutation	No data	+	Ulitzur and Barak 1988	Beryllium chloride
Eukaryotic organisms:					
Fungi:					
Saccharomyces cerevisiae	Gene mutation	No data	—	Simmon 1979	Beryllium sulfate
Mammalian cells:					
Chinese hamster ovary K1-BH4 cell	Gene mutation	No data	+	Hsie et al. 1979	Beryllium sulfate

Table 2-9. Genotoxicity of Beryllium and Its Compounds *In Vitro*

Species (test system)	End-point	With activation	Without activation	Reference	Compound
Chinese hamster ovary cell	Chromosomal aberration	No data	—	Brooks et al. 1989	Beryllium sulfate
Chinese hamster CHL cells	Chromosomal aberration	—	—	Ashby et al. 1990	Beryllium sulfate
Chinese hamster V79 cells	Gene mutation	No data —	+ —	Miyaki et al. 1981; Strupp 2011b	Beryllium chloride Beryllium metal
Human lymphocytes	Chromosomal aberration	No data	+	Larramendy et al. 1981	Beryllium sulfate
Rat hepatocytes	DNA-repair	No data	—	Williams et al. 1989	Beryllium sulfate
Syrian hamster cells	Chromosomal aberration	No data	+	Larramendy et al. 1981	Beryllium sulfate

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

2.21 MECHANISM OF ACTION

Beryllium is a highly charged ion; like magnesium, it is also implicated in a variety of physiological functions. Beryllium can transport across the cell membranes with ease and target enzymes and receptors in the nucleus (Witschi 1970). Beryllium exposure is predominantly through inhalation, and the respiratory tract is the primary target where it evokes an immune response and affects the expression of numerous receptors thus altering normal physiology. Genes associated with receptors like estrogen receptor α (ER) and $p16^{INK4a}$ genes were examined to evaluate whether they potentially contributed to the development of lung cancer associated with exposure to particulate beryllium metal. In this study by Belinsky et al. (2002), lung tumors were induced in F344/N rats by beryllium metal at all exposure concentrations after a single, nose-only exposure to 4 different exposure levels of aerosol leading to lung burdens of 40, 110, 360 and 430 μg. Methylation of the p16 and ER genes were found to be common (80 and 50%, respectively) in beryllium-induced lung tumors; both genes were methylated in 40% of the tumors. Sequencing revealed dense methylation (~80% of all CpG sites) throughout exon 1 of the ER gene. The methylation was reported to have inhibitory effects on gene transcription; p16 genes were found to be less expressed by 30-60 fold when compared to unmethylated tumors. Therefore, beryllium-induced tumors can be, in part, explained through inactivation of the p16 and ER genes. Furthermore, the inactivation of the p16 gene by exposure to beryllium metal supports a possible role for oxidative stress and inflammation in the etiology of human lung cancer (Belinsky et al. 2002).

Gene profiling was conducted to better elucidate the molecular mechanism of cell transformation and tumorigenesis induced by beryllium. Cell lines were derived from tumors developed in nude mice injected subcutaneously with BALB/c-3T3 cells morphologically transformed with beryllium sulfate. The expression profiles of 1176 genes, belonging to several different functional categories, were examined in

the tumor cells as well as in the non-transformed control cells. It was found that expression of the cancer-related genes was upregulated; expression of genes involved in DNA synthesis, repair, and recombination were downregulated in the tumor cells when compared with the control cells. As a result, it appears that beryllium-induced cell transformation and tumorigenesis are concomitant and possibly a result of alterations in gene expression related to cancer, DNA synthesis, repair and recombination. These alterations in gene expression may be responsible for conferring the proliferative advantage resulting in cell transformation and tumorigenesis (Joseph et al. 2001).

Because BeSO4 was found to be weakly mutagenic, a proteomic study was conducted to better elucidate the proteins regulated by beryllium. Thirty-two proteins were identified that were differentially regulated by BeSO4 and/or 1-methyl-3-nitro-1-nitrosoguanidine (MNNG) in the *E. coli* test system. Furthermore, a regulation of proteins involved in glycolysis, the citric acid cycle (CAC), and the pentose phosphate pathway (PPP) was observed. PPP and CAC cycle effects can be linked to oxidative stress reactions due to beryllium exposure, providing insight into beryllium's mode of action. Because the identified *E. coli* model has human homologs, this system may be helpful in identifying the mechanisms of beryllium's effect in humans (Taylor-McCabe et al. 2006).

Beryllium has been observed to behave as an inducer of premature senescence in cells causing proliferation arrest with early expression of the primary senescence markers (p53, p21, p16, and SA-β-gal) after young human fibroblasts were treated with BeSO4. Chromatin immunoprecipitation experiments showed that Be2+ caused p53 to associate with the promoter region of the CDKN1A gene suggesting that Be2+ may affect p53 activation in a manner similar to that seen during senescence. Therefore, Be2+ may be characterized as a potential pharmacological inducer of premature senescence (Coates et al. 2007). BeSO4 may also inhibit the growth of cancer cells with a pathway distinct from the DNA damage response (Gorjala and Gary 2010).

The role of p53, the tumor-suppressing transcription factor, in mediating beryllium-induced cytostasis was evaluated in A172 cells treated at 10 μM $BeSO_4$. $BeSO_4$ was found to cause a 300% increase in CDKN1A mRNA and a 90% reduction of CCNE2 mRNA. Up-regulation of CDKN1A (cyclin-dependent kinase inhibitor p21) and down-regulation of CCNE2 (cyclin E2) were associated with the p53-dependent cytostatic response. The regulation of mRNA levels for each of these two-cell cycle regulatory genes during cytostatic response requires p53 function (Gorjala et al. 2016). Beryllium fluoride at low concentrations was found to exert mitogenic effects in peritoneal macrophages by elevating $[Ca^{2+}]_i$, which triggers the activation of $p21^{ras}$-dependent mitogen activated protein kinases signaling cascades (Misra et al. 2002).

Glycogen synthase kinase 3β (GSK-3β) is a key regulator in signaling networks that control cell proliferation, metabolism, development, and other processes. Many investigators have noted connections between GSK-3β signaling, p53, and cellular senescence. $BeCl_2$ was shown to inhibit purified recombinant GSK-3β *in vitro* (Ryves et al. 2002). $BeSO_4$ inhibits endogenous GSK-3β in cultured human cells. Exposure to Be^{2+} was about 1,000-fold more potent in producing a decrease in GSK-3β kinase activity than classical inhibitor, Li^+, when treating intact cells. Treating cells by adding Be2+ to the extracellular medium caused inhibition of GSK-3β activity in cells that express endogenous GSK-3β at normal levels. This inhibitory effect was seen in normal human fibroblasts and in glioma tumor cells (Mudireddy et al. 2014).

2.21.1 Mechanisms of Toxicity Associated with Respiratory Effects

The respiratory tract is the primary target of beryllium toxicity following inhalation exposure. In humans, CBD and beryllium sensitization are the primary non-cancer effects observed. Lung cancer has also been observed in beryllium workers. In animals, the respiratory tract effects include emphysema, pneumonitis, and lung cancer.

CBD is a life-long immune sensitization and subsequent inflammatory response due to beryllium exposure. The disease may appear after removal from exposure and has been observed to have a latency of 20 years (Clayton et al. 2014; Schubauer-Berigan et al. 2017; Kriebel et al. 1988a). Sensitization is a cell-mediated response in the presence of beryllium and is currently measured by the BeLPT. Sensitization is thought to precede the development of CBD. Although the mechanism has not been fully elucidated, a number of studies using BAL fluid from individuals with CBD provide information on some of the components of the toxic sequence. Beryllium interacts with antigen presenting cells in the lungs (alveolar macrophages) and becomes physically associated with a major histocompatibility (MHC) class II molecule (Newman 1996b; Saltini et al. 1989). The MHC class II-beryllium-peptide complex is recognized by the T-lymphocyte receptor with the help of $CD4^+$ molecules. This interaction triggers $CD4^+$ T-lymphocyte activation and proliferation. There is evidence to suggest a selective expansion of certain $CD4^+$ lymphocyte subsets (Fontenot et al. 1999).

Studies in animals support a mechanism where beryllium compounds are taken up by alveolar macrophages and participate in a hypersensitivity immune response to a beryllium-containing antigen (Eidson et al. 1991). Duckett et al. (2000) report that once BeSO4 is injected (subcutaneously) into the lung, it passes through the vascular wall and into the surrounding pulmonary tissues, where it is then phagocytized by macrophages resulting in acute vasculitis. Noncaseating granulomas were present in the vascular wall of the lung.

Inhalation exposure to beryllium may decrease the overall rate of lung clearance by damaging alveolar macrophages, indicating an important role of alveolar macrophages in beryllium-induced granulomatous disease as well as the rapid impairment of alveolar macrophage function by phagocytized BeO (Sanders et al. 1975).

Using the human monocyte cell line THP-1, Ding et al. (2009) studied cellular beryllium uptake and its related biological effects. A considerable amount of beryllium was incorporated into THP-1 macrophages, with amounts varying based on administered concentration, compound solubility, and exposure duration. There was a greater uptake of particulate BeO than soluble $BeSO_4$ (Ding et al. 2009).

Beryllium was found to increase the $CD14^{dim}CD16+$ cells in the lung of CBD subjects. Beryllium stimulates the compartmentalization of a more mature CD16+ macrophage phenotype, and in turn these macrophages are a source of Th1 cytokines and chemokines that perpetuate the beryllium immune response in CBD (Li et al. 2015). Using both a human and murine model of CBD, Falta et al. (2021) demonstrate that beryllium exposure resulted in a cycle of innate and adaptive immune activation. This cycle was characterized by an innate induction of inflammatory chemokine production resulting in an adaptive immune response to these chemokines presenting as neoantigens in the lung (Falta et al. 2021).

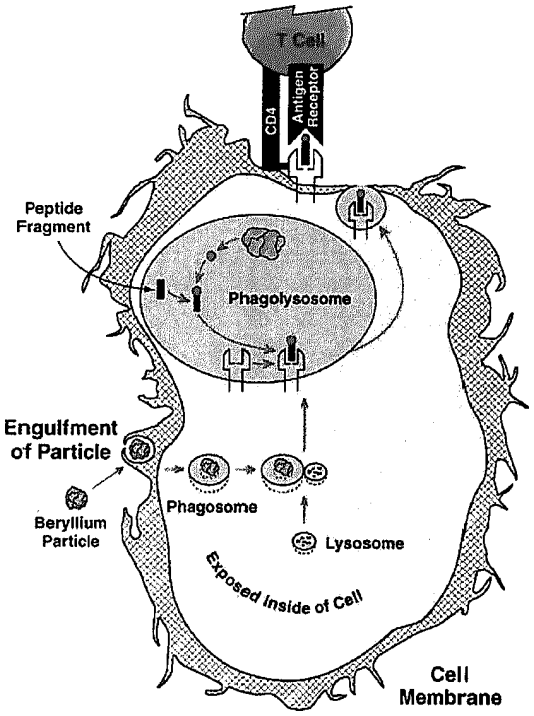
Day et al. (2005) demonstrated a mechanism of bioavailability for beryllium where the macrophage behaves both as a phagocytic and antigen-presenting cell. In this model, particles deposited in the alveolar region of the lung are phagocytized by macrophages and sequestered within phagolysosomes. Macrophages not cleared by mechanical processes remain in the alveoli, enter the lymphatic system, or are sequestered in the alveolar interstitium. Dissolved beryllium in the macrophages may then be available and drive a cell-mediated immune response (see Figure 2-4). While Day postulated that beryllium interacted with antigens, it is now thought that beryllium may bind to MHC molecules (Dai et al. 2010). Canine alveolar macrophages indicate similar results (Day et al. 2005).

An *in vivo* study exposed mice to soluble or crystalline forms of beryllium in the trachea, which resulted in the promotion of alveolar macrophage death impacting the mobilization of immunogenic dendritic cells (Wade et al. 2018). Pulmonary exposure to $BeSO_4$ and $Be(OH)_2$ promoted the release of IL-1α and DNA into the lung and neutrophil influx. These act as damage-associated molecular patterns (DAMPs) to enhance dendritic cell function during beryllium sensitization.

Skin exposure to soluble beryllium compounds causes systemic sensitization in humans and animals. Duckett et al. (2000) and Redlich and Herrick (2008) suggest a greater research focus on the role of skin exposure in promoting beryllium sensitization and CBD. Penetration of poorly soluble particles through intact skin has been proposed as a mechanism for beryllium sensitization. Tinkle et al. (2003) suggested

the following mechanism: The beryllium oxide (BeO) particle penetrates through the outer stratum corneum layer of the epidermis to the inner immunologically active layer of the epidermis thereby starting the sensitization process. The concept of particle penetration through intact skin is controversial, as it appears that surface coatings and skin motion are important factors (Tinkle et al. 2003). The release of ions from beryllium particulate compounds through dissolution in sweat on the skin surface may be an alternative pathway for inducing beryllium sensitization in exposed individuals.

Figure 2-4. Hypothesized Pathway for Cellular Processing of Beryllium-Containing Particles from Phagocytosis to Antigen Presentation



Source: Day et al. 2005

Beryllium was found to stimulate the TNF-α pathway in CBD macrophages by a transcription factor-independent mechanism and a mechanism involving an IFN-γ-induced AP-1 up-regulation (Hamada et al. 2000). The antigen-specific inflammatory response to beryllium is a cell-mediated process involving cytokines. The role of cytokines in CBD has been reported in several studies.

Using alveolar macrophages that are present in BAL fluid from individuals with CBD, Bost et al. (1994) found increased levels of mRNA levels for tumor necrosis factor α (TNF-α) and interleukin (IL)-6 cytokines. TNF-α levels in the BAL fluid were also found to be elevated. Tinkle et al. (1996) reported similar results using BAL cells from CBD patients in that there were elevated levels in TNF-α, IL-6, IL-2, and interferon-gamma (IFN-γ) when exposed to beryllium; IL-4 and IL-7 were not increased in these

studies (Tinkle et al. 1996, 1997). The proportion of IL-10 and IL-6 release and the correlated p45 phosphorylation are factors in determining the Be-mediated immune response in healthy individuals (Chaudhary et al. 2004).

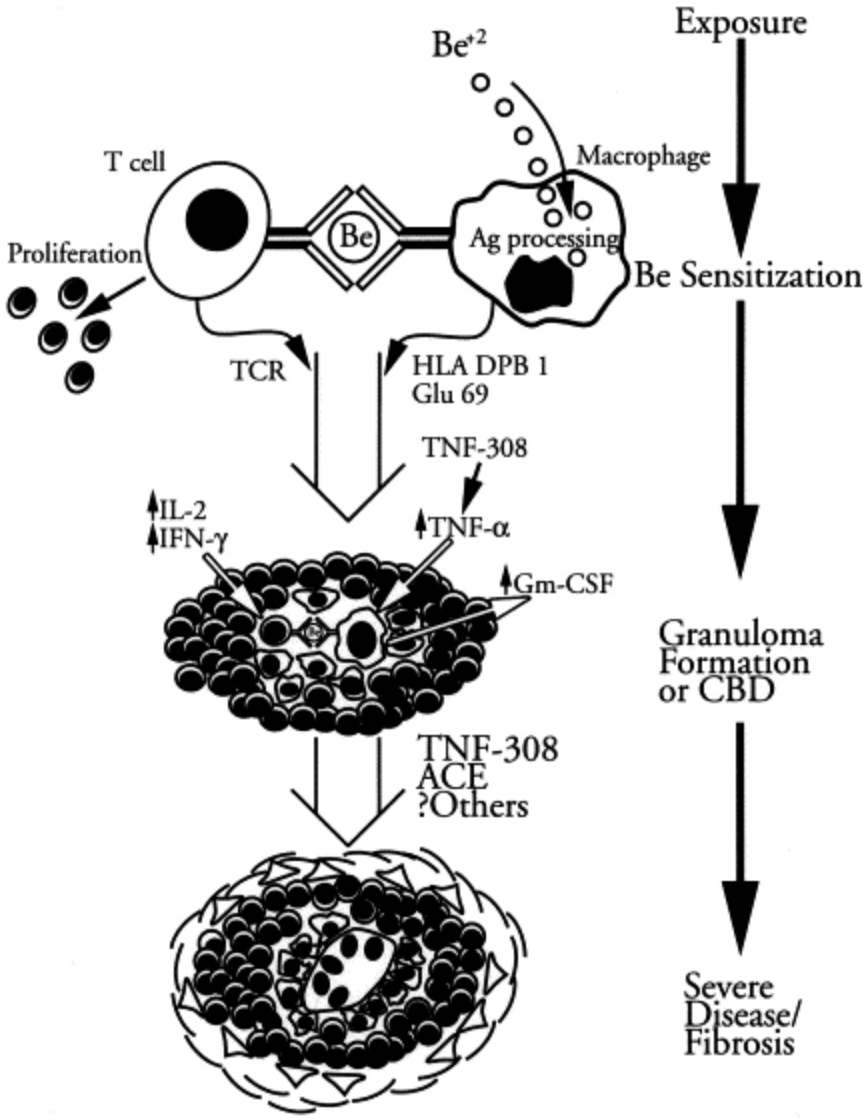
In CBD, as in other delayed-type hypersensitivity diseases, IL-2 is involved with the proliferation and regulation of T lymphocyte and IFN-γ, respectively (Tinkle et al. 1997). BAL cells from subjects with CBD were reported to produce IL-2, α-sIL-2R, and IFN-γ, but not IL-4 when stimulated with beryllium sulfate. However, in the absence of beryllium sulfate stimulation, the response was the same as in controls and showed no measurable levels of IL-2, α-sIL-2R, IL-4, or IFN-γ release. While IL-2 has a dose-dependent role in T-lymphocyte proliferation, T-lymphocyte proliferation is only partially dependent on it. Beryllium sulfate stimulated T-lymphocyte proliferation was found to remain elevated in the presence of anti-IL-2 antibodies. Additionally, INF-γ levels were also decreased in the presence of anti-IL-2 antibodies, suggesting that it is also partially dependent on IL-2. Beryllium also stimulates IL-18, and beryllium cytokine responses are nitric oxide (NO) sensitive. NO may have a potent dampening effect on the capacity of beryllium to induce IFNγ responses in CBD lavage cells and to stimulate lavage cell IL-18 (Barna et al. 2002).

TNF-α and cytokine/chemokine genes are likely to contribute to beryllium sensitization and CBD pathogenesis. The JAK pathway and the JAK2 gene contribute most significantly to ongoing inflammation in the lung in response to beryllium. A JAK2 inhibitor significantly decreased the proliferation of PBMCs in the blood BeLPT after both 10 and 100 μM $BeSO_4$ treatment for 4 days; it was also found to decrease TNF-α and IFN -γ production (Li et al. 2016).

There appears to be a genetic factor associated with susceptibility to CBD. Because MHC class II molecules play a critical role in the T-lymphocyte proliferation and the development of CBD, genes related to the MHC class II (e.g., human leukocyte antigen, HLA–DPDR, DQ, DP) probably play a role in susceptibility to the disease. Analysis of the MHC class II genes shows the presence of specific HLA–DP DPB1 alleles in individuals with CBD (Wang et al. 1999; Richeldi et al. 1993, 1997). Genetic susceptibility to CBD is discussed in greater detail in Section 3.2.

Several studies have examined the mechanisms of beryllium toxicity; most of the studies focused on CBD. Figure 2-5 shows that numerous genes interact with the environment in the development of beryllium sensitization, the progression from beryllium sensitization to CBD, and its development to a more severe disease state (Maier 2002).

Figure 2-5. Steps and Genetic Variants in the Development of Beryllium Sensitization, CBD, and More Severe Forms of Disease[a]



[a]This drawing outlines the steps in the development of beryllium sensitization, CBD, and more severe forms of disease, along with the potential genetic variants associated with each of these steps. Some individuals who are exposed to beryllium develop sensitization after beryllium is internalized and then processed and presented in the context of class II MHC to T cells with appropriate T-cell receptors. These T cells respond by proliferating to beryllium. The class II MHC DPB1 with a glutamic acid at position 69 (Glu69) is a risk factor for sensitization. Following the development of sensitization, some individuals develop an inflammatory response to beryllium in the lung, characterized by IFN-γ, IL-2, and TNF-α production along with the formation of granulomas. Beryllium-stimulated TNF-α production is associated with the - 308 A TNF-α promoter variant.
Source: Maier 2002.

Several papers have extensively reviewed mechanistic data (Amicosante and Fontenot 2006; Dai et al. 2013; Falta et al. 2010; McCleskey et al. 2009; Sawyer and Maier 2011). The following discussion is

taken from these reviews, supplemented with data from the primary studies; primary sources were also evaluated to verify the accuracy of the reviews.

CBD is a granulomatous lung disease that is characterized by an accumulation of beryllium specific, $CD4^+$ T cells. Originally, beryllium was believed to behave like a traditional hapten (Clayton et al. 2014). However, Clayton et al. (2014) reports that this is not the case, as beryllium binds in an MHC complex and changes the peptide binding properties of this immune response molecule. The changes in this complex caused by beryllium binding allow it to be recognized by T-cell receptors and initiate a hypersensitivity response (Clayton et al. 2014; Dai et al. 2013). The binding takes place with glutamic acid at codon 69 of the human leukocyte antigen HLA–DP gene or at position 71 of the HLA–DPDR and forms an antigen-presenting complex (APC) (Falta et al. 2010). Bill et al. (2005) also observed that beryllium recognition was dependent on the glutamic acid at position 69 of the HLA-DP protein and position 71 of the HLA-DR protein; therefore, it was speculated that changes in this position can modify binding and affect beryllium sensitivity. Polymorphisms in this position and their impact on sensitivity to beryllium sensitization and CBD are discussed in Chapter 3, Section 3.2.

HLA–DP alleles have also been strongly associated with CBD inflammatory T-cell-mediated lung disease caused by hypersensitivity to beryllium. Soluble HLA–DP molecules expressing βGlu69 but not HLA–DP molecules with a lysine can bind beryllium *in vitro* with high affinity, suggesting susceptibility to CBD (Amicosante et al. 2001; Fontenot et al. 2006).

The TCR-activated beryllium-specific $CD4^+$ T cells proliferate and secrete Type 1 helper T (Th1) cytokines such as IL-2, IFN-γ, and TNF-α. The release of Th1-type cytokines initiates macrophage activation, accumulation, and aggregation, and the development of granulomatous inflammation. A study showed that HLA-DP Glu69- and HLA-DR Glu71-expressing molecules can induce beryllium-specific proliferation and IFN-γ expression by lung CD4+ T cells (Bill et al. 2005). $CD4^+$ T cells from the lungs of individuals with active CBD displayed a phenotype that demonstrated expansion of TCRs that are specific to beryllium and are compartmentalized in the lungs (Clayton et al. 2014). Most beryllium-specific CD4+ T cells in blood and lung of patients with beryllium sensitization and CBD expressed an effector memory phenotype, regardless of IFN-γ or IL-2 production. The proliferation ability of CD4+T cells after exposure to beryllium depends on several factors including the maturation state of the memory T cell; this is well correlated with how severely the lungs are inflamed as mediated by the CD4+T cells (Fontenot et al. 2005). The frequency of beryllium-specific, cytokine-secreting CD4+ T cells in blood was found to be significantly greater in CBD patients (Pott et al. 2005). Furthermore, Falta et al. (2013) identified peptides

that can form a complex that is recognized by CD4+T cells in CBD patients. These peptides act to bind to the MCHII and beryllium.

There is also evidence to indicate beryllium specific $CD4^+$ T may use a pathway other than the APC for activation. Two beryllium-specific T cells have been observed in the BAL fluid of CBD patients: cells that have the co-stimulatory CD28 molecule and cells that are CD28 negative. Beryllium-specific $CD28^+$ $CD4^+$ T cells in the blood have been reported to be sequestered in the CBD lung where CD28 expression is down-regulated. The absence of CD28 molecules results in increased IFN-γ expression and a decreased IL-2 secretion. $CD28^-$ $CD4^+$ T cells exhibit HLA–DP and LFA-1 co-stimulatory surface molecules and can present beryllium to other T cells. This allows for the T cell to activate and proliferate in the absence of APCs. It also appears that APCs are involved in the early stages of establishing sensitization and responding to re-exposure to beryllium (Chain et al. 2013).

Among CBD subjects with Be-specific CF4+ T cells in their lungs, programmed-death 1 (PD-1) protein has been found to be up-regulated. PD-1 was found to be increased in BAL CD4+ T cells and was also found to be highly expressed in beryllium-specific T cells in beryllium sensitization and CBD subjects. The PD-1 pathway appears to be involved in regulating the proliferation of beryllium-induced T cells. However, this pathway is not sufficient by itself to down-regulate T cell function (Palmer et al. 2008).

Available data suggest beryllium increases oxidative stress in the lungs of those with CBD by directly generating reactive oxygen species (ROS) and depleting thiol antioxidants. As a result, the elevated levels of ROS result in induced macrophage apoptosis via caspases (3-, 8-, and 9-).

Based on these mechanistic data, Sawyer and Maier (2011) proposed a pathogenic mechanism that explained the development of lung inflammation and granuloma formation in CBD, which occur during beryllium exposure and after termination. Upon exposure, macrophages and dendritic cells (DCs) in the skin and respiratory tract endocytose beryllium. The HLA–DP-beryllium antigen complexes are produced as a response to the beryllium particles. In the regional lymph nodes, the APCs activate naïve T cells through a mechanism that is dependent on B7/CD28 co-stimulation proliferating to become beryllium-specific T effector memory cells. In the lungs, the $CD28^+$ T effector memory cells, along with APCs, form interstitial mononuclear cell infiltrates. Next, CD28 is down-regulated, and HLA-DP and LFA-1 expression are up-regulated in the beryllium-specific $CD4^+$ T cells, allowing them to self-present the beryllium antigen within the granuloma.

Persistent levels of beryllium are present in CBD lung granulomas. Even after termination of beryllium exposure, beryllium in the lung is endocytosed by granuloma macrophages, which consequently undergo ROS and caspases mediated apoptosis. Be-induced, human lung-adherent macrophage apoptosis could

contribute to the host's continued re-exposure to beryllium leading to chronic granulomatous inflammation (Kittle et al. 2002). These apoptotic macrophages are endocytosed by other healthy macrophages, which in turn release beryllium in a manner that promotes presentation to beryllium-specific $CD28^-$ $CD4^+$ T cells. As a result, the activated $CD4^+$ T cells further proliferate to generate increased levels of cytokines. The cytokines sustain chronic inflammation by incorporating blood mononuclear phagocytes and beryllium specific $CD4^+$ T effector memory cells into the granuloma (Sawyer and Maier 2011).

Mack et al. (2010, 2014) proposed an additional mechanism that would explain the continued lung damage after exposure to beryllium terminated. These studies found a relationship between the percentage of $CD4^+$ regulatory T cells expressing forkhead box P3 (FoxP3) in the BAL fluid and the severity of CBD disease. The investigators proposed that the dysfunction of FoxP3-expressing $CD4^+$ regulatory T cells enhanced development and perpetuation of an exaggerated immune response in the lungs (Mack et al. 2010, 2014).

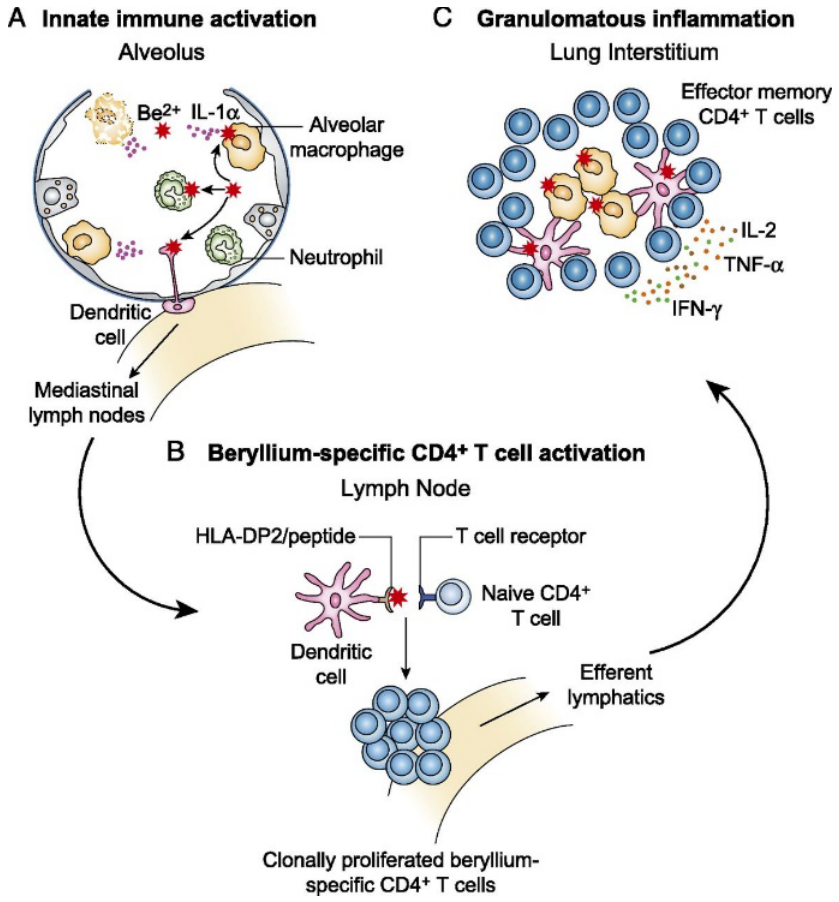
Fontenot et al. (2016) reviewed the recent advances in understanding of T cell recognition of beryllium including the interaction between environmental exposure and genetic susceptibility of granulomatous inflammation. The development of CBD due to susceptibility and the interaction between the gene and environment can be explained by the latest understanding of the adjuvant properties of beryllium, the unique features of HLA–DP2, the stimulatory peptides that capture and coordinate beryllium, and structural changes caused by the formation of Be to the MHCII-peptide complex. Beryllium is coordinated by amino acid residues derived from the HLA–DP2 β-chain and peptide (Amicosante et al. 2009). Be-specific TCR recognizes a Be-loaded HLADP2– peptide complex with charge and conformational changes. Findings by Clayton et al. (2014) provide a structural basis for the development of CBD. Beryllium binds internally to HLA–DP2–peptide complexes, leading to structural and biophysical changes and the creation of neoantigens. Post-translational modifications can change the formation of the peptide binding to the MHCII molecule, and this may potentially alter T cell recognition (Fontenot et al. 2016).

The authors further reviewed the interaction between innate and adaptive immunity in the development of CBD and the generation of an inappropriate immune response in genetically susceptible individuals. Beryllium exposure activates the innate immune system through the pattern-recognition receptors, which leads to cell death, and activation and migration of DCs to lung-draining lymph nodes. The cascade of events results in the development of an adaptive immune response that is characterized by beryllium-specific, T-helper type 1–polarized, $CD4^+$ T-cells and granuloma formation in the lung. The binding of

beryllium to HLA-DP molecules that possess the glutamic acid at position 69 generates a structural change to the HLA-DP peptide complex, which increases the susceptibility of CBD developing (Fontenot 2018; Dai et al. 2010). Figure 2-6 illustrates the pathogenesis of CBD.

ABD is usually observed at relatively high beryllium exposure levels, has a short period of induction, and is usually resolved within a couple of months after exposure. However, recent research suggests that acute inflammatory reactions to beryllium can occur at low beryllium exposure levels, too (Cummings et al. 2009). Early research on ABD suggested that it was an inflammatory response to beryllium, but new evidence suggests that acute inflammatory reactions to beryllium may also be an immunological response and part of the continuum of CBD (Cummings et al. 2009), although this is not fully established. A review by the National Research Council elaborates on the animal models of pulmonary immunotoxicity and sensitization, where the authors conclude that the animal models are inadequate when it comes to replicating the symptoms and effects observed in human CBD (NRC 2008).

Figure 2-6. Pathogenesis of CBD[a]



[a](A) Be exposure results in cellular death and the release of DNA and IL- 1a into the lung, followed by IL-1R–dependent expression of keratinocytes and neutrophil recruitment. Ingestion of Be also results in dendritic cell (DC) activation and trafficking to lung-draining lymph nodes. (B) DCs expressing HLA–DP molecules with a glutamic acid at amino acid position 69 of the b-chain present Be (red stars) to CD4+ T cells, resulting in T cell activation, proliferation, and trafficking to the lung. (C) Clonally expanded CD4+ T cells in the lung are CD28 independent, express an effector memory T cell phenotype, and secrete Th1-type cytokines, including IFN-g, IL-2, and TNF-α. The release of IFN-g and TNF-α promotes macrophage accumulation, activation, and aggregation, resulting in the development of granulomatous inflammation. Within granulomas, HLA–DP–expressing APCs present the Be-peptide complex to Ag-experienced CD4+ T cells.

Source: Fontenot et al. 2016

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

Studies on toxicokinetics of beryllium in humans are scarce and solely based on indirect measurement of exposure. No available toxicokinetic models have been published that simulate the absorption, distribution, and elimination of beryllium from the human body. Most studies on toxicokinetics of beryllium are in animals.

- Absorption
  - Most beryllium is absorbed via the lungs, particularly among occupationally exposed individuals. Data are not available on the rate and extent of absorption of inhaled beryllium in humans.
  - In animal models, significant absorption of soluble beryllium (e.g., beryllium salts) was observed, compared to insoluble beryllium (e.g., beryllium oxide).
  - Beryllium binds to proteins and nucleic acids within the epidermis, making absorption through intact skin unlikely.
  - No studies were located regarding absorption in humans after oral exposure to beryllium or its compounds. However, human ingestion of beryllium is thought to occur inadvertently via hand-to-face activity following dermal handling of beryllium, or because of mucociliary transport of inhaled beryllium out of the respiratory tract and to the gastrointestinal tract followed by ingestion or by mixed exposure. In animals, beryllium and its compounds are poorly absorbed from the gastrointestinal tract.
- Distribution
  - The lung and respiratory tract are the primary target of inhalation exposure for animals and humans.
  - Absorbed beryllium is distributed throughout the body independent of exposure route. The extent of distribution is dependent on beryllium species, particle size, and solubility.
  - The accumulation of beryllium after absorption through the lung or GI tract is duration specific. Beryllium can accumulate in the liver, lungs, lymph nodes, and bones.
  - Beryllium can be transferred across the placenta.

- Metabolism
    - Beryllium and its compounds are not biotransformed, but soluble beryllium salts are partially converted to less soluble forms in the lung.
- Excretion
    - Beryllium is slowly cleared from the lung; clearance half-lives range from days to years in animals. Pulmonary clearance of beryllium is multiphasic where a fast clearance rate is followed by slower elimination rates.
    - Beryllium can be excreted via breast milk.
    - In animal studies, 99% of beryllium is excreted in feces and <1% is excreted in urine after oral exposure.

3.1.1 Absorption

Limited data are available regarding beryllium absorption via inhalation in humans. Deposition and clearance of beryllium are affected by the form of beryllium, the solubility, size of the inhaled particle, and dose (WHO 2001).

Two case studies of accidental human inhalation exposure suggest potential lung deposition of beryllium. Due to an accidental leakage of beryllium dust in a laboratory, 25 people were exposed to an undetermined concentration for 10–20 hours. The day after exposure, mean serum beryllium levels were 3.5±0.47 ppb beryllium, compared to 1.0 ppb in unexposed controls. Six days later, the mean serum level of the exposed group had decreased to 2.4±0.3 ppb beryllium (Zorn et al. 1986). After accidental exposure of eight male workers to <8 ng Be/m^3 as beryllium chloride for 4–6 hours/day for 10 days, beryllium levels in urine and blood increased 4-fold above normal levels (1 ng Be/g) in urine and blood of unexposed individuals (Stiefel et al. 1980).

Soluble beryllium compounds are absorbed more readily than insoluble beryllium compounds. For example, approximately 20% of the initial lung burden was absorbed following inhalation or intratracheal instillation of soluble beryllium salts. However, absorption was slower and less substantial for similar administration of the less soluble compound, beryllium oxide (Delic 1992; WHO 2001). Studies in guinea-pigs and rats indicate that 40–50% of inhaled soluble beryllium salts are absorbed and retained in the respiratory tract (Delic 1992; HSE 1994; WHO 2001). Soluble beryllium salts can become stored in inflammatory scar tissue, or insoluble precipitates can be formed (Reeves and Vorwald 1967).

Calcination affects absorption of beryllium from the lungs in beagle dogs. More calcined (at 1000°C) BeO (62%), was retained in the lungs 180 days after exposure than BeO calcined at 500°C (17%).

Many studies have demonstrated that the lung is the primary target of inhalation exposure in animals and humans. Beryllium in the atmosphere is mainly particulate matter, and deposition in the lungs depends on particle size (especially aerodynamic diameter), form, and solubility (IRSST 2012). Particle size influences deposition rates in humans and in mice, with mice exhibiting a wider variation in rates than humans. The rate of pulmonary deposition between mice and humans for total particles (Be and BeAl) differed by a factor of 20 with humans having the higher deposition rate based on experimental data from IRRST (2012). For fine particles (Be, BeO, BeAl), the rates of deposition between humans and mice were dependent of the form of beryllium. For beryllium, the deposition rate was 1.2 times higher in humans than in mice and 22.5 times higher in humans for BeAl. IRSST (2012) reports mice with deposition rate five times higher than in humans for BeO (Table 3-1). The lung concentration of fine particulate BeO was significantly higher than the other fine particulate beryllium forms.

Table 3-1. Percentage of Lung Deposition as a Function of MMAD

Chemical form	MMAD (μm)	Rate of pulmonary deposition in mice (%)	Rate of pulmonary deposition in humans (%)
Be-T	4.1	0.5	10
Be-F	1.5	11	15
BeO-F	0.4	40	8
BeAl-T	6.5	0.25	5
BeAl-F	4.4	0.4	9

Source: IRSST 2012
MMAD = Mass median aerodynamic diameter; T = Total particulate matter; F = Fine particulate matter; Rates determined using data from Raabe et al., 1988 and IRSST, 2006

Genotoxic actions in metal toxicity often are a result of the ion form. Strupp (2011a) compared the dissolution behavior of beryllium metal and beryllium chloride (a soluble beryllium compound) in an ion formation test. The conditions were designed to simulate inhaled beryllium metal in the human lung (Strupp 2011a). Beryllium chloride dissolved immediately up to the limit of solubility in the normal lung medium and ~90% in the lysosomal fluid with the lower pH, and the amount dissolved did not significantly increase over 28 days. In contrast, beryllium metal increasingly dissolved over time in both fluids, but remained lower than the amount of beryllium chloride that dissolved. The data indicate that dissolution kinetics of the soluble forms and the metal are largely different (Strupp 2011b).

Stefaniak et al. (2012) investigated solubilization of 17 beryllium-containing materials (ore, hydroxide, metal, oxide, alloys, and process intermediates) using artificial human airway epithelial lining fluid. Beryllium-containing particles deposited in the respiratory tract dissolved into the artificial lung epithelial lining fluid and created ions that can be absorbed in the lung and interact with immune cells resulting in

sensitization. The highest releases, based on mass, of ionic beryllium were observed from the beryl ore particles (from 3.88% for the smaller size particle samples to 11.78% for the larger size particles) in 7 days, while release from the other beryllium sources was < 1%. Dissolution half-times ranged from 30 days (reduction furnace material) to 74,000 days (hydroxide). The rapid clearance of beryllium ions leads to an increased release in the respiratory tract via dissolution in airway lining fluid (Stefaniak et al. 2012).

In rats exposed to an aerosol of beryllium sulfate (Reeves and Vorwald 1967) accumulation of beryllium was found in either the lungs or tracheobronchial lymph nodes. Half of the initial pulmonary load was cleared quickly; the rest was retained in the lungs for longer periods and may have been incorporated into pulmonary cell nuclei. Beryllium accumulation in tracheobronchial lymph nodes was greater in males than in females. The authors suggest that body weight only partially contributed to the difference. Males exhibited a greater enlargement of the lymph nodes than females. According to the authors, this indicates that there were sex differences associated with beryllium exposure where males were more sensitive than females (Reeves and Vorwald 1967).

Beryllium is retained and accumulated in the lungs upon repeated exposure. Pulmonary accumulation of beryllium after repeated chemical exposure could lead to beryllium sensitization, and potentially the development of CBD (Benson et al. 2000). For example, C3H/HeJ mice exposed to beryllium metal for several months resulted in beryllium lung burdens of generally >20 μg/lung with the development of lesions that had Be-containing macrophages, granulomatous pneumonia, lymphocytic interstitial aggregates, and mononuclear interstitial infiltrates (Finch et al. 1998; Nikula et al. 1997). Rodent vs. human responses differ. Humans develop fibrosis and heart enlargement with CBD, and rodents do not.

Studies suggest that beryllium is unlikely to be systemically absorbed through intact skin because beryllium binds to proteins and nucleic acids of the epidermis, leading to poor diffusion. Beryllium has been demonstrated to bind to alkaline phosphatase and nucleic acids in guinea pig epidermis *in vitro* (Belman 1969). This binding could account for the inefficient transfer of beryllium from the epidermis to the blood. Skin exposure to soluble beryllium salts can lead to beryllium sensitization in humans (Curtis 1951).

Skin ulceration in workers exposed to beryllium occurred when skin was accidentally cut or abraded (Williams et al. 1987). Beryllium exposure on injured skin may allow a larger fraction of the applied dose to be absorbed into the body, compared to intact skin. Ivannikov observed a significant absorption of beryllium into systemic circulation during a 24-hour exposure to $BeCl_2$ applied directly to the skin of live animals with three types of wounds: 7.8 - 11.4% for abrasions (superficial skin trauma), 18.3 - 22.9% for cuts (skin and superficial muscle trauma), and 34 - 38.8% for penetrating wounds (deep muscle trauma)

(Ivannikov et al. 1982). In situations where both skin injury and the level of dermal exposure to beryllium-containing dust are high, dermal exposure to beryllium may contribute to systemic exposure (Deubner et al. 2001b).

The beryllium occupational air standard is intended to protect workers from high inhalation exposures. However, beryllium is also slightly absorbable through the skin, particularly if the skin is broken. Skin absorption of beryllium may create skin ulcers and damaged skin can increase the amount of beryllium absorbed as described further below (Kreiss et al. 2007).

CBD cases at a copper-beryllium alloy finishing facility were more likely to have reported ulcers or small craters in the skin, compared to employees without CBD (IRSST 2012; Schuler et al. 2005), suggesting a possible role of skin contact in sensitization, especially following exposure to fine particles. In an *in vitro* study, Tinkle et al. (2003) observed that fine particles (0.5- and 1.0-µm) penetrated the stratum corneum, epidermis, and dermis of human skin, thereby initiating an immune response when beryllium particles were <1 µm in diameter with the skin in motion. Topical application of beryllium salts and beryllium oxide to C3H mice generated beryllium-specific cutaneous sensitization (Tinkle et al. 2003). These examples suggest that skin contact with poorly soluble beryllium oxide particles can cause beryllium sensitization in animal and humans.

Deubner et al. (2001c) calculated the expected amount of workplace beryllium exposure through intact and damaged skin, and then compared this to the expected dose from inhalation of workplace air (Kent et al. 2001), or to the OSHA exposure limit (2 µg/m^3) established at that time (Table 3-2). These calculations assume a dermal loading rate of beryllium on skin of 0.43 µg/cm^2, based on the studies of loading on skin after workers performed cleaning duties (Sanderson 1999), multiplied by a factor of 10 to approximate the workplace concentrations, and the very low absorption rate of 0.001 percent.

Table 3-2. Hypothetical Calculation of Workday Beryllium Doses: Dermal Versus Inhalation

	Dermal (µg/workday)		Inhalation (µg/workday)
	Undamaged skin	Damaged skin	
Lower limit	0.0036	0.0318	0.116
Maximum value	1.68	5.36	1.63

Source: Deubner et al. 2001c

No studies were located regarding absorption in humans after oral exposure to beryllium or its compounds. Accidental ingestion of beryllium can be assumed from hand-to-face activity following dermal loading of beryllium or as a result of mucociliary transport of inhaled beryllium out of the

respiratory tract and to the gastrointestinal tract, with the former being more likely (Table 3-3). Actual loading and ingestion of beryllium in the workplace is not known, thus several assumptions are incorporated into calculations to approximate the assumed exposures.

Table 3-3. Hypothetical Calculation of Workday Beryllium Doses: Ingestion versus Inhalation

	Ingestion (µg/workday)					Inhalation (µg/workday)
	Hand to mouth	Tracheobronchial-mucociliary-aided ingestion	Head airways ingestion	Total dose via ingestion	Alternative ingestion scenario[a]	
Lower limit	0.0330	0.0003	0.0032	0.0365	10	0.116
Maximum value	4.02	0.0041	0.0865	4.11	20	1.63

Source: Deubner et al. 2001*c*

Beryllium and its compounds are poorly absorbed from the gastrointestinal tract in animals. The amount absorbed depends on the dose and solubility of the compounds and is limited by the formation of insoluble colloidal phosphate in the intestine (IRSST 2012).

Less than 1% of radiolabeled beryllium in mice, rats, monkeys and dogs was absorbed from the gut after oral dosage. The lower large intestine received the greatest amount of radiation from ingestion of the radionuclide. The amount of Be^7 in the urine indicates the degree of absorption. In rats, mice, dogs, and monkeys, intestinal absorption of beryllium varies, but in general, beryllium was poorly absorbed. The urinary output of rats, mice, dogs, and monkeys was 0.11, 0.24, 0.38, and 3.71% of the total dose, respectively, with most of the radiolabel excreted in the feces (104, 98, 107, and 108%, respectively) (Furchner et al. 1973). Urinary excretion was 0.9 and 0.2% beryllium when administered to male Sprague-Dawley rats at 0.019 and 0.19 mg beryllium/kg/day via drinking water for 24 weeks, while 60 – 90% appeared in the feces. 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). Rats exposed to 31 mg beryllium/kg/day as beryllium sulfate in drinking water for 2 years excreted very little beryllium via the urine (Morgareidge et al. 1975).

3.1.2 Distribution

Following inhalation exposure, beryllium can be retained and may accumulate in lung tissue upon repeated exposure (Benson et al. 2000). Absorbed beryllium primarily transports and distributes via the bloodstream and has been found to widely distribute to various organs in animals. The size, form, and route of exposure of beryllium affects levels of accumulation among various tissues and organs.

A study of children living in southern Poland measured the concentration of beryllium in the pharyngeal tonsils of 379 children (176 girls, 203 boys) between the ages of 2 and 17 years (median 6.0 years) (Nogaj et al. (2014). The average concentration found in pharyngeal tonsil samples was 16 ng/g with a range of 1 to 58 ng/g. The mean concentration of beryllium was higher ($p<0.05$) in girls than in boys, and concentrations also varied significantly by location.

After absorption of beryllium, short-term accumulation happens in the liver, especially when concentrations are high. In the long term, beryllium distributes to the lymph nodes and bones (IRSST 2012). The half-life of skeletal beryllium has been estimated at 450 days (WHO 2001). A study by Krachler et al. (1999a) provides evidence that beryllium is transferred across the human placenta and excreted via breast milk. Beryllium has been identified in human umbilical cord and maternal blood (IRSST 2012). The levels of beryllium in umbilical cord serum and in colostrum were higher than in maternal serum (Krachler et al. 1999a).

In the past, beryllium concentrations in several human organs have been reported 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 details regarding the source of the organs were not provided. In eight males accidentally exposed to <8 ng beryllium/m^3 as beryllium chloride for 4–6 hours/day for 10 days, the beryllium levels in urine and blood increased 4-fold above the levels of <1ng beryllium/g of either blood or urine in unexposed individuals. Beryllium concentration in serum reached a steady state 10 hours after exposure. Since transport and distribution of beryllium occurs in the blood, the authors also evaluated the distribution of beryllium in individual components of the blood and reported that 60-70% of beryllium was bound to two serum proteins: prealbumin and γ-globulin (Stiefel et al. 1980).

Rats exposed to 34.25 μg 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. The beryllium concentration in tracheobronchial lymph nodes peaked between 36 and 52 weeks and decreased thereafter (Reeves and Vorwald 1967). Beryllium concentrations in serum and urine samples of Wistar rats and guinea pigs exposed to 2–40 mg beryllium/m^3 as an aerosol of beryllium nitrate for 16 hours, were up to 36 and 300 ng Be/g, respectively.

Concentrations of beryllium in the blood of guinea pigs increased exponentially and reached a steady-state after 8–12 hours of exposure with a concentration in serum of 10 ng Be/g (Stiefel et al. 1980). In rats and hamsters exposed to an aerosol of beryllium oxide particles, initial alveolar depositions ranged from

12 µg to 160 µg beryllium with a retention half-life of about 6 months. Only the pulmonary lymph nodes accumulated detectable amounts of translocated beryllium oxide (Sanders et al. 1975).

Beryllium tissue burdens were examined in C3H/HeJ male mice exposed to 0 or 250 µg/m^3 fine particle of (<5 µm) beryllium as beryllium metal, beryllium oxide (BeO), or beryllium aluminum (BeAl) via nose-only inhalation chamber for 6 hours/day, 5 days/week for 3 weeks and sacrificed 1 week after exposure termination (Muller et al. 2010; 2011; IRSST 2012). Mass median aerodynamic diameter (MMAD) was measured using a Marple Personal Cascade Impactor with the smallest reading for BeO (0.41±0.03 µm) and the largest for BeAl (4.40±1.64 µm). As compared to controls, significant increases in beryllium concentrations were observed in the spleen, liver, kidney, lung, and blood. Significantly higher levels of beryllium in the liver, kidney, and blood and lower levels in the spleen were found in the BeAl group as compared to the other beryllium groups. No differences in beryllium levels in spleen, liver, kidney, or blood were found between the Be metal and BeO groups.

Pulmonary beryllium concentrations were significantly different in the three beryllium groups; the highest concentration was found in the BeO group and the lowest concentration was found in the BeAl group. The pulmonary concentration in the mice exposed to fine particulates was highest in the BeO group at approximately 25 times more than the BeAl group (~3,500 ng/g) and four times higher than the Be group (~15,000 ng/g) . In the lung, mice were exposed to fine (4.4±1.64 µm) and larger particles of BeAl (MMAD 6.5±1.96 µm), there was an almost 3-fold increase in fine particle vs. larger particle concentrations (IRSST 2012).

Distribution from the lungs to other organs is dependent on the form of beryllium. In beagle dogs exposed to BeO calcined at 500°C, 14% and 8.8% of the initial lung burden was found in the skeleton and tracheobronchial lymph nodes, respectively 64 days post exposure. After 180 days, 16% of the initial lung burden was found in the skeleton, which was comparable to the amount retained in the lungs. The liver also saw increases in beryllium over time. In contrast, the distribution of BeO calcined at 1000°C 64 days post exposure was different than BeO calcined at 500°C. The lungs retained 88% of the initial lung burden, 1.9% was found in the tracheobronchial lymph nodes and 1.5% in the skeleton. At 180 post exposure, 62% of the initial lung burden was still present. The difference in distribution was attributed to the greater solubility of BeO calcined at 500°C (Finch et al. 1990; Finch et al. 1988; Haley et al. 1989).

Wagner et al. (1969) also found that after exposure to beryl ore, concentrations were highest in lungs followed by the skeleton, liver, and kidney. Beryllium sulfate distribution is affected more by solubility and absorption rate than are beryllium oxide or beryllium ores (Wagner et al. 1969). Wagner et al. (1969) and Stokinger et al. (1950) exposed different species, including mice, hamsters, guinea pigs, dogs, cats,

monkeys, goats, rats and rabbits, via inhalation to beryllium (Table 2-1) and found little variation in the beryllium distribution with the highest amounts retained in the lungs or tracheobronchial lymph nodes, followed by femur, spleen, liver, and kidney. Only the pulmonary lymph nodes accumulated detectable amounts of translocated BeO. Seven days post exposure, no detectable beryllium concentrations appeared in the liver, skeleton, or urine of rats or hamsters exposed to BeO (Rhoads and Sanders 1985; Sanders et al. 1975).

No studies were located regarding distribution in humans after oral exposure of beryllium or its compounds. In the case of inhalation, a portion of the inhaled material is transported to the gastrointestinal tract by the mucociliary escalator or by the swallowing of the insoluble material deposited in the upper respiratory tract (Kjellström and Kennedy 1984). Beryllium is thought to be poorly absorbed from the gastrointestinal tract in animals; however, beryllium that 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). Beryllium was retained in the gastrointestinal tract of mice exposed to a radioactive dose of beryllium chloride by gavage. The amount found in the tissues other than intestinal was <0.1%. Three hours after exposure, the accumulation of radioactivity was greatest in the liver followed by the kidney, mesenteric lymph nodes, lungs, blood, and carcass (LeFevre and Joel 1986).

After exposure of male Sprague-Dawley rats to beryllium sulfate at 0.019 and 0.190 mg beryllium/kg/day via drinking water for 24 weeks, beryllium content ranged from 1 to 3 μg, most of which appeared in the bones followed by blood and liver. The pattern of beryllium distribution to rat tissues and organs indicated that as the exposure duration increases, accumulation levels also increase (Reeves 1965).

Other studies indicate that in animals, high levels of beryllium accumulate in bone 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).

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. Intraperitoneal injection of beryllium sulfate in rats elicited brain accumulation of beryllium in a dose-dependent manner (Drobyshev et al. 2019).

3.1.3 Excretion

Excretion of absorbed beryllium is generally via urine, whereas unabsorbed ingested beryllium is excreted through the feces (WHO 2001). 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 Be/g in unexposed individuals (Stiefel et al. 1980).

Concentrations of Be measured in the exhaled breath condensate (Be-EBC) and urine of workers exposed occupationally to 0.015 – 0.354 μg m^{-3} cumulative beryllium exposure index (CBEI) in an aluminum production plant indicates inhalation exposure (Hulo et al. 2016). Concentrations of 1.01±0.16 (mean± standard error) ng Be/L in the EBC of exposed subjects after adjustment for smoking status were higher than in controls (0.62±0.08 ng/L). Urinary concentrations of 14.85±3.61 ng g $creatinine^{-1}$ in workers and 15.16±2.88 ng g $creatinine^{-1}$ in controls were not substantially different between groups. Metal concentrations measured in EBC of workers were not correlated with concentrations in their urine (Hulo et al. 2016). Due to an accidental leakage of beryllium dust in a laboratory, 25 people were exposed to an undetermined concentration for 10–20 hours. The mean serum level of the exposed group had dropped to similar levels as the unexposed group two to eight weeks after exposure, suggesting a biological half-life of 2 to 8 weeks (Zorn et al. 1986). The detection of beryllium in the lungs ~30 years after occupational exposure to beryllium powder and dust for ~6 years in a fluorescent light bulb factory indicated that beryllium can be recovered from the lungs of workers with CBD years after exposure has ceased (Verma et al. 2003).

Inhaled beryllium is cleared from the respiratory tract by various mechanisms. More soluble forms of beryllium are cleared by absorption, whereas less soluble or insoluble forms may reside in the lungs for many years after exposure. Clearance mechanisms for less soluble or insoluble forms of beryllium depend on the deposition location in the respiratory tract (Table 3-4).

Table 3-4. Clearance Mechanisms for Less Soluble and Insoluble Forms of Beryllium

Location	Clearance Mechanism
Nasal Passages	Sneezing, mucociliary transport, dissolution
Tracheobronchial region	Coughing, mucociliary transport, phagocytosis, dissolution
Alveolar	Phagocytosis, translocation, dissolution

Sources: OSHA 2015 and Schlesinger et al. 1997

Following deposition, beryllium is slowly cleared from the lung. Clearance half-lives range from days to years in animals. Evidence suggests that clearance may be biphasic with an initial rapid clearance via mucociliary transport from the lungs to the gastrointestinal tract followed by a slower phase involving

translocation to the tracheobronchial lymph nodes, uptake by alveolar macrophages, and solubilization (WHO 2001). The rapid phase half-time ranges from 1 to 60 days and the slow phase half-time is 0.6-2.3 years in rats. The half-time depends on the solubility of the beryllium compound with more soluble forms having a shorter half-time than less soluble forms. After prolonged inhalation exposure to beryllium sulfate, pulmonary clearance half-time was approximately 2 weeks and thereafter the elimination rate diminished rapidly. Clearance of beryllium chloride, a soluble beryllium salt, is faster than that of the oxide. Though soluble beryllium salts also precipitate out in the respiratory tract, their initial clearance is faster than the clearance of insoluble or sparingly soluble forms (Magos 1991; WHO 2001). Hart et al. (1980) exposed guinea pigs for 55 minutes nose-only to 230 μg Be/m^3 as beryllium chloride. Immediately after the end of exposure, 34% of the initial body burden was in the gastrointestinal tract, indicating significant mucociliary clearance during exposure. By 48 h post exposure, 50% of the initial lung burden had been removed by mucociliary clearance or alveolar clearance. However, 34% of the initial body burden was still present at 14 days, primarily in the lungs, indicating that clearance is biphasic (Hart et al. 1980). Most inhaled beryllium metal remains in the lung of experimental animals for an extended period of time (Finch et al. 1990).

Haley et al. (1990) exposed rats for 50 minutes nose-only to a mean concentration of 800 μg/m^3 of beryllium metal. The clearance half-time of beryllium over the period studied was 240 days. Clearance of beryllium from 3 to 171 days post exposure was best described by a single-component negative exponential function (Haley et al. 1990).

Hart et al. (1984) exposed male F344 rats to 447 μg Be/m3 as beryllium oxide heat-treated at 560°C and found rapid clearance of beryllium from the lavageable lung compartment (fluids and free lung cells, half-time < 2 days) but minimal clearance in 21 days from the non-lavageable compartment (lung tissue). Female and male rats exposed to beryllium oxide were able to clear 12% and 21% of the alveolar lung burden within 63 days of exposure respectively. Female and male hamsters cleared 38% and 45% of the beryllium in the alveoli respectively in the same amount of time. The study indicates that male rats are better able to clear beryllium particles from the lungs than female rats. The biological half-life for beryllium oxide in the rat lung was estimated to be 6 months (Sanders et al. 1975). Approximately 95% of the beryllium was excreted through the feces. Stiefel et al. (1980) found that 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). Clearance half-times have been reported to be 180–260 days in rats (Finch et al. 1990; Strupp 2011b).

In dogs exposed nose-only to 28±9 µg/L as beryllium oxide calcined at 500°C or 1000°C (the solubility of beryllium oxide decreases as the temperature at which it is calcined increases) for sufficient durations to result in low (14-15 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. 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-life of 54 days. Whole-body clearance after exposure to beryllium oxide calcined at 1000°C was described by a single-component negative exponential function with a half-life of 310 days. Clearance from the lung was more rapid and greater amounts were translocated to the liver, blood, and skeleton in the dogs exposed to beryllium calcined at the lower temperature than in dogs exposed to beryllium calcined at the higher temperature. Lung clearance of both was described by a single-component negative exponential function. Lung clearance half-lives were 64 days for 500°C calcined beryllium oxide and 240 days for 1000°C calcined beryllium oxide. Fecal excretion predominated at early times after exposure to either beryllium oxide aerosols and at all time periods for 1000°C calcined beryllium oxide, while urinary excretion predominated at later times. 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 higher temperature by 180 days. Thus, beryllium oxide calcined at 500°C was cleared more rapidly than beryllium oxide calcined at 1000°C (Finch et al. 1990). Although clearance of beryllium oxide calcined at the lower temperature was relatively fast during the first few days after exposure due to mucociliary clearance, later clearance may result from slow translocation of tracheobronchial lymph nodes, macrophage clearance from the pulmonary to the tracheal regions, and pulmonary solubilization of beryllium followed by mobilization through blood to liver and bone or excretion in urine (Finch et al. 1990)

Benson et al. (2000) investigated the pulmonary toxicity and clearance of Beryllium/copper (BeCu) alloy (2% Be; 98% Cu) and metal beryllium particles with MMAD of 1–3 µm in female C3H/HeJ mice administered 12.5, 25, and 100 µg BeCu alloy or 2 and 8 µg beryllium metal via intratracheal instillation and reported slow lung clearance of beryllium metal with a half-life of 2 weeks to a year.

Beryllium deposited in the lungs of rats exposed for 30-180 minutes to beryllium oxide fired at 1000°C was cleared biphasically as well. 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 (Rhoads and Sanders 1985). In the Muller et al. (2010b) study discussed in Section 2.14, increased levels of beryllium were found in the mice's urine after 1, 2, or 3 weeks of exposure and 1 week after

exposure termination. During the exposure period, urinary beryllium levels were much lower in the beryllium oxide group than in the beryllium metal or beryllium aluminum groups. In the beryllium oxide group, beryllium urinary levels were similar after 1, 2, or 3 weeks of exposure, whereas in the beryllium metal and beryllium aluminum groups, the highest levels occurred after 1 week of exposure (Muller et al. 2010b).

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 drinking water indicated that 99% of the dose was excreted in the feces and <0.5% was excreted in the urine. 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. 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 (Morgareidge et al. 1975). Rats, monkeys, mice, and dogs orally exposed to radioactive beryllium chloride excreted 98% of the dose via the feces. About 50% was excreted within 1/4 day after parenteral dosage (Furchner et al. 1973). No studies were located regarding excretion in humans or animals after dermal exposure to beryllium or its compounds.

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

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

No PBPK modeling studies were located for beryllium.

3.1.5 Animal-to-Human Extrapolations

As reviewed in EPA (1998) and Finch et al. (1996), several animal models of human CBD have been developed, but no models to date mimic all aspects of the human disease. Numerous studies in dogs,

monkeys, and rats have reported granulomatous inflammation in the lungs. However, the lung lesions do not histopathologically resemble CBD in humans; effects are transient or are not consistently associated with beryllium-specific immune responses.

Studies in mice suggest that mice may be an appropriate model (Huang et al. 1992; Nikula et al. 1997). In the model developed by Huang et al. (1992), mice were preimmunized with beryllium sulfate and then administered a single intratracheal dose of beryllium sulfate (Huang et al. 1992). A number of mice displayed symptoms consistent with CBD such as the influx of $CD4^+$ T lymphocytes into the lungs, sensitization of T lymphocytes to beryllium, interstitial inflammation, and granuloma formation. However, these effects were observed at 8 months and were resolved by 10 months. The study by Nikula et al. (1997), in which mice received a 90-minute nose-only exposure to beryllium metal, also found many similarities between effects observed in mice and human CBD. The study authors concluded that this mouse model can be used to study the influence of dose, exposure pattern, and physicochemical form of beryllium on the development of CBD. A comparison of the histologic characteristics of beryllium-induced disease in humans and mice is presented in Table 3-5.

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

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

Source: Nikula et al. 1997

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to beryllium are discussed in Section 5.7, Populations with Potentially High Exposures.

Children are not small adults and have needs and behaviors that may result in higher exposures. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. As children grow their nutritional needs change from breast milk or formula to solid foods. They may eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Specific information on the exposure of children to beryllium is limited. Nadal et al. (2005) found that beryllium concentrations in the hair of children in Tarragona County, Spain were below the limit of detection (0.13 μg/g) in urban areas, near a chemical complex, and near a large oil refinery and two incinerators. A cancer risk assessment of teenagers living in New York City and Los Angeles measured beryllium concentrations in personal samples of air of 0.002 ng/m^3 in New York City and 0.003 ng/m^3 in Los Angeles (Sax et al. 2006). Sax et al. (2006) concluded that EPA models of beryllium concentrations tended to overestimate personal cancer risks for beryllium. An x-ray health survey was conducted in 1948 in the neighborhood surrounding a beryllium manufacturing facility in Lorain, Ohio. In this survey, 2,000 children were examined, and none of the children exhibited signs of chronic berylliosis disease (AEC 1948).

As with adults in the general population, small exposures in children occur from normal ingestion of food and drinking water and inhaling air. These exposures may be higher in areas with naturally high beryllium

soil levels, and near beryllium processing sites, electric power plants, and waste sites containing beryllium. There is suggestive evidence that beryllium is transferred across the placenta and excreted via breast milk.(Krachler et al.1999a). No information on beryllium levels in amniotic fluid, meconium, or neonatal blood was located.

At waste sites, beryllium that is found in excess of natural background levels is most likely to be in soil and presents a special hazard for young children. Hand-to-mouth activity and eating contaminated dirt will result in oral exposure to beryllium. The hazard depends on the form of beryllium present at the waste site. Beryllium in soil at waste sites is almost entirely in the form of insoluble oxides and hydroxides of beryllium which would be expected to be less biologically available than more soluble forms (see Section 5.4.1).

Household products are not likely to contain beryllium except for copper-beryllium wire, which is used in and around the home in electronics or other electrical devices. Products used in crafts, hobbies, or from cottage industries may contain significant amounts of beryllium, so exposure is expected to be higher when undertaking these activities.

The on-going process of development for neonates and breast-fed infants may make them more susceptible to the effects of a contaminant. Mothers exposed to beryllium can pass it to their neonates and breast-fed infants. A study by Krachler et al. (1999a) provides suggestive evidence that beryllium is transferred across the placenta and excreted via breast milk. The levels of beryllium in umbilical cord serum and in colostrum were higher than in maternal serum. The average concentrations of beryllium in the umbilical cords of healthy newborn children were measured for arterial (1.3 µg/L), venous (0.8 µg/L), and mixed (0.6 µg/L) sera (Krachler et al. 1999b). No information on beryllium levels in amniotic fluid, meconium, or neonatal blood was located.

Beryllium exposure to children from parents' work clothes, skin, hair, tools, or other objects from the workplace is possible if the parent uses beryllium at work. In a report to Congress by NIOSH, several historical cases of home contamination by beryllium were reported (NIOSH 1995). Workers who do not change their work clothes at the end of the workday can increase the probability of home contamination with beryllium.

Data on the toxicity of beryllium in children is limited. Dietary studies with beryllium carbonate have found beryllium rickets in young rats (Guyatt et al. 1933; Jacobson 1933; Kay and Skill 1934). The potential of beryllium to induce developmental effects has not been adequately investigated. A chronic study did not find developmental effects (gross and skeletal malformations, fetal survival, and fetal body weights were examined) in dogs exposed to beryllium sulfate in the diet (Morgareidge et al. 1976).

However, intratracheal and intravenous exposure studies have found increases in fetal/neonatal mortality, internal abnormalities, and behavioral abnormalities in rat and mouse offspring (Mathur et al. 1987; Tsujii and Hoshishima 1979).

A fecal test for an infant who was clinically diagnosed with Bartter syndrome (kidney disorder causing imbalance of some ions and related molecules in the body) revealed elevated levels of beryllium and other heavy metals. The mother was occupationally exposed to beryllium-copper alloy through lead soldering for 14 years. This case study suggests beryllium exposure may be transferred to the infant *in-utero* or through lactation (Crinnion and Tran 2010). This observation is supported by findings from Sharma et al. (2002) who observed beryllium crossed the placental barrier and accumulated in the offspring of pregnant rats exposed to a single dose of beryllium as 50 mg/kg beryllium nitrate. The results of a study by Krachler et al. (1999a) suggest that beryllium is transferred across the placenta and via maternal milk. Beryllium levels in the umbilical cord sera and in colostrum were higher than maternal sera levels (Krachler et al. 1999a).

No human or animal data were located that examined possible age-related differences in the toxicokinetics of beryllium. There are no data on the toxicokinetic properties of beryllium in children or immature animals.

Subsequent sections of this chapter (Sections 3.3 and 3.4) discuss the available information on biomarkers of beryllium exposure and effect, as well as interactions between beryllium and other chemicals. The available information is from adults and mature animals; no child-specific information was identified. It is likely that this information will also be applicable to children.

A susceptible population will exhibit a different or enhanced response to beryllium than will most persons exposed to the same level of beryllium in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of beryllium, or compromised function of organs affected by beryllium. Populations who are at greater risk due to their unusually high exposure to beryllium are discussed in Section 5.7.

There are strong data to suggest that a genetic susceptibility factor may predispose certain individuals to development of CBD. CBD is a hypersensitivity granulomatosis characterized by beryllium hypersensitivity and mediated by CD4+ T cells (Rossman 2001). However, not all individuals with beryllium hypersensitivity will develop CBD. Genetic differences in the MHC seem to determine whether an individual is able to present beryllium to a T cell and mount a proliferative response (Maier 2002).

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

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

Other animal data indicates 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 131 mg beryllium/kg/day as beryllium sulfate in the diet for 2 years developed transient glucosuria while renal effects were not observed in males (Morgareidge et al. 1975).

Translocation of beryllium from bone to liver eventually causes a systemic disease characterized by weight loss and liver necrosis (Clary et al. 1972). This study exposed guinea pigs and mice to radioactive beryllium oxide intratracheally after hormone biosynthesis was inhibited by metyrapone injection. The results indicated that altered adrenal hormone synthesis shifted beryllium concentrations from bone to liver, causing weight loss. 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.

A human leukocyte antigen (HLA) class II marker has been strongly associated with CBD (Lombardi et al. 2001). Studies conducted by Fontenot et al. (2000) and Lombardi et al. (2001) suggest that the HLA–DP allele, in particular alleles with HLA–DP containing Glu at DP69, are involved in the presentation of beryllium to CD^{4+} T cells, which are involved in the pathogenesis of CBD (Fontenot et al. 2000; Lombardi et al. 2001). Richeldi et al. (1993) found a higher frequency of allelic variants of the HLA–DP gene coding for a glutamate in position 69 of HLA–DPB1 chain (HLA–DPB1 Glu^{69}) among individuals with CBD than in beryllium-exposed individuals without the disease (Richeldi et al. 1993). The HLA–DPB1 Glu^{69} DNA marker was found in 5 of 6 beryllium workers with CBD, 0 of 2 beryllium-sensitized individuals without disease and 36 of 119 (30%) unsensitized beryllium-exposed individuals (Richeldi et al. 1997).

Further analysis by Wang et al. (1999) found the Glu^{69} marker on the HLA–DPDBP1 gene was not very predictive of CBD (predictive value of 0.36). However, the presence of the relatively rare HLA–DP allele, HLA–DPnon*0201 DPB1 Glu^{69}, had a predictive value of 0.57. Wang et al. (1999) also found a higher percentage of homozygous Glu^{69} carriers in the CBD group as compared to controls. The study authors estimated that carriers of the Glu^{69}/Glu^{69} markers or non-*0201Glu^{69} allele accounted for 85% of the CBD cases and only 16% of unaffected beryllium-exposed individuals. Additional studies by this group found that most beryllium-sensitized individuals without CBD also carried rare HLA–DPnon*0201 Glu^{69} DPB1 alleles (Wang et al. 2001).

It is likely that CBD is a multigenetic disease with a number of genetic factors contributing to the development of an immune response to beryllium. Rossman et al. (2002) also suggested that HLA–DPB1-E69 is a marker for susceptibility to hypersensitivity and not just a progression marker for CBD. The study also found that HLA amino acid epitopes on HLA–DPDRB1 and -DQB1, in concert with or independently of HLA–DPB1-E69, may be associated with progression to CBD (Rossman et al. 2002). Stubbs et al. (1996) also found allelic differences in the -DR (D-related)) isotype of class II HLAs. The HLA–DPDRB1 alleles associated with beryllium sensitization were *0103, *09, *1302, *0403, and *0302 (Stubbs et al. 1996).

Newer studies have shown that 68– 93% of beryllium-sensitized workers and 84–92% of workers with CBD carried the HLA–DPB Glu69 allele, compared to 36–48% in beryllium workers without beryllium sensitization or CBD (Amicosante et al. 2005; McCanlies et al. 2004; Rosenman et al. 2011; Saltini et al. 2001; Sato et al. 2007b; Van Dyke et al. 2011a, 2011b). A 6-fold increase in the risk of beryllium sensitization or CBD was found in beryllium workers positive for HLA–DPDBP1 Glu69 (OR 6.06; 95% CI 1.96–18.7) (Van Dyke et al. 2011a). Separating beryllium sensitization from CBD, Sato et al. (2007b) calculated ORs of 8.2 (95% CI 4.2–15.9) and 11.9 (95% CI 5.5–23.5), respectively.

Rosenman et al. (2011) found higher prevalence of HLA–DPB Glu69 homozygotes and heterozygotes among subjects with beryllium sensitization or CBD as compared to beryllium-exposed non-sensitized subjects (Table 3-6); however, there were no differences between the workers with CBD or beryllium sensitization. Van Dyke et al. (2011b) showed that subjects with beryllium sensitization or CBD were more likely to be HLA–DPB1 Glu69 homozygotes (25.7 and 19.7%, respectively) than non-sensitized subjects (4.3%). The study also found differences in the HLA–DPB1 Glu69 alleles; subjects with beryllium sensitization had a significantly higher frequency of *0201 (51.4%) and *0601 (12.9%) alleles than non-sensitized subjects (26.3 and 1.2%, respectively); a higher frequency of *0601 alleles was also found in subjects with CBD (18.0%). Logistic regression modeling showed that carriage of a single *02 allele, a single non-*02 allele, or a *02 and a non-*02 allele was significant predictors of beryllium sensitization or CBD; the ORs are summarized in Table 3-6. Similarly, Rosenman et al. (2011) found a significantly higher distribution of non-HLA–DPB1*0201 alleles in CBD subjects; 10 alleles were more frequently found (*0202, *0301, *0601, *0901, *1001, *1101, *1401, *1601, *1701, and *7101). Silveria et al. (2012) demonstrated that beryllium-sensitized or CBD subjects were more likely to carry non-HLA–DPB1*02 alleles than *02 alleles (Silveira et al. 2012).

Table 3-6. Risk of BeS and CBD by HLA–DPB1 Glu69 Genotype in Beryllium Workers

Genotype	Odds ratio (95% CI)
BeS	
Homozygote	3.54 (1.29–9.51)
Heterozygote	3.28 (1.63–6.64)
CBD	
Homozygote	2.90 (1.16–7.14)
Heterozygote	6.88 (3.53–13.55)

BeS = beryllium sensitization; CBD = chronic beryllium disease; CI = confidence interval; Glu69 = glutamic acid at position 69

Source: Rosenman et al. 2011

Two studies conducted by Van Dyke (2011a, 2011b) examined the relationship between beryllium exposure carriage of the HLA–DPB1 Glu69 genotype and beryllium sensitization or CBD and found that both exposure and E69 genotype contribute to the development of CBD. The OR for beryllium sensitization and CBD (combined) among HLA–DPB1 Glu69 carriers with beryllium exposure >0.1 μg/m^3 was 24.1 (95% CI 4.77–122) (Van Dyke 2011a). The top half of Table 3-7 shows the significant predictors (type of allele) for beryllium sensitization based on multiple logistic regression (Van Dyke et al. 2011b).

The predictors of CBD using a similar multiple logistic regression model are shown in the bottom half of Table 3-7 (Van Dyke et al. 2011b). Among workers with a lifetime weighted average beryllium exposure of 2 μg/m^3, the ORs for CBD were increased from 5-fold for E69-negative genotypes to more than 100-fold for the E69 homozygotes (Van Dyke et al. 2011b). Among workers with a lifetime weighted average beryllium exposure of 2 μg/m^3, the ORs (95% CI) for CBD were 4.91 (1.46–16.56) for HLA–DPB1 Glu69 genotype, 17.01 (3.80–76.17) for single *02 allele, 58.77 (13.43–257.2) for single non-*02 Glu69 allele, and 110.7 (19.87–619.3) for Glu69 copy number with one *02 allele plus one non-*02 GluE69 allele (Glu69 homozygote) (Van Dyke et al. 2011b).

Table 3-7. Risk of BeS and CBD by HLA–DPB1 Glu69 Genotype in Former and Current Beryllium Workers

Genotype	Odds ratio (95% CI)
Beryllium sensitization	
Single *02 allele	12.01 (4.28–33.71)
Single non-*02 Glu69 allele	29.54 (10.33–84.53)
Glu69 copy number with one *02 allele plus one non-*02 Glu69 allele	55.68 (14.8–209.40)
CBD	
Single *02 allele	3.46 (1.42–8.43)
Single non-*02 Glu69 allele	11.97 (5.12–28.00)
Glu69 copy number with one *02 allele plus one non-*02 Glu69 allele	22.54 (7.00–72.62)

BeS = beryllium sensitization; CBD = chronic beryllium disease

Source: Van Dyke et al. 2011b

To date, 43 HLA-DPb1 alleles that code for Glu69 (E69) have been described. E69 alleloforms of MHC class II antigen-presenting proteins with the greatest negative surface charge convey the highest risk of CBD, however, irrespective of allele, they convey equal risk of beryllium sensitization. The same alleles that cause the greatest risk of CBD are also thought to be important for the progression from beryllium sensitization to CBD (Snyder et al. 2008).

The HLA–DPB1^{E69} allele is a susceptibility marker that has been suggested as useful for pre-employment screening. HLA–DPB1^{E69} allele has been shown to be associated with CBD and beryllium sensitization in at least three sufficiently-sized, well characterized study populations (Maier et al. 2003; Rossman et al. 2002) and several smaller studies, and essentially all of the studies agree (as reviewed in Weston 2011). Inheritance of HLA–DP DPB1^{E69} (HLA–DP beta 1E69) carries an increased risk of 2- to 30-fold in beryllium exposed workers (Weston et al. 2005). However, positive predictive value ranged only 8.3 – 14.3% for carriers with an assumed disease frequency of 5%. For high risk subgroups with disease frequencies of 15%, the range of positive predictive values was found to span between 25 – 43%. Allelic/carrier frequencies were found to be 0.21/0.33, 0.24/0.40, 0.27/0.47, and 0.38/0.59 for

Caucasians, African-Americans, Hispanics, and Chinese, respectively, indicating Chinese could be at highest risk of developing CBD (Weston et al. 2002).

Although HLA-DPB1-Glu69 is associated with the development of CBD, it cannot fully explain susceptibility. About 15% of CBD patients do not possess a Glu69-containing HLA-DP allele, suggesting that other MHC class II alleles may be involved in disease susceptibility. In CBD patients without a Glu69-containing HLA-DP allele, an increased frequency of HLA-DR13 alleles has been described, and these alleles possess a glutamic acid at position 71 of the β-chain (Bill et al. 2005). Studies have also examined the frequencies of other HLA genotypes among individuals who were DPB1 Glu69 negative; 100% were positive for DRB E71, compared to 19.2% in controls. The HLADPB1 Glu69 and HLA–DPDRB Glu71 genotypes accounted for 100% of the beryllium-sensitized and CBD subjects compared to 50.3% in the beryllium exposed non-sensitized workers. Sato et al. (2007b) found that 70% of the CBD subjects who were HLA–DPB1 Glu69 negative were HLA–DPDRB1*13 carriers; the prevalence in the non-sensitized workers was 15.7%, and no association was found for beryllium sensitization. Another study found that HLA–DPDRP Phe47 was significantly associated with beryllium sensitization /CBD among HLA–DPB1 Glu69 negative subjects; 95% of the HLA–DPB1 Glu69 negative subjects were positive for HLA–DPDRP Phe47 (Amicosante et al. 2005).

There are other genes that may be involved in regulating the immune and inflammatory response in the pathogenesis of this disease. Several studies have examined the association of polymorphisms with CBD or beryllium sensitization. Functional gene polymorphisms of the TNF-α and transforming growth factor (TGF) β1 genes are suspected to modify the course of granulomatous disorders.

High TGF-β1 protein production has been associated with several diseases including pulmonary sarcoidosis. TGF-β1, a multifunctional cytokine involved in mediating the fibrotic/Th1 response, has several genetic variants which might predispose individuals to these lung diseases. Genotype GG produces more TGF-β1, which inhibits cytokine production and IL-2 dependent T cell activation, potentially limiting the inflammatory response. A single nucleotide polymorphism (SNP) in the TFNA gene promotor, -308 (A for G), may increase the release of TNF-α from Be stimulated BAL cells of CBD patients. Both TGF-β1 (codon 25) polymorphisms and TNFA (-308) were analyzed in patients with CBD. Both TGF-β1 polymorphism and TFNA (-308) genotype frequencies from United States CBD patients differed significantly from those of European and Israeli patients/controls (Gaede et al. 2005).

The genotype profile of the CBD positive sub-cohort of European and Israeli patients was 62.5% CC/GC compared to 13.8% in healthy controls ($P<0.001$). This pattern was not observed in the U.S. cohort.

However, for TNFA2 allele, the U.S. CBD positive cohort had increased frequencies of the TFNA SNP (28.20% vs. 8.96% in healthy controls; P<0.005) (Gaede et al. 2005).

Increase in TGF-β1 (codon 25) genotype (CC or GC) frequency associated with a low TGF-β1 protein release suggests that they are involved in the pathogenesis of CBD. This indicates that multiple genes can determine susceptibility for the same immunopathological reaction and disease (Gaede et al. 2005). For example, the TNF-α response is independent of the activation of beryllium-specific HLA-DP restricted T-cells (Amicosante et al. 2002).

Gene polymorphisms associated with the control of the immune response, such as TNF-α and TGF-β1, act in synergism with a specific immune response gene such as HLA-DPB1-Glu69 or other HLA-class II polymorphisms; driving the immune response to beryllium and in the development CBD (Gaede et al. 2005). Using DNA from sarcoidosis cases/controls, TGF-β1-variants were analyzed by sequence-specific primer PCR. Specific TGF-β genotypes and haplotypes are associated with a more severe pulmonary phenotype in both sarcoidosis and CBD, although not affecting disease susceptibility per se. The -509C and codon 10T were significantly associated with disease severity indicators in both CBD and sarcoidosis (Jonth et al. 2007).

TNF- α may also play a central role in the determination of susceptibility to beryllium hypersensitivity (Dotti et al. 2004). Examining TNF-α polymorphisms, Saltini et al. (2001) found a significantly higher frequency of the TNF-α-308*02 allele among subjects with beryllium sensitization or CBD, as compared to controls; however, there were no significant differences between the frequencies in CBD or beryllium sensitized subjects (Saltini et al. 2001). In contrast, McCanlies et al. (2007) did not find significant associations between TNF-α-308*02 or TNF-α-238*02 and beryllium sensitization or CBD. Similarly, Sato et al. (2007a) did not find any significant differences in the frequencies of several TNF-α promoter polymorphisms in subjects with beryllium sensitization, CBD, or the combined groups.

Relationships between CBD disease severity and TNF-α promoter polymorphisms have been reported (Maier et al. 2001; Sato et al. 2007a). TNF-α expression was not upregulated for THP-1 macrophages upon beryllium stimulation in comparison to the untreated control cells. Alveolar macrophages (THP-1 monocytes into macrophages) could have some level of tolerance to beryllium and this may explain why most Be-exposed individuals remain healthy throughout life (Ding et al. 2009).

Studies by Sato et al. (2010), Bekris et al. (2006), and McCanlies et al. (2010) looked for associations between polymorphisms of genes coding for CC chemokine receptor 5 (CCR5), glutamate cysteine ligase (GCL, rate-limiting enzyme for glutathione synthesis), and several interleukins (IL-1A, IL-1B, IL-1RN,

IL-2, IL-9, and IL-9R). No significant differences in the frequency of CCR5 polymorphisms were found between subjects with beryllium sensitization, CBD, or controls (subjects exposed to beryllium but not sensitized), suggesting that CCR5 or GCL polymorphisms do not increase susceptibility (Sato et al. 2010). However, polymorphisms were found to be associated with the progression of CBD. Greater declines in lung function were found among CBD subjects who were homozygous for specific CCR5 polymorphisms or carried specific CCR5 alleles. When analyzed in a combined group of beryllium sensitized and CBD subjects, associations were found between BAL lymphocyte percentages and specific CCR5 polymorphisms.

Bekris et al. (2006) found differences in GCL polymorphisms between CBD subjects and beryllium sensitized subjects or controls (exposed to beryllium but not sensitized). However, no differences in GCL polymorphisms were found between the controls and beryllium sensitized subjects (Bekris et al. 2006). In the McCanlies et al. (2010) study, the frequency of three IL-1A single nucleotide polymorphisms were significantly different in subjects with CBD compared to those with beryllium sensitization or non-sensitized subjects (Table 3-8). The authors controlled for HLA-DPBI^{Glu69} status in the analyses, as it is well documented that this can also impact sensitivity to CBD. In Table 3-8, various changes were observed depending on the substitution that was observed due to the specific polymorphism. It demonstrates that specific changes in the IL-1A gene can lead to greater susceptibility to developing CBD.

Table 3-8. Adjusted[a] OR and 95% CI for Significant IL-1A SNPs for Different Genetic Models

SNP/Genetic Model	CBD vs Non-sensitized OR (95% CI)	BeS vs Non-sensitized OR (95% CI)	CBD vs BeS OR (95% CI)
IL-1A-1142			
Additive			
AC vs AA	2.23 (1.27-3.93)[b]	0.68 (0.36-1.27)	3.04 (1.34-6.91)[b]
CC vs AC	0.76 (0.34-1.69)	0.76 (0.24-2.41)	1.04 (0.26-4.11)
Dominant			
CC, AC vs AA	2.03 (1.18-3.48)[b]	0.63 (0.35-1.15)	3.02 (1.36-6.70)[b]
Recessive			
CC vs AC, AA	1.05 (0.48-2.28)	0.64 (0.22-1.85)	1.49 (0.40-5.57)
IL-1A-3769			
Additive			
AG vs GG	1.75 (1.03-2.96)[b]	0.70 (0.39-1.24)	2.29 (1.08-4.85)[b]
AA vs AG	0.95 (0.43-2.12)	0.84 (0.26-2.66)	1.15 (0.31-4.33)
Dominant			
AA, AG vs GG	1.73 (1.45-2.88)[b]	0.65 (0.37-1.13)	2.51 (1.21-5.19)[b]
Recessive			
AA vs AG, GG	1.36 (0.64-2.88)	0.74 (0.26-2.17)	1.86 (0.53-6.50)

Table 3-8. Adjusted[a] OR and 95% CI for Significant IL-1A SNPs for Different Genetic Models

SNP/Genetic Model	CBD vs Non-sensitized OR (95% CI)	BeS vs Non-sensitized OR (95% CI)	CBD vs BeS OR (95% CI)
IL-1A-4697			
Additive			
CT vs TT	1.91 (1.13-3.23)[b]	0.69 (0.38-1.20)	2.56 (1.21-5.41)[b]
CC vs CT	0.82 (0.37-1.81)	0.73 (0.23-2.29)	1.18 (0.31-4.39)
Dominant			
CC, CT vs TT	1.72 (1.04-2.85)[b]	0.62 (0.36-1.08)	2.56 (1.24-5.29)[b]
Recessive			
CC vs CT, TT	1.04 (0.48-2.25)	0.63 (0.22-1.82)	1.51 (0.42-5.43)

[a]All ORs adjusted for plant and HLA-DPBI^{Glu69}
[b]Significant ORs

A = adenine; BeS = beryllium sensitization; C = cytosine; CBD = chronic beryllium disease; CI = confidence interval; G = guanine; IL = interleukin; OR = odds ratios; SNP = single nucleotide polymorphisms; T = thymine

Source: McCanlies et al. 2010

Alveolar macrophages from patients with CBD and beryllium sensitization demonstrated significantly greater cell surface CD16 (encoded by the FCGR3A gene). The V158F polymorphism (with significantly higher frequencies of the 158V allele and 158VV homozygotes) of the FCGR3A gene is associated with CBD compared to beryllium sensitized subjects and controls and may impact lung function in CBD. FCGR3A 158VV homozygous genotypes could contribute to the accelerated lung function decline in CBD. The FCGR3A polymorphisms may serve as a risk factor of CBD (Liu et al. 2019). It is possible that this polymorphism could be related to other adverse effects, but further research is needed.

Poorly soluble beryllium materials undergo dissolution in artificial sweat, suggesting that skin exposure is a biologically plausible pathway for development of sensitization. Skin surface acidity, which is regulated by sweat chemistry and bacterial hydrolysis of sebum lipids, varies by anatomical region and may be an exposure-modifying factor for beryllium particle dissolution (Stefaniak et al. 2010).

Beryllium is used in dental alloys where prolonged exposure may cause some toxic effects. Haberman et al. (1998) examined the use of beryllium dental materials which may cause allergic contact dermatitis in some patients. Prolonged exposure to beryllium in dental alloy causes symptoms consistent with gingivitis, oral lichen planus, leukoplakia, aphthous ulcers, and pemphigus (Haberman et al. 1998).

Although, beryllium is poorly absorbed after ingestion, gastro-intestinal conditions might result in increased absorption. For example, Magos (1991) reported that about 20% of the dose is absorbed from the acidic stomach. The majority of the dose is precipitated as in insoluble form in the gut (Magos 1991).

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

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

The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for beryllium from this report are discussed in Section 5.6, General Population Exposure.

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to Beryllium are discussed in Section 3.3.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by Beryllium are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

An alternative approach to assessing beryllium exposure is biological monitoring. There are several tests for measuring beryllium in excreta (e.g., saliva, urine) or other biological tissue (e.g., hair or blood), or measuring a biological effect (e.g., enzyme induction or inhibition) (Frame et al. 1974; Foreman et al. 1970; IARC 1980; Martinsen and Thomassen 1986; Xiao-Quan et al. 1989). Biological monitoring has

the advantage of measuring the total absorbed dose from all routes of exposure, and it is becoming more common and accepted as the understanding of the pharmacokinetic process and feasibility of monitoring improves. Biomonitoring for assessing worker exposure to beryllium would provide an integrated assessment of total worker exposure, and an indication of exposure over time. (Deubner et al. 2001b).

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. The urinary levels appear to be directly proportional to atmospheric levels at 8 ng/m^3 (Zorn et al. 1986). These are the only available data that associate airborne beryllium levels with urinary levels in humans. The latest NHANES data for beryllium show beryllium levels below the limit of detection for the entire population for years 1999-2010 (Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, January 2019).

Biomarkers of oral or dermal exposure to beryllium were not located, probably because very little beryllium is absorbed after exposure by these routes. Reduction in inhalation exposure to beryllium has not resulted in a comparable reduction in the occurrence of beryllium sensitization or CBD, perhaps due to dermal exposure to beryllium particles. Skin exposure may be sufficient to cause an immune response (e.g., beryllium sensitization), while inhalation exposure may be necessary for manifestation of CBD. Biological monitoring of beryllium in bodily fluids could be used to assess for the contribution of both the inhalation and dermal routes to total beryllium exposure. Early attempts at biological monitoring found that beryllium levels in urine indicated whether exposure to beryllium occurred but did not correlate to exposure level or severity of disease (Klemperer et al. 1951; DeNardi et al. 1953; Stoeckle et al. 1969). More recent analytical chemistry methods have greatly improved feasibility of biological monitoring for beryllium (Apostoli and Schaller 2001; Wegner et al. 2000; Saribal 2019; Goullé et al. 2005; Caldwell et al. 2005; Devoy et al. 2013). Apostoli and Schaller (2001) used inductively coupled plasma-mass spectrometry (ICP-MS) to demonstrate that levels of airborne beryllium correlated with levels of urinary beryllium among metallurgical workers. These successes hold promise for future development of approaches to assess and minimize dermal and inhalation exposures to beryllium. (Day et al. 2006a).

Biopsy tissue has been analyzed to determine beryllium concentrations in the body (Nadal et al. 2019). Lung tissue of two employees of a beryllium extraction and processing plant, where beryllium concentrations exceeded the April 2018 and earlier recommended standards of 2 µg beryllium/m^3 for an 8-hour day and 25 µg beryllium/m^3 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). New lower standards (effective May 11, 2018) are provided in Chapter 7. 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 the exposure to beryllium but may not confirm the presence of CBD. Therefore, further testing is required to confirm that these granulomas are a direct result of beryllium exposure, as CBD manifests identically to sarcoidosis, and is often misdiagnosed (Cullinan et al. 2017; Mayer et al. 2014; Chen et al. 2019) . Though one can determine the beryllium concentration in the lung using lung biopsy, it as an invasive procedure and does not provide information on how recently the exposure occurred because beryllium form, solubility, and particle size influence the amount of time the different types are present in the lung.

For occupational health monitoring, the internal dose of beryllium received by the lungs is more relevant than urinary or atmospheric beryllium. Beryllium in the exhaled breath condensate (EBC), was shown to be a good marker of occupational exposure in an aluminum (Al) production plant (Hulo et al. 2016). Hulo et al. (2016) measured the concentrations of beryllium in EBC (Be-EBC) and urine of controls and workers recently exposed to beryllium occupationally and calculated a cumulative beryllium exposure index (CBEI). Concentrations of Be-EBC (1.01±0.16 (mean + standard error) and 0.62±0.08 ng L^{-1} in exposed vs. controls) were significantly higher in exposed subjects after adjustment for smoking status, but urinary concentrations (14.85±3.61 (mean + standard error) and 15.16±2.88 ng g $creatinine^{-1}$ in exposed vs. controls) were not significantly different between groups. Concentrations of Be-EBC and Al-EBC of exposed subjects were highly correlated ($r = 0.85$; $p < 0.0001$). Concentrations of Be-EBC were significantly correlated with CBEI, but, not with urinary concentration. Due to its relationship with CBEI, but not with urinary concentrations of beryllium, Be-EBC could be used as a marker of occupational exposure and provide additional toxicokinetic information in occupational health studies (Hulo et al. 2016).

The contribution of skin exposure to beryllium causing beryllium sensitization has been recognized for over 60 years (Curtis 1951; Day et al. 2006b; Stefaniak et al. 2010). Studies suggest that hair follicles could be a marker of exposure to relatively insoluble particles <1 mm in diameter (Tan et al. 1996; Tinkle et al. 2003).

Drolet-Vives et al. (2009) evaluated whether hair and bone beryllium levels could be used as biomarkers of beryllium exposure. In the study, groups of C3H/HeJ mice were nose-only exposed to filtered air (n=7) or 250 μg/m^3 beryllium metal with a fine (MMAD 1.5 μm; n=40) or large (MMAD 4.1 μm; n=35) particle size for 6 hours/day, 5 days/week for 3 weeks. Beryllium levels in washed hair were significantly higher in groups of beryllium-exposed mice sacrificed 1 week after exposure as compared to controls. A significantly higher beryllium hair level was found in the mice exposed to fine beryllium and sacrificed 3 weeks post exposure as compared to those sacrificed 1 week after exposure. Beryllium exposure also significantly increased bone beryllium levels; the levels in the mice exposed to fine beryllium were

significantly higher than in the large particle beryllium group. Beryllium levels in the bone of mice killed 3 weeks after termination of exposure to fine beryllium metal was significantly higher than in those killed after 1 week. A report of beryllium accumulation in hair and bones of mice exposed to contaminated dusts suggested the potential use of hair and bone as biomarkers of beryllium exposure (Drolet-Vives et al. 2009).

The amount of beryllium found in the lungs could be used to differentiate CBD from sarcoidosis and controls. In a study by Verma et al. (2003), CBD cases had a much higher average beryllium level in the lungs than both sarcoidosis cases and controls. However, occupational history is an equally important factor in the differentiation between CBD and sarcoidosis (Verma et al. 2003).

3.3.2 Biomarkers of Effect

ABD affects most regions of the respiratory tract; some reported symptoms include nasopharyngitis, shortness of breath, labored breathing, and chemical pneumonitis.

Beryllium sensitization does not typically present with signs or symptoms however consistent abnormal or borderline results for blood and/or lung BeLPT results are a biomarker of effect. Likewise subclinical CBD does not present with clinical signs but BeS individuals do have histopathological evidence in the lung. Clinical CBD is an effect biomarker when BeS individuals have histopathological evidence in the lung with respiratory symptoms, changes on chest radiographs, or altered pulmonary physiology.

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

Silveria et al. (2017) observed disease phenotypes associated with baseline patient characteristics, suggesting that CBD is a heterogeneous disease with variable severity. Lung physiology tests, including pulmonary function tests (PFT) plus data from exercising twice gave unique and meaningful information towards the characterization of CBD and sarcoidosis. These tests may be used in future studies to define mechanisms and risk factors for CBD severity (Silveira et al. 2017).

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 CBD and sarcoidosis.

A patch test using soluble beryllium salts was evaluated in 32 patients with known CBD (Curtis 1959) and 18 other lung disease patients. The patch test was positive in all 32 CBD patients and negative in 16 of 18 patients with other lung diseases, indicating that the patch test may be useful in the diagnosis of CBD. However, the patch test using soluble beryllium compounds may be sensitizing and may exacerbate the condition in patients with CBD (Stoeckle et al. 1969; Tepper and VanOrdstrand 1972) (Cotes et al. 1983; Epstein 1983). Therefore, this method is not recommended as a diagnostic tool.

Analysis of secretions and cells of the lower respiratory tract obtained using outpatient bronchoscopy with bronchoalveolar lavage and transbronchial biopsy is useful for detecting granulomatous lung disease sub-clinically (Kreiss et al. 2007). However, it alone cannot distinguish CBD from sarcoidosis (Mayer et al. 2014). The presence of beryllium in the bronchoalveolar fluid, aids the CBD diagnosis.

CBD develops sequentially. Beryllium-exposed workers may develop immunologic beryllium sensitization without CBD. Some with beryllium sensitization develop CBD. Initially, CBD is sub-clinical (sCBD), meaning it is mild and largely asymptomatic. Many individuals with sCBD will progress to advanced CBD. Beryllium sensitization precedes CBD and develops after as little as 9 weeks of beryllium exposure (Harber and Su 2014; Maier 2001). Since CBD is caused by an immune reaction to beryllium, assessments of beryllium hypersensitivity, most often the BeLPT, are used in both medical surveillance and the diagnosis of beryllium sensitization and CBD, even at the sub-clinical stage (Maier 2001). The BeLPT measures cell proliferation via thymidine incorporation in cultured cells in the presence or absence of beryllium salts.

The standards for classifying individuals with beryllium sensitization and CBD have evolved with time. At one-point, patch tests were used to diagnose beryllium sensitization. Then an abnormal BeLPT without evidence of lung disease indicated beryllium sensitization. Now, beryllium sensitization is operationally defined by having two or more positive BeLPTs. At least two abnormal beryllium sensitization tests with evidence of a granulomatous inflammatory response in the lung is considered diagnostic of CBD (Schuler et al. 2012). The determinants of progression from beryllium sensitization to CBD are uncertain, however higher exposures and the presence of a genetic variant in the HLA–DP β-chain appear to increase the risk (Balmes et al. 2014; Rogliani et al. 2004).

Both peripheral blood cells and bronchioalveolar lavage cells can be used in the BeLPT. In early studies, abnormal blood BeLPT results were found in 100% of the subjects with CBD (Williams and Williams 1983; Williams and Williams 1982). Normal results were found in all individuals who were suspected of

having CBD, and abnormal results in approximately 2% of the healthy beryllium workers (Williams and Williams 1983). Despite these results, the blood BeLPT test was not widely used because it was very difficult to perform and not very reproducible. Refinement of the test methodology resulted in a more reproducible test that could be used as a screening tool (Newman 1996a).

A number of large-scale screening studies have utilized blood BeLPT for identifying beryllium sensitization in workers (Kreiss et al. 1993, 1996, 1997; Newman et al. 2001; Stange et al. 2001). In these studies, the majority (53–86%) of the workers with consistently abnormal blood BeLPT results were also diagnosed as having CBD. Using the blood BeLPT to screen workers for beryllium sensitization and CBD is not foolproof. Kreiss et al. (1993, 1996) found a small percentage of workers with CBD and normal or inconsistent blood BeLPT results. Deubner et al. (2001d) assessed the predictive value of the blood BeLPT as a screening tool for CBD. The incidences of CBD among workers with a single unconfirmed abnormal blood BeLPT result was 7/19 (37%), Forty-five percent of the workers had CBD and confirmed abnormal blood BeLPT results (34/75), and 49% of workers with first-time double abnormal blood BeLPT results (both laboratories in agreement) had CBD (17/35) (Deubner et al. 2001d). One limitation of the blood BeLPT is high inter- and intra-laboratory variability. Using split blood samples, Stange et al. (1996b) found an 85–96% agreement rate among three laboratories; however, the agreement rate was only 21–33% for positive blood BeLPT results. Similarly, Deubner et al. (2001d) found poor to moderate agreement in blood BeLPT results among three laboratories.

Stange et al. (2004) examined the sensitivity and specificity of the BeLPT test using data from >25,000 BeLPT tests from 12,194 workers employed at 18 DOE sites (national laboratories, production, and support sites); most of the workers were employed at the Rocky Flats Environmental Technology Site. At 17 of the sites, workers were exposed to beryllium or beryllium oxide; at the last site, workers were exposed to beryllium-copper alloy. 458 subjects with no known beryllium exposure were also tested. A false positive result was defined as an abnormal test result that could not be confirmed by additional BeLPT retests conducted within 2 months of the original sample. Data from the subjects with no known beryllium exposure were used to calculate the false positive rate.

The diagnosis of BeS based on blood BeLPT results alone may have been problematic in older studies. False positive rates in four laboratories conducting the BeLPT ranged from 0.00 to 3.35%, with an average false positive rate of 1.09% (Stange et al. 2004). False negative results were assessed among workers with two or more abnormal results and were defined as a normal result occurring within 2 years of the initial abnormal result. Overall, the false negative rate was 31.7% when only normal and abnormal results were considered and 27.7% when borderline-abnormal rates were considered abnormal (Stange et al. 2004). Methodological and diagnostic criteria have improved the reliability of the BeLPT throughout

the years. Splitting samples, defining the amount of proliferation needed to be considered abnormal or borderline, increasing the number of indices with proliferative responses, and repeat sampling have increased the sensitivity and specificity of the BeLPT. With these changes, the BeLPT has sensitivity estimated at 88% with a 96% specificity (Balmes et al. 2014). It is recommended that any probable BeS diagnosis that has solely used blood lymphocyte proliferation be followed up with a BAL BeLPT as many will rely on the BAL results to either support or reverse a BeS diagnosis.

Inter-laboratory agreement of abnormal results from the four test laboratories ranged from 26.2 to 61.8%; there was a greater agreement (36.6–64.7%) when only sensitized cases were considered. The intra-laboratory agreement of abnormal results ranged from 80.4 to 91.9%. Test sensitivity, the probability that a patient with CBD will have an abnormal BeLPT result, was 68.3%. Test specificity, the proportion of normal tests in all patients who do not have CBD, was 96.9%.

The study also evaluated the predictability of the BeLPT and found that 25.3% of the participants with one abnormal BeLPT result and 38.9% of the participants diagnosed with beryllium sensitization were diagnosed with CBD (Stange et al. 2004). Using the data from the Stange et al. (2004) study, Middleton et al. (2006) examined two algorithms used for BeLPT testing. In the first algorithm, one laboratory analyzed the initial blood sample and two laboratories analyzed a split sample for confirmation of abnormal or borderline tests. Using this algorithm, the test sensitivity was 65.7%; the specificity was estimated to be 99.9%. In the second algorithm, split samples sent to different laboratories were used for the initial and confirmation (abnormal and borderline results) tests. The test sensitivity was 86.0% using the second algorithm, and the test specificity was 99.8% (Middleton et al. 2006).

Middleton et al. (2008) examined the sensitivity and specificity of three beryllium sensitization criteria using the Stange et al. (2004) data. The three criteria were: (1) one abnormal BeLPT result; (2) one abnormal and one borderline (or abnormal) BeLPT result; or (3) two abnormal BeLPT results. The sensitivities of the three criteria were similar: 68.2, 65.7, and 61.2%, respectively (the respective specificities were 98.89, 99.92, and 99.98%). The positive predictive value (the likelihood that a person who meets the criteria is truly sensitized to beryllium) varies with the beryllium sensitization prevalence in the test population. If the prevalence in the test population is low (1%), then the positive predictive values for three criteria were 38.3, 89.3, and 96.8%; thus, the first criteria only correctly predicted beryllium sensitization for 38.3% of the subjects with one abnormal test result. At a 10% prevalence of beryllium sensitization, the positive predictive values were 87.2, 98.9, and 99.7% (Middleton et al. 2008).

In a subsequent analysis, Middleton et al. (2011) estimated the predictability of several combinations of results when three BeLPT tests were administered (single test in the first round and split samples in the

second round); this analysis also used the Stange et al. (2004) data set. The positive predictive values at 1–10% population beryllium sensitivity prevalence rates were >99% when three abnormal or two abnormal and one borderline test results were identified. When three borderline results were found, the positive predictive values were 83.7 and 98.3% at 1 and 10% population prevalence, respectively. When the results were one abnormal, one borderline, and one normal, the positive predictive values were 55.7 and 93.2% for 1 and 10% prevalence, respectively (Middleton et al. 2011).

Common interpretation strategies aim to limit false positives to 5%. A continuous variable is used in the BeLPT test and is called the stimulation index. The stimulation index is considered positive if it is greater than a criterion value, which is chosen to limit false positives to 5%. Nevertheless, beryllium-exposed workers in screening programs have the test performed many times, often on an annual basis. The test is imperfect, having both false positives and false negatives. Sensitization is operationally defined by having two or more positive BeLPTs, and the likelihood of having at least two positive tests increases as the number of tests increases. Simple measures such as sensitivity/specificity are less applicable when screening testing is applied multiple times (Harber and Su 2014). When prevalence is less than 50%, repeat testing will ultimately reduce accuracy. This adverse effect is increasingly important with more testing cycles, lower prevalence, and lower specificity.

Skin patch testing in three individuals with CBD resulted in strongly positive reactions to beryllium sulfate application, presenting extensive granulomatous inflammation in the skin. T cell clones in skin overlapped with those in BAL in all patients tested. Analysis of peripheral blood T cells before and after patch testing demonstrate T cell influx and mobilization into the blood during granulomatous inflammation (Fontenot et al. 2002).

Nonspecific immunologic findings in CBD include an increase in serum gamma-globulin levels (Resnick et al. 1970). The existence of specific antibodies to beryllium have been reported (Clarke 1991). While the results of peripheral blood BeLPTs have been variable in patients with CBD (Kreiss et al. 1989; Newman et al. 1989; Saltini et al. 1989; Stokes and Rossman 1991; Williams and Williams 1983), the results of lung BeLPTs have been consistently positive (Rossman et al. 1988; Saltini et al. 1989).

Martin et al. (2011) investigated whether a cytokine-based assay of $CD4^+$ T cells would be a better predictor of beryllium sensitization than the BeLPT test. The investigators used an enzyme-linked immune spot (ELISspot) analysis to measure IFN-γ secreting $CD4^+$ T cells. In a study of former beryllium workers, similar rates of sensitization were found using BeLPT (8.1%) and an IFN-γ ELIS spot response test (10%); however, among current workers, the BeLPT identified 1.3% sensitized workers compared to 9.9% identified using the IFN-γ ELISspot response test. The investigators suggested that the difference in

the test results among the current workers was due to the poor proliferation of beryllium-specific $CD4^+$ T cells after antigen exposure with no alteration on the cell's ability to secrete TH1-type cytokines such as IFN-γ. The IFN-γ ELISspot response test had a sensitivity of 85% and a specificity of 100%. The study also demonstrated that the IFN-γ ELISspot response test could also be used to differentiate between beryllium sensitization and CBD. More than 93% of the beryllium-sensitized subjects had less than 10 spot-forming units (SPU) and subjects with >40 SFUs had an 81% probability of progressing to CBD (Martin et al. 2011).

3.4 INTERACTIONS WITH OTHER CHEMICALS

Most studies involving chemical interactions were performed to assess whether a substance could ameliorate beryllium toxicity. Mortality rates were lower if rats exposed to 2.59 mg beryllium/m^3 as beryllium sulfate were injected daily with ferric ammonium citrate beginning 4 days prior to beryllium exposure (Lindenschmidt et al. 1986; Sendelbach and Witschi 1987a). The protective action of iron on beryllium toxicity may be related to the ability of iron to increase ferritin synthesis, making more ferritin available to bind with beryllium (Lindenschmidt et al. 1986). Ferritin chelates with beryllium to protect against the inhibition of phosphoglucomutase (Joshi et al. 1984).

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

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

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

BeSO4 and beryllium chloride were weak mutagens by themselves, but a strong comutagen when used in conjunction with 1-methyl-3-nitro-1-nitrosoguanidine (MNNG). BeSO4 significantly enhanced the

mutagenicity of MNNG up to 3.5-fold over MNNG alone in a forward mutant detection system developed in *Escherichia coli* (Taylor-McCabe et al. 2006).

Benson et al. (2000) investigated the pulmonary toxicity and clearance of Beryllium/ copper (BeCu) alloy (2% Be; 98% Cu) and beryllium metal in female C3H/HeJ mice by administering 12.5, 25, and 100 μg BeCu alloy or 2 and 8 μg beryllium metal via intratracheal instillation. Slow lung clearance of the beryllium component (half-time of 2 weeks to a year) indicated that beryllium accumulates in the lung upon repeated exposure, while the Cu component rapidly clears the lung. The presence of Cu does not affect pulmonary beryllium clearance when comparing dose groups of 2 μg beryllium as a component of the 100 μg BeCu and beryllium alone (Benson et al. 2000).

Maternal and developmental beryllium-induced toxicity in rats altered metabolic indices. Treatment of Tiron (4,5-dihydroxybenzene 1,3-disulfonic acid disodium salt) restored metabolic indices largely to normal in both mothers and fetuses. Tiron may be effective in restoring altered biochemical parameters due to the available binding sites and the stability constant of the metal–chelator complex formed. Two molecules of Tiron may form a stable complex by substituting their hydrogen atoms and binding to beryllium with its oxygen atom (Sharma et al. 2000; 2002). Beryllium concentration in liver and kidney of adult female rats after intraperitoneal administration of 1 mg/kg beryllium nitrate for 3 weeks decreased following the therapy of 471 mg/kg chelating agent, Tiron (Shukla et al. 1998).

A chelating agent, 2,3-dimercapto-1-propanesulfonic acid (50 mg/kg), administered to male rats depleted beryllium from the liver, spleen and kidneys, but resulted in the redistribution of beryllium to the blood (Flora et al. 1995). Tiferron has been shown to have an antioxidant effect mobilizing beryllium ions from different tissues and recovering beryllium-induced systemic toxicity in combination with α-tocopherol and piperine respectively; however, combination of tiferron and piperine presented more pronounced therapeutic potential (Nirala et al. 2007). Likewise, crocin “saffron” protects against beryllium chloride toxicity in rats through diminution of oxidative stress and enhancing gene expression of antioxidant enzymes (El-Beshbishy et al. 2012).

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Beryllium is a naturally occurring element found in earth's rocks at levels of 1–15 mg/kg. It appears in Group IIA of the periodic table and the most common oxidation state is Be(+2) although an oxidation state of (0) has been observed in certain compounds. Because of its high reactivity, beryllium is not found as the free metal in nature. There are approximately 45 mineralized forms of beryllium. The important beryllium minerals in the world are beryl ($3BeOAl_2O_36SiO_2$) and bertrandite ($Be_4Si_2O_7(OH)_2$). Beryl has been known since ancient times as the gemstones: emerald (green), aquamarine (light blue), and beryl (yellow). Beryllium, like other metals, can form organometallic complexes. Table 4-1 lists common synonyms, trade names, and other pertinent identification information for beryllium and its compounds.

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

Characteristic	Beryllium	Beryllium chloride	Beryllium fluoride
Synonym(s) and Registered trade name(s)	Beryllium-9; glucinium; glucinum; beryllium metallic	Beryllium dichloride	Beryllium difluoride
Chemical formula	Be	$BeCl_2$	BeF_2
Chemical structure			
CAS registry number	7440-41-7	7787-47-5[d]	7787-49-7
EPA hazardous waste	P015[b]	No data	No data
DOT/UN/NA/IMDG shipping	UN1567/IMO6.1	NA1566/IMO6.1	NA1566/IMO6.1
HSDB	512	357	355
Characteristic	**Beryllium hydroxide**	**Beryllium Oxide**	**Beryllium phosphate ($3H_2O$)**
Synonym(s) and Registered trade name(s)	Beryllium hydrate; beryllium dihydroxide	Beryllia; beryllium monoxide; Thermalox 995	Beryllium orthophosphate
Chemical formula	$Be(OH_2)$	BeO	$Be_3(PO_4)_2$-3H2O
Chemical structure			
CAS registry number	13327-32-7	13044-56-9	35089-00-0[b]
EPA hazardous waste	No data	No data	No data
DOT/UN/NA/IMDG shipping	UN1566/IMO6.1	UN1566/IMO6.1	No data
HSDB	350	1607	No data
Characteristic	**Beryllium nitrate**	**Beryllium sulfate**	**Beryllium carbonate (basic)**
Synonym(s) and Registered trade name(s)	Nitric acid, beryllium salt	Sulfuric acid, beryllium salt	Basic beryllium carbonate; bis[carbonato(2-)] dihydroxy triberyllium
Chemical formula	$Be(NO_3)_2$	$BeSO_4$	$Be_3(OH)_2(CO_3)_2$[c]
Chemical structure			
CAS registry number	13597-99-4 (anhydrous) 7787-55-5 (trihydrate) 13510-48-0 (tetrahydrate)[c]	13510-49-1 (anhydrous) 14215-00-0 (tetrahydrate)[c]	66104-24-3[b]
EPA hazardous waste	No data	No data	No data
DOT/UN/NA/IMDG shipping	UN2464/IMO5.1[d]	UN1566/IMO6.1[d]	No data
HSDB	1431	347	No data

[a] All information from HSDB except where noted
[b] EPA 2019
[c] Lide 2005
[d] NOAA 2019

CAS = Chemical Abstracts Service; 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

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Beryllium exists as a solid, but brittle metal at room temperature and atmospheric pressure. It is part of the metal family and consistent with the high charge-to-radius ratio, beryllium has a strong tendency to form compounds with covalent bonds; even compounds with the most electronegative elements (e.g., BeF_2). Its properties are characterized as stronger than steel and lighter than aluminum; these make it attractive for applications such as in aircrafts and cell phones. No data are available on the vapor pressure of beryllium or its compounds. Although beryllium belongs to Group IIA of the periodic table, it is chemically very similar to aluminum, which also has a high charge-to-radius ratio. Like aluminum, the hydroxide of beryllium can act as either a base or acid (Cotton and Wilkinson 1980; Drury et al. 1978; EPA 1998). The interaction of cosmic-ray particles in the atmosphere produces a number of radionuclides including beryllium-7 (Be-7) and beryllium-10 (Be-10). The radioactive half-life of Be-7 is 53.29 days, and the radioactive half-life of Be-10 is 1.51×10^6 years (UNSCEAR 2000). Table 4-2 lists important physical and chemical properties of beryllium and its compounds.

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

Property	Beryllium metal	Beryllium chloride	Beryllium fluoride	Beryllium hydroxide	Beryllium oxide
Molecular weight	9.012	79.918	47.01	43.027	25.011
Color	Gray	White-yellow	White	White	White
Physical state	Solid; hexagonal crystals[b]	Orthorhombic crystals or needles	Glassy hygroscopic mass	Powder	Amorphous powder or hexagonal crystals
Melting point	1287 °C	415 °C	555 °C	138 °C (Decomposes)	2578 °C
Boiling point	2468 °C	482 °C	1283 °C	Not applicable	3787 °C
Density	1.85 g/cm^3 [b]	1.90 g/cm^3	2.1 g/cm^3	1.92 g/cm^3	3.01 g/cm^3
Taste	No data	Sweet[b]	No data	No data	No data
Odor	Odorless	Sharp, acrid[b]	Odorless	None	Odorless
Odor threshold:	Not applicable	No data	Not applicable	Not applicable	Not applicable
Solubility:					
Water	Insoluble	71.5 g/100 mL water at 25 °C	Very soluble	3.44 mg/100 mL[c]	2 µg/100 mL
Organic solvent(s)	No data	Soluble in ethanol, ethyl ether, pyridine	Slightly soluble in ethanol, more soluble in mixture of alcohol and ether	No data	No data
Inorganic solvent(s)	Soluble in acid and alkaline solutions[b]	No data	No data	Soluble in hot concentrated acid and alkali	Soluble in concentrated acids
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 at 20°C	No data	No data	No data	No data	No data
Henry's law constant at 25 °C	No data	No data	No data	No data	No data
Degradation half-life in air via reaction with OH radicals	No data	No data	No data	No data	No data

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

Dissociation constants:					
$pK_{a,1}$	No data	No data	No data	No data	No data
$pK_{a,2}$	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 in air	No data	No data	No data	No data	No data
Conversion factors[b]	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Explosive limits	No data	No data	No data	No data	No data
Property	Beryllium phosphate	Beryllium nitrate	Beryllium carbonate (basic)	Beryllium sulfate	Beryllium sulfate (tetrahydrate)
Molecular weight	104.991	133.02	181.069[c]	105.07	177.13
Color	White	White	White[c]	Colorless	Colorless
Physical state	Solid	Crystals	Powder[c]	Tetragonal crystals	Tetragonal crystals
Melting point	100 °C (decomposes)	60 °C	No data	550-600 °C (decomposes)	100 °C (loses $2H_2O$) 400 °C (loses $4H_2O$)
Boiling point	No data	142 °C (decomposes)	No data	No data	No data
Density	No data	1.557 g/cm^3	No data	2.443 g/cm^3	1.713 g/cm^3
Taste	No data	No data	No data	No data	No data
Odor	None	None	None	None	None
Odor threshold:	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Solubility:					
Water	Slightly soluble[e]	Soluble	Insoluble (cold) Decomposes (hot)	Insoluble	41.3 g/ 100 mL[c]
Organic solvent(s)	Soluble in acetic acid[e]	Soluble in alcohol	No data	No data	No data
Inorganic solvent(s)	No data	No data	Acid, alkali	No data	No data
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

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

Vapor pressure at 20°C	No data	No data	No data	No data	No data
Henry's law constant at 25 °C	No data	No data	No data	No data	No data
Degradation half-life in air via reaction with OH radicals	No data	No data	No data	No data	No data
Dissociation constants:					
$pK_{a,1}$	No data	No data	No data	No data	No data
$pK_{a,2}$	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 in air	No data	No data	No data	No data	No data
Conversion factors[b]	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Explosive limits	No data	No data	No data	No data	No data

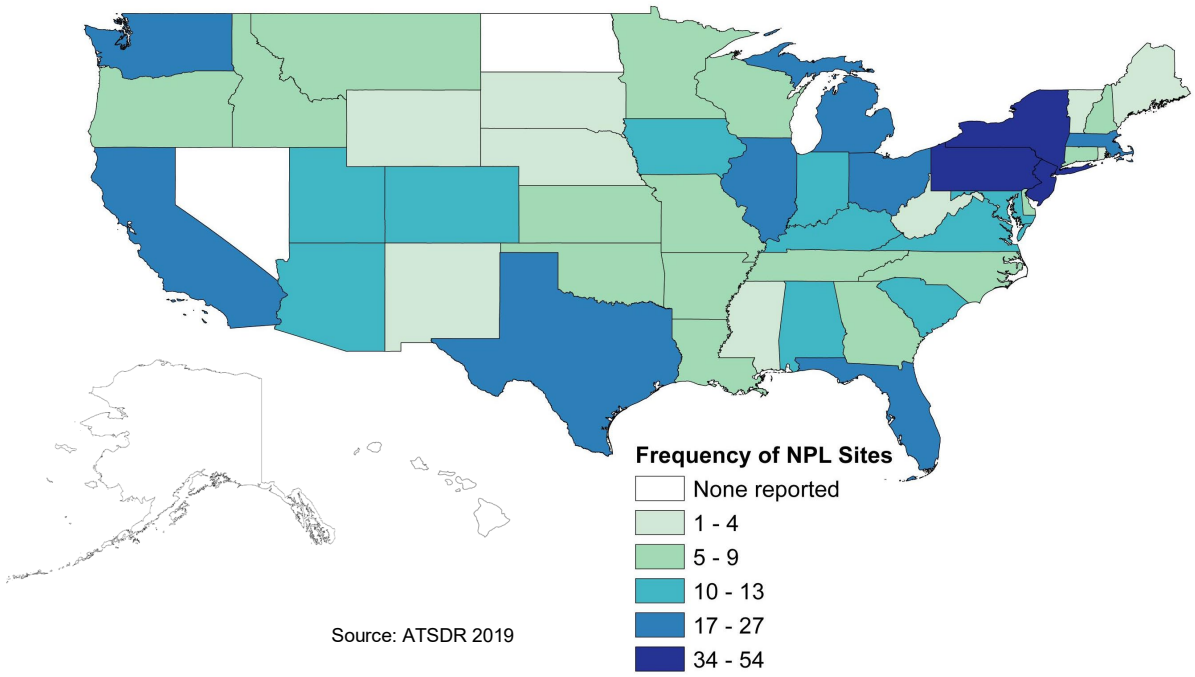
[a] All information from HSDB except where noted
[b] These compounds do not exist in the atmosphere in the vapor phase; therefore, an air conversion factor is not applicable.
[c] Lide 2005
[d] EPA 1987
[e] PubChem 2019

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Beryllium has been identified in at least 540 of the 1,867 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2019). However, the number of sites evaluated for Beryllium is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 530 are located within the United States, 2 are located in the Virgin Islands, one is located in Guam, and 7 are located in Puerto Rico (not shown).

Figure 5-1. Number of NPL Sites with Beryllium Contamination



- Beryllium is an element that occurs naturally in the earth's rocks. It is estimated that more than half of the world's resources of beryllium are located in the United States. Beryllium is a critical mineral with many uses in industrial components, consumer electronics, automotive electronics, defense applications, telecommunications infrastructure, energy applications, and medical applications.
- Beryllium is released to air, water, and soil from natural and anthropogenic sources. Natural sources include windblown dust, volcanic particles, and atmospheric deposition. An estimated 29,231 pounds (13,258.8 kg) of beryllium and 487,939 pounds (221,325.6 kg) of beryllium compounds were released to the environment in 2017 from U.S. manufacturing and processing facilities.
- Beryllium cannot be degraded in the environment, but it can change form.

- Beryllium has been detected in air at levels up to 8.9 ng/m^3, but most concentrations are below 0.2 ng/m^3.
- The primary route of exposure to beryllium and beryllium compounds is inhalation. The general population may also be exposed to beryllium through dermal contact or through drinking water and food.
- People who work in beryllium manufacturing, fabricating, and reclaiming industries are potentially exposed to higher levels of beryllium than the general population. Beryllium carried home on shoes, clothing, and skin of occupationally exposed individuals from the workplace may increase the risk of beryllium exposure to their family members.

The major anthropogenic emission source to the environment is the combustion of coal and fuel oil, which releases particulates and fly ash that contain beryllium into the atmosphere (DOE 1996). Other anthropogenic processes, such as ore processing, metal fabrication, beryllium oxide production and use, and municipal waste combustion, release only a fraction of the amounts emitted from coal and oil combustion (Cleverly et al. 1989; EPA 1987; Fishbein 1981). Approximately 50 beryllium minerals occur in nature (Taylor et al. 2003). Beryllium is naturally emitted to the atmosphere by windblown dusts and volcanic particles (EPA 1987). The median concentration of beryllium in air in the United States is 0.15 ng/m^3 (EPA 2018a).

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 wastewater effluents from beryllium or related industries and the runoff from beryllium-containing waste sites (EPA 1980, 1981). Deposition of atmospheric beryllium aerosols from both natural and anthropogenic sources is also a source of beryllium in surface waters. In 2019, dissolved beryllium was detected in 692 of 2,533 surface water samples in the United States (27.3%) with an average concentration of 0.18 µg/L (WQP 2020). Dissolved beryllium was detected in 222 of 1,065 groundwater samples in the United States (20.8% of samples) with an average concentration of 0.27 µg/L (WQP 2020).

Some beryllium compounds are naturally present in soil, but the concentration of beryllium in localized soils may increase because of the disposal of coal ash, municipal combustor ash, industrial wastes that contain beryllium, and deposition of atmospheric aerosols. The average concentration of beryllium in U.S. soils is 1.8 mg/kg (n=93,090) (USGS 2016).

Beryllium released to the atmosphere from combustion processes and ore processing will probably be present as beryllium oxide. Atmospheric beryllium particulates will eventually settle to the earth's surface by dry deposition or may be removed from the atmosphere by wet deposition (i.e., precipitation).

Upon reaching water and soil, beryllium will probably be retained in an insoluble form in sediment and soil and will be generally immobile. Although chemical reactions may transform one beryllium compound into another, beryllium cannot be degraded by environmental reactions. However, the data regarding transformation reactions of beryllium in water and soil are limited.

Bioconcentration of beryllium in plants and animals is low. In plants, uptake of beryllium appears to be restricted to the root system; no significant translocation of beryllium to the above ground parts of the plant has been observed. Beryllium is not expected to bioconcentrate in aquatic animals (EPA 1980). The beryllium concentrations in both raw carrots and field corn grown in the United States were <25 µg/kg, fresh weight (Wolnik et al. 1984).

The general population is exposed to beryllium through inhalation of air and consumption of food and drinking water. The total beryllium intake by the general U.S. population cannot be estimated due to the lack of data regarding beryllium content in food. People who work in beryllium manufacturing, fabricating, and reclaiming industries are potentially 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.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Beryllium is an element that is present in the earth's rocks in amounts ranging from <1–15 mg/kg. About 60% of the more than 100,000 tons of the world's identified resources of beryllium are in the United States; the Spor Mountain area in Utah, the McCullough Butte area in Nevada, the Black Hills area in South Dakota, the Sierra Blanca area in Texas, the Seward Peninsula in Alaska, and the Gold Hill area in Utah contain most of these resources (USGS 2019). The beryllium minerals of commercial interest are beryl (i.e., $Be_3Al_2Si_6O_{18}$) and bertrandite (i.e., $Be_4Si_2O_7(OH)_2$).

In the United States, bertrandite, which contains <1% beryllium, is the principal mineral mined. In 2018, 170 metric tons of beryllium were mined in the United States (USGS 2019). The U.S Geological Survey (USGS) in 2019 estimated that United States resources of bertrandite reserves in Utah contained 21,000 tons of beryllium. Outside of the United States, beryl is the principal beryllium mineral mined. At its operations in Utah, Materion converted bertrandite ore (from open pit mines) and beryl (which was imported) into beryllium hydroxide that was then either sold to NGK Insulators, Ltd. in Japan or shipped to the company's plant in Ohio to be converted into metal, oxide, and downstream beryllium-copper master alloy (USGS 2019, 2020).

Beryllium hydroxide is the basic raw material to produce beryllium metal, alloys, and compounds. Bertrandite ore is wet milled, leached with sulfuric acid, and then extracted from the acid leachate with di(2-diethylhexyl) phosphate in kerosene at elevated temperature. The beryllium is then treated with aqueous ammonium carbonate to form an aqueous ammonium beryllium carbonate complex, which is then heated to precipitate beryllium as carbonate. Continued heating liberates carbon dioxide and beryllium hydroxide (i.e., Be(OH)2). Beryllium hydroxide is then recovered by filtration and is used to produce products such as beryllium metal, beryllium alloys, and beryllium oxide (Ballance et al. 1978; Drury et al. 1978).

Information on beryllium process production is from Balance et al. (1978). Through 1977, beryllium metal was produced by a couple of U.S. companies using the Schenzfeier-Pomelee purification process. The process starts with beryllium hydroxide and forms intermediates with the use of heat and reduction by magnesium. Water leaching or electro-refining further purifies the metal product.

Beryllium oxide was produced by dissolving technical-grade beryllium hydroxide in sulfuric acid, precipitating out hydrated beryllium sulfate, which is then calcined at 1,150–1,450 °C (Ballance et al. 1978). Copper-beryllium alloy was produced from beryllium oxide, carbon reduction in the presence of molten copper, and an arc-furnace set at 1,800–2,000 ˚C. Other beryllium alloys start with a copper beryllium alloy and melt in other metals (Ballance et al. 1978). It is unclear whether there are newer processes for producing beryllium metal, beryllium oxide, and beryllium alloys.

In 2017, Materion produced beryllium hydroxide, beryllium metal, metal-matrix composites, ceramics, and beryllium strip and bulk products at plants in Elmore, Ohio, Fremont, California, Tucson, Arizona, and Shoemakersville, Pennsylvania (USGS 2020). IBC Advanced Alloys Corp. produced beryllium-aluminum alloys, beryllium-copper alloys, and its own proprietary alloys at plants in Franklin, Indiana, New Madrid, Missouri, Royersford, Pennsylvania, and Wilmington, Massachusetts (USGS 2020). Beryllium alloys were also produced by Belmont Metals Inc. in Brooklyn, New York and by NGK Metals Corp. in Sweetwater, Tennessee (USGS 2020). Beryllium oxide ceramic components and compound materials were manufactured in Haskell, New Jersey by American Beryllia Inc., and beryllium metal sheets and foil were manufactured in Los Angeles, California by American Elements (USGS 2020). Recent production and mine shipments have decreased from 270 metric tons of beryllium content in 2014 to an estimated 170 metric tons of beryllium content in 2018 (USGS 2019).

Table 5-1 lists the number of facilities in each state that manufacture or process beryllium (not including beryllium compounds). Table 5-2 lists the same information for beryllium compounds only. Included in

these tables are the activities and uses of beryllium and beryllium compounds and the range of maximum amounts of beryllium and beryllium compounds that are stored on site (TRI17 2019).

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
CA	1	0	99	9, 12, 14
GA	2	11000	109998	8, 14
IL	2	10000	99999	8
IN	1	1000	9999	8
KS	1	100	999	8
LA	1	0	99	12, 14
MO	2	20000	199998	8
NC	1	10000	99999	14
NV	1	10000	99999	12
NY	1			
OH	3	10000	100098	7
PA	1	10000	99999	1, 2, 3, 9
TN	1	10000	99999	7, 8
VA	1	10000	99999	9

Source: TRI17 2019; Data are from 2017

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

1. Product
2. Import
3. Used Processing
4. Sale/ Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	1	100,000	999,999	1, 13, 14
CA	1	0	99	9, 12, 14
FL	3	11,100	110,997	1, 5, 9, 12, 14
GA	5	32,000	319,995	1, 3, 4, 5, 8, 9, 10, 13,14
IL	3	20,000	199,998	1, 5, 8
IN	6	23,000	230,193	1, 5, 7, 8, 12, 13, 14
KS	1	100	999	8
KY	3	21,000	209,997	1, 5, 9, 12, 13
LA	1	0	99	12, 14
MI	1	2,000	19,998	12
MO	3	21,000	209,997	8, 14
MT	1	10,000	99,999	1, 5, 12, 14
NC	4	31,000	309,996	1, 5, 9, 12, 14
ND	2	2,100	20,997	1, 5, 13

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
NM	3	20,100	200,997	1, 3, 4, 5, 9, 12, 13, 14
NV	1	10,000	99,999	12
NY	1			
OH	6	130,000	1,300,095	1, 3, 4, 5, 7, 9, 12, 13, 14
PA	5	22,100	220,995	1, 2, 3, 5, 7, 9, 12
TN	2	20,000	199,998	1, 5, 7, 8, 12
TX	3	12,000	119,997	1, 3, 4, 5, 9, 12, 13, 14
UT	1	100,000	999,999	1, 4, 6
VA	1	10,000	99,999	9
WI	1	10,000	99,999	11
WV	2	20,000	199,998	1, 3, 4, 5, 9, 12, 13

Source: TRI17 2019; Data are from 2017

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

1. Product
2. Import
3. Used Processing
4. Sale/ Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

5.2.2 Import/Export

From 2014 to 2018, approximately 62 to 86 metric tons of beryllium were imported into the United States (USGS 2019). These imports include estimates of beryllium content of imported ores and concentrates, oxides and hydroxides, unwrought metals (including powders), beryllium articles, wastes and scrap, beryllium-copper master alloys, and beryllium-copper plates, sheets, and strip. In 2007, U.S. exports of beryllium-containing ores were 150 metric tons of beryllium metal equivalents (Welch 2012). Exports in the years 2014 to 2018 were between 26 and 38 metric tons of beryllium (USGS 2019). These exports include estimated beryllium content of exported unwrought metals (including powders), beryllium articles, and wastes and scrap.

5.2.3 Use

Beryllium is included in a list of critical minerals (83 FR 23295) published by the U.S. Department of the Interior in May 2018 (USGS 2019). As a critical mineral, beryllium is identified as a nonfuel mineral or mineral material that is essential to the economic and national security of the United States, has a supply chain that is vulnerable to disruption, and is essential in the manufacturing of products (USGS 2019). Using sales estimates to forecast apparent uses, 22% of beryllium products are used in industrial components, 21% in consumer electronics, 16% in automotive electronics, 9% in defense applications,

8% in telecommunications infrastructure, 7% in energy applications, 1% in medical applications, and 16% in other applications (USGS 2019). U.S. consumption of beryllium-based products from 2017 to 2018 increased 20% likely due to sales of beryllium to the consumer electronics, defense, energy, and industrial components markets (USGS 2019).

The most common form of processed beryllium is beryllium alloy strip and bulk products, and it is used in all application areas. The majority of unalloyed beryllium metal and beryllium composite products are used in defense and scientific applications (USGS 2019). In the medical field, beryllium is used to produce pacemakers, lasers, high-resolution X-ray images, and dental alloys (Taylor et al. 2003). Recently, beryllium has been used in the construction of golf clubs and bicycle frames (Taylor et al. 2003).

Given its structural, mechanical, and material properties, beryllium is useful in the aerospace industry. Beryllium is used in aircraft bearings and bushings and as a component of fuel containers for solid propulsion jet and rocket fuel systems, gyros, and reentry vehicles. One beryllium alloy, Beralcast® is used to manufacture U.S. military fighter planes, helicopters, and missile systems (Taylor et al. 2003). The United States began using beryllium in weapons components during World War II, and beryllium is still used in the nuclear weapons program (Taylor et al. 2003).

Beryllium is also used in the electronics industry in the manufacture of springs, switches, relays, and connectors for computers, telecommunications, appliances, and automotive applications (Taylor et al. 2003). Beryllium oxide ceramics are used as semiconductor devices and integrated circuits (Taylor et al. 2003).

5.2.4 Disposal

The most significant amount of beryllium waste results from pollution control methods such as solid particulate scrubbers. Since beryllium is a valuable element, the most desirable method of handling beryllium waste is to recycle it to the producers. The leading beryllium producer in the United States has a comprehensive recycling program for its beryllium products and recovers approximately 40% of the beryllium content of new and old beryllium alloy scrap (USGS 2019). While detailed data on the quantities of beryllium recycled in the United States are not available, recycled beryllium may account for as much as 20 to 25% of total beryllium consumption (USGS 2019).

The EPA has classified beryllium powder as a hazardous waste material (40 CFR Section 261.33). Under the Resource Conservation and Recovery Act (RCRA), compliance with labeling and disposal procedures as well as obtaining permits for discharges into air and water are required for beryllium powder. Beryllium

compounds (including beryllium) are classified as a Clean Air Act (CAA) hazardous air pollutant (HAP). Under the CAA, EPA has established national emission standards for stationary sources that emit, or have the potential to emit, beryllium to air. Beryllium solid waste should be placed into impermeable, sealed bags or containers (e.g., drums) that are labeled in accordance with the requirements of EPA regulations (Fishbein 1981). The EPA has also issued final regulations under the Clean Water Act for specific nonferrous metal manufacturing operations including beryllium processing facilities. These regulations limit the discharge of beryllium containing pollutants into navigable waters and into publicly-owned treatment works (POTWs). Waste waters containing beryllium may therefore require treatment to reduce the concentration of beryllium. A typical treatment method for beryllium involves steps such as chemical precipitation, settling clarification, neutralization, filtration, and sludge dewatering (EPA 1982, 1988a). Waste waters that contain permissible levels of beryllium may be discharged into streams and POTW facilities (EPA 1982, 1988a).

A significant amount of beryllium waste results from pollution control methods such as containment of solid particulates or aqueous suspensions resulting from air-scrubbing processes. According to the TRI17 (2019), a total of 29,231 and 487,939 pounds of beryllium and beryllium compound wastes, respectively, were disposed of by various industries in 2017 (Section 5.3). Land disposal accounted for 75.4% with air and surface water disposal accounting for 24.3% and 0.02%, respectively. Likewise, beryllium compounds disposal had 95.7% on land, 0.3% to air, 0.02% to surface water, and 1.3% was injected underground. An additional 405 and 33,528 pounds of beryllium and beryllium compound wastes, respectively, were transferred to off-site locations within the United States.

5.3 RELEASES TO THE ENVIRONMENT

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

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

Releases of beryllium and beryllium compounds are required to be reported under Superfund Amendments and Reauthorization Act Section 313; consequently, data are available for this compound in the Toxics Release Inventory (TRI) (EPA 2005). According to the TRI, a total of 29,231 pounds (13,259 kg) of beryllium and 487,939 pounds (221,326 kg) of beryllium compounds were released to the environment in 2017 (TRI17 2019).

5.3.1 Air

Estimated releases of 7,109 pounds (~3.2 metric tons) of beryllium to the atmosphere from 10 domestic manufacturing and processing facilities in 2017, accounted for about 24.3% of the estimated total environmental releases from facilities required to report to the TRI (TRI17 2019). These releases are summarized in Table 5-3. Estimated releases of 1,441 pounds (~0.65 metric tons) of beryllium compounds to the atmosphere from 40 domestic manufacturing and processing facilities in 2017, accounted for about 0.29% of the estimated total environmental releases from facilities required to report to the TRI (TRI17 2019). These releases are summarized in Table 5-4.

In addition to ore processing, beryllium is also released into the atmosphere during the production and use of beryllium alloys and chemicals. Beryllium is released into the atmosphere from anthropogenic sources including the combustion of coal and fuel oil, the incineration of municipal solid waste (MSW), the production, use, and recycling of beryllium alloys and chemicals, and, to a minor extent, the burning of solid rocket fuel.

Beryllium emissions from coal and fuel oil combustion account for a majority of the U.S. beryllium emissions from natural and anthropogenic sources (EPA 1987). The average beryllium concentration in U.S. coal is between 1.6 and 2.0 µg/g (Nalbandian 2012). A study by the Department of Energy (DOE) and the University of North Dakota examined the emissions of toxic trace elements from coal-fired power plants (DOE 1996). The data in this study show that stack concentrations are 2–3 orders of magnitude greater than the range of ambient air concentrations for beryllium (DOE 1996). The median stack concentration for beryllium was 0.8 µg Be/m^3, and the average emission from the nine coal-fired power plants was 22.6 pounds/year (range 0.49–55.8 pounds/year). It is unclear whether the easing of emission standards for coal-fired powerplants (June 19, 2019) have influenced these data as no new comprehensive studies have been published.

In 1986, there were 494 of 7,835 incinerated municipal waste streams containing beryllium in the United States (Behmanesh et al. 1992). In 2016, there were 71 power plants in the United States that generated electricity from burning municipal solid waste (EIA 2018). At a municipal WTE facility in Commerce, California, stack emissions for beryllium were measured at 0.2 μg/m^3 (Hasselriis and Licata 1996). The stack emissions from individual municipal WTE facilities are about the same order of magnitude as stack emissions from individual coal-fired power plants; however, the number of municipal WTE facilities in the United States is a factor of 20 less than the number of coal-fired power plants.

Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use Beryllium[a]

		Reported amounts released in pounds per year[b]						Total Release	
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On and off-site
NV	1	1	0	0	21,712	72	21,713	72	21,785
OH	3	7,000	0	0	0	0	7,000	0	7,000
TN	1	23	0	0	318	0	23	318	341
NC	1	56	0	0	0	0	56	0	56
GA	2	29	0	0	15	0	29	15	44
PA	1	0	5	0	0	0	5	0	5
VA	1	0	0	0	0	0	0	0	0
LA	1	0	0	0	0	0	0	0	0
IL	2	0	0	0	0	0	0	0	0
IN	1	0	0	0	0	0	0	0	0
MO	2	0	0	0	0	0	0	0	0
KS	1	0	0	0	0	0	0	0	0
CA	1	0	0	0	0	0	0	0	0
NY	1	0	0	0	0	0	0	0	0
Total	19	7,109	5	0	22,045	72	28,826	405	29,231

Source: TRI17 2019; Data are from 2017

RF = Reporting Facilities; UI = Underground Injection

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

From 2001 to 2004, beryllium released from emission stacks at Brush Ceramic Products facility ranged from less than 0.005 to less than 1.588 g Be/day and did not exceed National Emission Standard for Hazardous Air Pollutants (ATSDR 2005a). Emissions were measured from vents, baghouse stacks, and an exhaust duct.

Natural emission sources of beryllium include windblown dusts and volcanic particles. The beryllium amounts released to the atmosphere from these sources are comparable with anthropogenic sources.

Beryllium has been identified in air samples collected from 3 of the 540 current or former NPL hazardous waste sites where it was detected in some environmental media (ATSDR 2019).

Table 5-4. Releases to the Environment from Facilities that Produce, Process, or Use Beryllium Compounds[a]

		Reported amounts released in pounds per year[b]							
								Total Release	
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On and off-site
AK	1	0	0	0	110,000	0	110,000	0	110,000
IL	1	662	0	0	66,114	0	6,677	0	66,776
OH	3	322	16	6,421	48,466	4,559	48,804	10,980	59,784
TX	4	66	1	0	70,052	0	70,119	0	70,119
KY	3	38	0	0	29,762	0	29,800	0	29,800
PA	4	101	4	0	20,448	0	20,362	191	20,553
MI	1	0	0	0	11,232	0	11,232	0	11,232
UT	1	22	0	0	11,085	0	11,107	0	11,107
VA	1	22	0	0	11,000	0	11,022	0	11,022
WV	1	16	0	0	9,885	0	301	9,600	9,901
IN	5	35	37	0	14,725	20	14,257	560	14,817
NC	3	16	0	0	15,716	0	15,732	0	15,732
NM	3	8	0	0	14,461	8,220	14,470	8,220	22,690
FL	3	40	35	0	9,493	0	9,568	0	9,568
MT	1	20	0	0	7,120	76	7,140	76	7,216
TN	1	15	0	0	5,029	0	5,044	0	5,044
GA	3	33	0	0	7,500	0	7,533	0	7,533
ND	2	25	0	0	5,021	0	1,145	3,901	5,046

Table 5-4. Releases to the Environment from Facilities that Produce, Process, or Use Beryllium Compounds[a]

	Reported amounts released in pounds per year[b]								
								Total Release	
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On and off-site
MO	1	0	0	0	0	0	0	0	0
WI	1	0	0	0	0	0	0	0	0
Total	43	1,441	93	6,421	467,109	12,875	454,411	33,528	487,939

Source: TRI17 2019; Data are from 2017

RF = Reporting Facilities; UI = Underground Injection

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

5.3.2 Water

Estimated releases of 5 pounds (~0.002 metric tons) of beryllium to surface water from 19 domestic manufacturing and processing facilities in 2017, accounted for about 0.02% of the estimated total environmental releases from facilities required to report to the TRI (TRI17 2019). An additional < 1 pound (~0.00004 metric tons) was released to publicly owned treatment works (POTWs) (TRI17 2019). Beryllium releases (not including beryllium compounds) are summarized in Table 5-3. Beryllium compounds releases only are summarized in Table 5-4. Estimated releases of 93 pounds (~0.04 metric tons) of beryllium compounds to surface water from 43 domestic manufacturing and processing facilities in 2017, accounted for about 0.02% of the estimated total environmental releases from facilities required to report to the TRI (TRI17 2019). While beryllium compounds were released to surface water, none were reportedly released to POTWs (TRI17 2019).

Anthropogenic sources of beryllium released to water include industrial wastewater effluents. 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.

One study measured beryllium concentrations in rime (frosted objects in clouds or fogs) and snow at 10 remote mountain-top locations in the Czech Republic. Mean concentrations were reported as follows: soluble beryllium in rime 12.2 ng/L, soluble beryllium in snow 2.8 ng/L, insoluble beryllium in rime 13.0 ng/L, insoluble beryllium in snow 9.3 ng/L (Bohdalkova et al. 2012). Bohdalkova et al. (2012) also calculated that the total winter-time beryllium deposition rate, depending on the site, was up to ~15 µg/m^2.

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. Beryllium has been identified in water samples collected from 104 of 540 NPL hazardous waste sites, where it was detected in some environmental media (ATSDR 2019).

5.3.3 Soil

Estimated releases of 22,045 pounds (~10 metric tons) of beryllium to soils from 19 domestic manufacturing and processing facilities in 2017, accounted for about 75.4% of the estimated total environmental releases from facilities required to report to the TRI (TRI17 2019). Beryllium was not released via underground injection (TRI17 2019). These releases are summarized in Table 5-3. Estimated releases of 467,109 pounds (~211.9 metric tons) of beryllium compounds to soils from 43 domestic manufacturing and processing facilities in 2017, accounted for about 95.7% of the estimated total environmental releases from facilities required to report to the TRI (TRI17 2019). An additional 6,421 pounds (~2.9 metric tons) of beryllium compounds, constituting about 1.32% of the total environmental emissions, were released via underground injection (TRI17 2019). These releases are summarized in Table 5-4.

Beryllium is naturally present in soils and sediments between 0.48 and 3.52 mg/kg (Bilski et al. 2013). Coal fly ash and municipal solid waste incinerator ash are disposed of in landfills and used in building materials (Kalyoncu 1998). Coal fly ash contains beryllium at levels of 46 mg beryllium/kg ash (Stadnichenko et al. 1961). According to the American Coal Ash Association (ACAA), fly ash production has been decreasing over the last several years, and about 38 million tons of fly ash was produced in 2017 (ACAA 2017a, 2017b). This translates to about 1,585 metric tons of beryllium produced in coal fly ash, which is either used or potentially disposed of in landfills.

One study investigated the leaching of beryllium from plant growth media made of coal fly ashes, from ashes combined with the soil, and from ashes combined with the soil and sphagnum peat moss. In most cases, the concentration of beryllium in leachate didn’t depend on pore volume or on the concentration in substrates (Bilski et al. 2013). Leaching of beryllium from substrates was also not affected by the presence of soil or sphagnum peat moss (Bilski et al. 2013).

Land application of sewage sludge containing higher than background concentrations of beryllium can be a source of beryllium contamination of soil. Deposition of atmospheric aerosols on terrestrial surfaces is another source of beryllium in soil. Valberg et al. (1996) estimated the amount of time that it would take to double the ambient soil concentration of beryllium by dry deposition (at the point of maximum impact) near a municipal solid waste incinerator in Vermont. Their estimate was between 468 and 2,275 years, depending upon the ambient concentration of beryllium in the soil. Other quantitative data regarding the relative significance of these sources was not available. Beryllium has been identified in soil samples collected from 133 of 540 NPL hazardous waste sites, where it was detected in some environmental media (ATSDR 2019).

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Beryllium is more likely to be present in the sediment or absorbed by the suspended matter of a natural body of water, than present in solution. Beryllium is not likely to be detected above trace levels in the water due to hydrolysis of soluble beryllium salts in the sediment at neutral pH (Svilar et al. 2013).

Air. Beryllium in air is attached to particulate matter whose residence time in air is dependent upon particle size. A study of stack emissions from coal combustion reported that most beryllium is found on particles with diameters of <2.5 μm (Gladney and Owens 1976).

The transport of beryllium from the atmosphere to terrestrial and aquatic surfaces occurs through wet and dry deposition (Bohdalkova et al. 2012; EPA 1987). By analogy to other elements, a typical dry deposition velocity may be estimated for beryllium particles over vegetative surfaces as 0.25 cm/second (EPA 1987). The dry deposition rate of aerosol particles is a function of particle size, wind speed, and surface roughness. The process of wet deposition of airborne beryllium consists of wash-out and rain-out; wash-out involves the scrubbing of particles from the air by rain and rain-out involves their attachment to aerosols in clouds. The portion of beryllium particles transported from the atmosphere by wet deposition has not been estimated. Beryllium was detected but not quantified in rainwater from Fresno, California and was quantified in snow and rime in the Czech Republic, suggesting that transport of beryllium from the atmosphere to terrestrial and aquatic surfaces may occur by wet deposition (Bohdalkova et al. 2012; Salo et al. 1986). Beryllium containing soil can be resuspended in the atmosphere as a result of wind action.

Water. Beryllium is carried to rivers, lakes, and oceans by the process of land erosion. The amount of beryllium transported to surface waters from the land by wind-blown soil is estimated to be relatively small (Merrill et al. 1960). Acid deposition has been shown to accelerate chemical weathering of soil and

bedrock into drainage outflow, increasing the mobility of beryllium (Jagoe et al. 1993). Beryllium is highly mobile in acidic, organic-rich continental river water, but a significant scavenging effect is seen in the estuarine-ocean mixing zone (Taylor et al. 2003). The estimated residence time of beryllium in ocean water, before it is removed from the aqueous phase by sedimentation or other removal processes, is between 150 and 570 years (Merrill et al. 1960). Beryllium is more likely to be present in the sediment or absorbed by the suspended matter of a natural body of water, than present in solution. Beryllium is not likely to be detected above trace levels in water due to hydrolysis of soluble beryllium salts in the sediment at neutral pH (Svilar et al. 2013). Bhat et al. (2002) found that 80% of total beryllium in the environment is removed by rain.

Sediment and Soil. Beryllium binds strongly to soil fulvic acid; binding increases with increasing pH. Beryllium also forms complexes with marine fulvic acids at nearly neutral pH values (Esteves Da Silva et al. 1996). However, beryllium has a much stronger affinity for clay minerals than for organic matter. Beryllium is usually associated in soil at aluminum sites with clay minerals rather than iron oxides (Lum and Gammon 1985). It tends to displace divalent cations with smaller charge-to-ionic radius ratios (Fishbein 1981). For pH values <6, the distribution of beryllium between solution and solids is related to sorption at surface sites. At pH values >6, the solute concentration of beryllium is strongly controlled by the solubility of $Be(OH)_2$ (Aldahan et al. 1999). The sediment-water distribution coefficients (Kd) for beryllium are very high indicating a very low mobility in sediments. At pH values >6, Kd values are very high for most soils and sediments. For Lake Michigan sediments, Kd ranged between 105 and 106 (Hawley et al. 1986). Beryllium may accumulate in the surface organic layer of the sediment profile; however, there is no indication as to whether the organic matter content of sediment affects Kd (Lum and Gammon 1985). The presence of organic matter did not significantly affect the Kd for saline systems (You et al. 1989); in seawater, Kd is, on average, between 316,000 and 794,000 (Hawley et al. 1986).

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

Other Media. The concentration of beryllium in plants is very low. Soluble forms of beryllium must be present for uptake to occur in plants. For collard seedlings, beryllium remains in the roots, and only small portions were translocated to above ground portions (Kaplan et al. 1990). Romney and Childress (1965) examined uptake of ^{7}Be in beans, barley, sunflowers, and tomato plants. Over 95% of ^{7}Be was found in the roots; very little was translocated to the foliage and fruits (Romney and Childress 1965). The

enrichment ratio of beryllium in oat grain and in alfalfa grown in both microcosms and field plots amended with beryllium containing fly ash was 1.0 (Tolle et al. 1983).

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

5.4.2 Transformation and Degradation

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

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

Water. The common beryllium silicates, like beryl, and phenacite, are highly insoluble in aqueous solution and resist chemical weathering (Taylor et al. 2003). The reaction of beryllium in water is controlled by chemical speciation by which one species is converted to another. Beryllium is highly hydrated in acid solutions, which is a consequence of its high charge to size ratio. The speciation of beryllium in solution is: $[Be(H_2O)_4]^{2+}$, $Be_2(OH)_3^{+}$, $Be_3(OH)_3^{3+}$, and possibly $Be_5(OH)_7^{3+}$ in acid solution (i.e., pH6); and $[Be(OH)_4]^{2-}$ in basic solution (i.e., pH>8) (Cotton and Wilkinson 1980). In the pH range of 6–8, typical of most waters, the speciation of beryllium is controlled by the formation of solid beryllium hydroxide, $Be(OH)_2$, which has a very low solubility (solubility product, $K_{sp}=10^{-21}$). Table 5-5 illustrates several precipitation reactions for beryllium under a neutral environment.

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

Table 5-5. Precipitation of Beryllium Compounds in a Neutral (pH 6.5-9.5) Environment

Compound	Reaction	Notes
Ammonium tetrafluoroberyllate (Ammonium beryllium fluoride)	$(NH_4)_2BeF_4$ —> $2[NH4]^+_{aq} + [BeF4]^2_{aq}$ Excess H_2O pH 7	Remains soluble in a neutral environment
Beryllium oxide	$BeO + H_2O$ —> $Be(OH)_2$ Excess H_2O pH 7	Forms insoluble beryllium hydroxide in a neutral environment
Beryllium hydroxide	$Be(OH)_2$ —> no reaction Excess H_2O pH 7	Beryllium hydroxide is insoluble in a neutral environment
Beryllium fluoride	$BeF_2 + 2\ H_2O$ —> $[BeF_2(H_2O)_2]_{aq}$ and other complexes Excess H_2O pH 7	Remains soluble in a neutral environment
Beryllium nitrate trihydrate	$Be(NO_3)_2{\cdot}3H_2O + 2MOH^a$ —> $Be(OH)_2 + 2[M]^+_{aq} + 2[NO3]^-_{aq} + 3H_2O$ Excess H_2O pH 7	Forms insoluble beryllium hydroxide in a neutral environment
Beryllium sulfate tetrahydrate	$BeSO_4{\cdot}4H_2O + 2MOH^a$ —> $Be(OH)_2 + 2[M]^+_{aq} + [SO4]2^-_{aq} + 4H_2O$ Excess H_2O pH 7	Forms insoluble beryllium hydroxide in a neutral environment
Beryllium oxalate trihydrate	$BeC_2O_4{\cdot}3H_2O + 2MOH^a$ —> $Be(OH)_2 + 2[M]^+_{aq} + [C_2O_4]2^-_{aq} + 3H_2O$ Excess H_2O pH 7	Forms insoluble beryllium hydroxide in a neutral environment
Beryllium basic acetate[b]	$Be_4O(C_2H_3O_2)_6 + 6MOH^a + H_2O$ —> $4Be(OH)_2 + 6[M]^+_{aq} + 6[C_2H_3O_2]^-$ Excess H_2O pH 7	Forms insoluble beryllium hydroxide in a neutral environment

Source: EPA 1998

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

Lithogenic beryllium has a long oceanic residence time of 600-1,000 years and may be supplied from eolian dust, fluvial inputs, and successive lateral transport (Tazoe et al. 2014). Tazoe et al. (2014) observed that beryllium concentration in the ocean increases with depth, reflecting its remineralization from settling particles.

Sediment and Soil. Typical transport and distribution processes for beryllium in soil include precipitation, complexation, and anion exchange. Important factors affecting the transformation of beryllium in soils and sediments include pH, ionic strength (i.e., salinity), concentration and distribution of species, composition of the mineral matrix, organic matter, biological organisms, and temperature (Section 5.4.1). Data suggesting the biotransformation of beryllium or its compounds in soil were not located.

5.5 LEVELS IN THE ENVIRONMENT

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

Table 5-6 shows the limits of detection typically achieved by analytical analysis in environmental media. Presented in Table 5-7 are the summary range of concentrations detected in environmental media. Table 5-8 indicates beryllium levels at NPL sites.

Table 5-6. Lowest Limit of Detection for Beryllium Based on Standards[a]

Media	Detection limit	Reference
Air	0.0002 ng/m^3	EPA 2014; EPA 2020
Surface wipe	0.0001 µg per wipe	NIOSH 2007, Method 9110 Surface wipes by Fluorometry
Water	0.02 µg/L	EPA 1994
Urine	0.12 µg/L	CDC 2011
Soil, sludge, sediments, and other solid wastes	0.3 µg/L	EPA 1988c

[a] Detection limits based on instrumentation and using appropriate preparation and analytics. These limits may not be possible in all situations.

Table 5-7. Summary of Environmental Levels for Beryllium

Media	Low	High	For more information
Outdoor air (ng/m^3)	0.0001	8.9	Section 5.5.1
Indoor air (ng/m^3)	NS	0.0045	Section 5.5.1
Surface water (µg/L)	0	32.6	Section 5.5.3
Groundwater (µg/L)	<1	18	Section 5.5.3
Drinking water (µg/L)	<0.005	5.2	Section 5.5.3
Food (µg/kg fresh weight)	ND	36	Section 5.5.4
Soil (mg/kg)	0.1	2.10	Section 5.5.2
Effluent (µg/L)	0	0.08	Section 5.5.4

ND = not detected, NS = not specified

Table 5-8. Beryllium Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median	Geometric mean	Geometric standard deviation	Number of quantitative measurements	NPL sites
Water (ppb)	5	7.26	8.83	159	104
Soil (ppb)	1,600	2,644	6.52	231	133
Air (ppbv)	6.15×10^{-7}	8.04×10^{-7}	2.43	4	3

[a] Concentrations found in ATSDR site documents from 1981 to 2019 for 1,867 NPL sites (ATSDR 2019). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

Since beryllium has been routinely manufactured, machined, and stored at the Lawrence Livermore National Laboratory (LLNL) since the 1950s, a study was conducted to determine its levels at various locations of the facility and in different environmental media (Sutton et al. 2012). Beryllium concentrations in airborne particles sampled from 1974 to 2010 at the main facility in Livermore, California ranged from 0.1 to 540 pg/m^3 with a median concentration of 12.6 pg/m^3. Beryllium levels at the LLNL test facility located between Livermore and Tracy, California ranged from 0.3 to 430 pg/m^3 with a median concentration of 11.0 pg/m^3 over the years 1981–2010 (Sutton et al. 2012). Monthly sampling at both facilities showed a clear seasonal variation in beryllium levels. Higher levels were typically observed in late summer/early fall when temperatures and wind speed are usually elevated, and precipitation is low for this part of the state. Lower levels of beryllium in particulate matter were observed in the winter months when precipitation is greater, and temperatures and wind speed are lower.

Beryllium has been monitored in ambient air at the Brush Wellman plant in Elmore, OH since 1958. From January 1997 to April 2002, maximum weekly average concentrations measured at 10 monitors ranged from 0.0012 to 0.0137 μg/m^3 (ATSDR 2006). Maximum monthly average concentrations ranged from 0.0004 to 0.0029 μg/m^3 (ATSDR 2006). In addition to these 10 monitors, a monitor in a parking lot north of the plant measured maximum weekly concentration of 0.0173 μg/m^3 from February 1-8, 1999 and a maximum monthly concentration of 0.0077 μg/m^3 from January 1999 to May 2001 (ATSDR 2006). Using air modeling at a Brush Wellman facility in Tucson, Arizona in 1999, the Arizona Department of Environmental Quality estimated that average annual ambient beryllium levels next to the plant were 0.008 μg/m^3 based on an emission rate of 4.28 g/day (ATSDR 2000). The maximum one-hour level was estimated to be 0.0014 μg/m^3 (ATSDR 2000). The estimated maximum levels in air were concluded to pose no apparent public health hazard to the surrounding community (ATSDR 2000). A school district located near this facility monitored ambient air from 2002 to 2005. Beryllium concentrations ranged from

0.0000038 to 0.0003087 μg/m^3 (ATSDR 2005a). No average concentrations exceeded National Emission Standards, Arizona Ambient Air Quality Guidelines, or the ATSDR cancer risk evaluation guide (ATSDR 2005a).

The average concentration of beryllium in Japanese cities was 0.042 ng/m^3, with a maximum concentration of 0.222 ng/m^3. Beryllium concentrations in Germany were 0.06–0.33 ng/m^3 in urban air (Svilar et al. 2013).

Beryllium in the ambient air is collected by EPA, state, local, and tribal agencies for EPA's Air Quality System (AQS). The data are available in pre-generated data files, and data from recent years are summarized in Table 5-9 (EPA 2018a). According to these results, the mean levels over the last few years are generally less than 0.2 ng/m^3. The detection limit for aerometric determination of beryllium by approved methods for monitoring hazardous air pollutants ranges from 0.00002 to 0.2 ng/m^3 depending on the method (EPA 2020). Averages at most of these monitoring stations are listed above the method detection limits. Measurements at 100 U.S. locations indicated an average daily beryllium concentration of <0.5 ng/m^3 (Drury et al. 1978; Fishbein 1981). Beryllium concentration in urban air is usually higher, possibly due to burning of coal and fuel oil. Most coal plants in the United States are located in Texas, Indiana, and Ohio (EIA 2019). Beryllium concentration is monitored in Ohio by AQS, and the highest mean concentrations are measured there (EPA 2018a). In populous cities where ambient concentrations of beryllium are monitored, average concentrations were 0.14 to 0.17 ng/m^3 in Minneapolis, 0.152 ng/m^3 in Los Angeles, 0.006 to 0.01 ng/m^3 in Philadelphia, and 0.152 ng/m^3 in San Francisco (EPA 2018a). In 1985, in Jacksonville, Florida, beryllium was below the limit of detection in air (Del Delumyea et al. 1997).

Table 5-9. Percentile Distribution of Annual Mean Beryllium (TSP) Concentrations (ng/m3) Measured in Ambient Air at Locations Across the United States

Year	Number of U.S. Locations	25th	50th	75th	95th	Maximum
2015	97	0.0074	0.10	0.15	0.28	0.91
2016	93	0.012	0.085	0.15	5.4	8.9
2017	85	0.011	0.088	0.15	0.28	0.65
2018	74	0.041	0.15	0.17	0.28	0.32

TSP = total suspended particles
Source: EPA 2018a

The ambient concentration of beryllium found in air near power stations in Castellon, Spain ranged from not detected to 1.61 ng/m^3 (Boix et al. 2001). Beryllium concentrations in atmospheric particulate samples in and around a beryllium processing facility near Navi Mumbai, India were 0.48±0.43 ng/m^3 (n=397). The levels of beryllium during the monsoon season were comparatively lower and often were below the detection limit (Thorat et al. 2001).

Sax et al. (2006) analyzed indoor and outdoor home air in New York City and Los Angeles. The mean concentration of beryllium in indoor home air was 0.0015 ng/m^3 in New York City and 0.0018 ng/m^3 in Los Angeles. The mean concentration in outdoor home air was 0.0028 ng/m^3 in New York City and 0.0018 ng/m^3 in Los Angeles.

Table 5-10. Outdoor Air Monitoring Data for Beryllium

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
Livermore, California	Outdoor air at LLNL main site	1974-2010	0.0001-0.54 ng/m^3	25.9 pg/m^3		Sutton et al. 2012
Between Livermore and Tracy, California	Outdoor air at LLNL experimental test facility	1981-2010	0.0003-0.043 ng/m^3	24.6 pg/m^3		Sutton et al. 2012
Elmore, Ohio	Outdoor air at Brush Wellman Plant	January 1997-April 2002	NS	0.0004-0.0029 µg/m^3	10 monitors; means are maximum monthly average concentrations	ATSDR 2006
Four air monitoring locations in Tucson, Arizona	Outdoor air near Brush Wellman Facility	November 19, 2002, to March 31, 2005.	0.0000038-0.0003087 µg/m^3	0.000008-0.000031 µg/m^3	Monitors were located at 3 elementary schools near the plant and the transportation building	ATSDR 2005
New York, New York	Outdoor home air	June-August 1999	NS-0.011 ng/m^3	0.0028 ng/m^3	96% of the 40 measurements were above the LOD	Sax et al. 2006
Los Angeles, California	Outdoor home air	February-March 2000; September-October 2000	NS-0.0060 ng/m^3	0.0018 ng/m^3	98% of the 41 measurements were above the LOD	Sax et al. 2006

Table 5-10. Outdoor Air Monitoring Data for Beryllium

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
Navi Mumbai	Outdoor air around a beryllium processing facility	1991-1996	0.01-2.5 ng/m^3	0.48 ng/m^3	5 sites were sampled for a total of 397 samples	Thorat et al. 2001
Castellon, Spain	Outdoor air near power stations	NS	ND-1.61 ng/m^3	NS		Boix et al. 2001
Jacksonville, Florida	Outdoor air	1945-1995	<LOD	<LOD		Del Delumyea et al. 1997

LOD = limit of detection; ND = not detected; NS = not specified

Table 5-11. Indoor Air Monitoring Data for Beryllium

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
New York, New York	Indoor home air	June-August 1999	NS-0.0034 ng/m^3	0.0015 ng/m^3	97% of the 40 measurements were above the LOD	Sax et al. 2006
Los Angeles, California	Indoor home air	February-March 2000; September-October 2000	NS-0.0045 ng/m^3	0.0018 ng/m^3	98% of the 41 measurements were above the LOD	Sax et al. 2006

LOD = limit of detection; NS = not specified

5.5.2 Sediment and Soil

Beryllium concentrations ranged from 0.4 to 1.4 mg/kg in four background samples collected several miles from a Brush Wellman facility manufacturing ceramic beryllium products in Tucson, Arizona in 1999 (ATSDR 2000). In 30 soil samples near the facility, beryllium levels were 0.3 to 3.0 mg/kg, and it was concluded that these levels did not present a public health hazard to the community (ATSDR 2000). Average concentration in the soil adjacent to the facility was 0.69 mg/kg and in the soil up to a quarter of a mile away from the facility was 1.05 mg/kg (ATSDR 2005a). In 2000, beryllium concentrations in soils at elementary schools and an administration building near this facility ranged from 0.17 to 1.2 mg/kg with average concentrations at these locations ranging from 0.40 to 0.83 mg/kg (ATSDR 2005a). These measurements also did not present a public health hazard to the community (ATSDR 2005a).

Beryllium concentrations in the soil of the main facility of the LLNL ranged from 0.10 to 0.71 mg/kg in 1988–1994 and 2007 (Sutton et al. 2012). Beryllium levels in the test facility located between Livermore

and Tracy, California ranged from 0.20 to 2.10 mg/kg from 1991 to 2010. Although beryllium concentrations in soils have been shown to vary considerably between different locations and geologies, the levels of beryllium in soil at the LLNL facilities appear comparable to levels found in the natural environment.

Beryllium was detected in the soil near a hazardous waste incinerator in Constanti, Catalonia, Spain; the mean concentrations were 0.40 mg/kg in 1996–1998 and 0.60 mg/kg in 2009 and 2011. In addition, mean levels of beryllium were higher in rural soils (0.62 mg/kg), than in urban areas (0.49 mg/kg) in 2011 (Vilavert et al. 2012). In Alcala de Henares, Spain, beryllium concentrations were 0.79 mg/kg in soil samples from the University of Alcala campus and 0.35 mg/kg in urban zones of the city (Granero et al. 2002). Table 5-12 provides more details on beryllium soil and sediment concentrations at discussed sites.

Beryllium is the 44th most abundant element in the Earth's crust. The average beryllium concentration in the Earth's crust is approximately 2–5.0 mg/kg (Drury et al. 1978; Griffitts and Skilleter 1990; Krám et al. 1998). Beryllium occurs in silicate minerals and feldspar minerals. The greatest known concentrations of beryllium are found in certain pegmatite bodies. Beryllium ores can contain several thousand mg beryllium per kg solid ore (Fishbein 1981).

Shacklette and Boerngen (1984) reported the average and range of beryllium concentrations in soils and other surficial materials in the conterminous United States as 0.63 and <1–15 mg/kg, respectively. Frink (1996) summarized several different studies and reported that the most likely concentration of beryllium in uncontaminated soils (in the Northeast United States) ranges from <1 to 7 mg/kg. The average concentrations of beryllium in the O or A horizons (sandy loam) and the B horizon (clay) in Maryland were 0.71 and 0.46 mg/kg, respectively (Sparling and Lowe 1996). The average concentration in Florida soils was 0.46 mg/kg with a range of 0.01–5.92 mg/kg (Chen et al. 1999). The average beryllium concentration in California soils was measured as 1.14 mg/kg (Chen et al. 1999). There are few beryllium rich soils in the United States, and these areas are in sparsely settled areas that are not important for food production (Griffitts and Skilleter 1990). The concentration of beryllium in soil around beryllium processing facilities in Navi Mumbai, India ranged from 1.42 to 2.75 mg/kg (Thorat et al. 2001). These levels were comparable to background levels reported in the literature.

In bottom sediments of the Detroit River and western Lake Erie, concentrations of beryllium ranged from 0.1 to 3.8 µg/g beryllium (Lum and Gammon 1985). The beryllium levels in the sediments of Lake Pontchartrain, Louisiana were 0.05–0.5 µg/kg dry wt (Byrne and DeLeon 1986). The concentration of beryllium in sediments from the Neosho River in southeastern Kansas ranged from 0.52 to 1.1 µg/g dry weight in 1992 (Allen et al. 2001). Beryllium concentrations in the sediment of the coastal Beaufort Sea

ranged from 0.3 to 2.3 μg/g (Trefry et al. 2003). Beryllium levels in the sediment of the Rongjiang River and its estuary were 5.11 to 8.02 mg/kg, with an average concentration of 6.60 mg/kg. However, only a fraction was bioavailable and reported as 0.23 – 0.33 mg/kg (Gu et al. 2018).

Sediment samples were taken from 15 stormwater ponds in the Minneapolis-St. Paul, Minnesota metropolitan area, and analyzed for contaminants. Beryllium was detected in 20% of the samples at a mean concentration of 0.83 mg/kg dry weight (Crane 2019).

Table 5-12. Concentrations of Beryllium in Soil and Sediment

Location	Value	Reference
LLNL main site		
Range	0.10–0.71 mg/kg	Sutton et al. 2012
Mean	0.31 mg/kg	
Median	0.28 mg/kg	
Brush Wellman facility in Tucson, Arizona		
Background samples		ATSDR 2000
Range	0.4-1.4 mg/kg	
Surface soil samples		
Range	0.3-3.0 mg/kg	
LLNL experimental test facility		
Range	0.20–2.10 mg/kg	Sutton et al. 2012
Mean	0.79 mg/kg	
Median	0.68 mg/kg	
Hazardous waste incinerator in Catalonia, Spain		
Mean in 1998	0.40±0.23 mg/kg	Vilavert et al. 2012
Mean in 2009	0.60±0.19 mg/kg	
Mean in 2011	0.60±0.18 mg/kg	
Alcala de Henares		
Campus zone		Granero et al. 2002
Mean	0.79±0.40 mg/kg	
Urban zone		
Mean	0.79±0.40 mg/kg	
Surface sediment of Rongjiang River		Gu et al. 2018
Mean	6.60 mg/kg dry wt	

Table 5-12. Concentrations of Beryllium in Soil and Sediment

Location	Value	Reference
Minneapolis-St. Paul, Minnesota		
Stormwater pond sediment		
Mean	0.83 mg/kg dry wt	Crane 2019
% detects	20%	

dry wt = dry weight; LNNL = Lawrence Livermore National Laboratory; kg = kilogram; mg = milligram; Other than ranges and medians, values are means± standard deviation

5.5.3 Water

The EPA's STORET database estimates that for years 1960–1988, the geometric mean concentration of total beryllium in the United States surface waters was 70 ng/L (Svilar et al. 2013). Average concentration estimates for total beryllium in U.S. surface waters from 2015 to 2020 were 0.17 µg/L with a range of 0 to 32.6 µg/L (WQP 2020). Dissolved beryllium was detected in 483 of 6,036 surface water samples analyzed for U.S. Geological Survey's National Water Information System from 2015 to 2020 with a mean concentration of 0.14 µg/L (WQP 2020). In lakes/reservoirs, dissolved beryllium was detected in 109 of 112 samples (97% of sites) with an average concentration of 0.09 µg/L (WQP 2020). In spring waters, dissolved beryllium was detected in 5 of 6 samples (83% of samples) with an average concentration of 0.09 µg/L (WQP 2020). In rivers/streams, dissolved beryllium was detected in 1,899 of 7,493 samples (25% of samples) with an average concentration of 0.23 µg/L (WQP 2020). The median total beryllium concentration of Great Lakes water samples ranged from <4 to 120 ng/L. The percentage of beryllium in suspended particulates of Great Lakes water samples ranged from 2 to 88% (Rossmann and Barres 1988). Beryllium concentrations measured in the Houston Ship Channel ranged from 8 to 24 ng/L (Saleh and Wilson 1999).

Beryllium concentrations in groundwater tend to be higher than in surface water (Taylor et al. 2003). The WPQ (2020) lists the number of detections of beryllium in groundwater water at several locations around the United States. In groundwater, dissolved beryllium was detected in 10 of 118 groundwater samples (8.5% of samples) with an average concentration of 0.27 µg/L; total beryllium was detected in 1,074 of 1,239 sites (87% of samples) with an average concentration of 0.09 µg/L. Beryllium was present in 14 samples from wells in the glacial aquifer system of the Northern United States out of 847 samples analyzed, with only one of the samples containing beryllium at concentrations ≥1 µg/L (USGS 2009).

For the USGS National Water-Quality Assessment Program, a comprehensive study of trace elements in groundwater across the United States was conducted from 1992 to 2003. In this study, the USGS

collected data from 5,183 monitoring and drinking-water wells representing more than 40 principal and other aquifers in humid and dry regions and in various land-use settings (USGS 2011). Very few detections (0.13%) exceeded the beryllium maximum contaminant level of 4 µg/L.

During a site visit to the Brush Wellman plant in Elmore, Ohio in 2001, beryllium was not found in any split well water samples taken from eight residencies near the plant (ATSDR 2006).

Leung and Jiao (2006) conducted a study to analyze the influence of urbanization on groundwater. It was found that beryllium was present in higher mean concentrations in the groundwater of a natural area (0.45 ppb), than in a developed area (0.18 ppb) in Hong Kong during the wet seasons. The natural area referred to an area without anthropogenic influence. The authors concluded that the water in the natural areas were more acidic and had a higher dissolved oxygen content and that changes in the concentrations might be due to natural processes such as water-rock interactions since the natural slopes were uphill to the developed spaces. The median concentration of beryllium in groundwater samples taken around the Denver, Colorado metropolitan area in 1993 was measured at <1 µg/L (Bruce and McMahon 1996).

Rainwater and streams also contain beryllium. In Australia, rainwater and streams had an average beryllium concentration of 0.05–0.08 µg/L (Meehan and Smythe 1967). In Great Britain rainfall had <0.06 µg beryllium/L. Streams however contained between 0.01 and 0.25 µg beryllium/L with higher concentrations in deforested areas (Neal et al. 1992).

Table 5-13. Groundwater Monitoring Data for Beryllium

Location(s)	Type	Date(s)	Range	Mean concentration	Notes	Reference
Elmore, Ohio	Split well water samples	May 31, 2001 and July 26, 2001	ND	ND	Samples were taken from 8 residencies near the Brush Wellman plant; LOD was 5 µg/L for the first set of samples; 2 µg/L for the second set of samples	ATSDR 2006
United States	Glacial aquifer system	1991-2001	0.032-1.2 µg/L	NS	847 samples analyzed; 98% of samples were below detection	USGS 2009
United States	Groundwater across the U.S.	1992-2003	<1-18 µg/L	NS	3,025 samples	USGS 2011

LOD = limit of detection; ND = not detected; NS = not specified; USGS = United States Geological Survey

Results from EPA's Six-Year Review of national drinking water regulations from 2006 to 2011 show that beryllium was found in 2,165 of 164,392 drinking water samples in concentrations ranging from 0.002 to 2000 µg/L (EPA 2016). The average concentrations of beryllium in bottled and tap water in the United States were <0.1 and 0.013 µg/L, respectively. Table 5-14 summarizes some selected data on the beryllium content of drinking water (Vaessen and Szteke 2000). In Australia, median concentrations in drinking water were measured at 0.02 µg/L with a range of 0.02 to 0.15 µg/L (Hinwood et al. 2015).

Table 5-14. Beryllium Content of Drinking Water

Product	Number of samples	Mean (µg/kg)	Range (µg/kg)
Mineral water (bottled)			
Spain			
Lanjaron	3	NS	0.12±0.01
Ortigosa del Monte	3	<0.6	<0.6
United States			
All samples	72	<0.1	<0.1–5.2
Domestic samples[a]	18	<0.1	<0.1–0.2
European samples[b]	54	<0.1	<0.1–5.2
Poland			
Nieszawa	3	0.17	NS
Zyweic Zdroj	3	0.15	NS
Tap Water			
Spain-Granada	3	NS	0.09±0.01
Germany-Mainz	NS	0.008[c]	<0.005±0.009
German-Weisbeden	NS	NS	0.034±0.002
Saudi-Arabia-Riyadh (schools)	59	1.24[c]	0.4–2.17
The Netherlands	266	<0.1	<0.1–0.2
	91	<0.05	<0.05–0.21
United States	NS	0.013[c]	0.01–0.7

Source: Vaessen and Szteke 2000

[a]nine brands

[b]28 brands

[c]arithmetic mean

NS = Not specified

Concentrations of beryllium in deep ocean water are fairly uniform globally, and concentrations in ocean water tend to be lower than in river water (Taylor et al. 2003). The concentration of total beryllium in seawater ranges from 0.02 to 0.9 ng/L, with an average of <0.5 ng/L (Measures and Edmond 1986; Merrill et al. 1960). Tazoe et al. (2014) reports mixed layer water from less than 200 m deep in the eastern North Pacific Ocean had a concentration of 7 pmol beryllium/kg. However, beryllium concentration increased

with depth from 200 to 3,500 m, reaching a concentration of 29 pmol/kg. This profile is similar to that of the western North Pacific Ocean (Tazoe et al. 2014).

5.5.4 Other Media

Beryllium was detected in 8 of 39 samples of effluent in facility wastewater sewers and streams with an average concentration of 0.03 µg/L (WQP 2020). In 197 samples of wastewater treatment plant effluent, beryllium was detected with an average concentration of 0.0004 µg/L (WQP 2020).

Beryllium was found in the carpets of the LLNL site, after vacuuming, at a concentration of 0.002– 0.480 µg/100 cm^2. Beryllium concentrations in overhead dust were reported to range from 19.4 to 151 µg/100 cm^2 at an industrial facility located in Schenectady, New York. Beryllium was also detected in surface dust at the front offices and wire annealing/pickling areas of a Copper-Beryllium alloy facility at 0.05–13.6 µg/100 cm^2 (Sutton et al. 2012).

Beryllium has been found in products made from aluminum, like shrapnel fragments; aluminum cans; and aluminum foil (Abraham et al. 2014). This study found that the beryllium content of shrapnel and aluminum cans were all approximately 100 ppb while the beryllium content of aluminum foil was 25 ppb (Abraham et al. 2014). While there is some concern that the beryllium in aluminum cans and plastic bottles may leach into the beverage contained inside, Abraham et al. (2014) found that the concentration of beryllium in carbonated water from aluminum cans and plastic bottles was below the detection limits (0.01 ppb). Kilinc et al. (2010) also studied beryllium levels in beverages and found mean concentrations of beryllium ranging from 0.03 to 0.94 ng/mL in 20 types of natural mineral water, flavored mineral water, energy drinks, curative mineral water, and thermal spring water purchased in Turkey. Results for Abraham et al. (2014) and Kilinc et al. (2010) are shown in Table 5-15.

Table 5-15. Concentration of Beryllium in Aluminum and Beverage Samples

Sample type	Beryllium Concentration (ppb)
Shrapnel fragments	105.3
Aluminum soda can	183.7
Aluminum beer can	120.0
Aluminum carbonated water can	110.7
Aluminum foil	25.0
Carbonated water from aluminum cans	<LOD
Carbonated water from plastic bottles	<LOD
Natural mineral water, 7 brands	0.05- 0.94
Cherry flavored mineral water, 3 brands	ND-0.05
Lemon flavored mineral water	ND
Orange flavored mineral water	0.20
Peach flavored mineral water	ND
Mixed fruit flavored mineral water, 3 brands	ND-0.16
Energy drink, 2 brands	ND-0.030

Table 5-15. Concentration of Beryllium in Aluminum and Beverage Samples

Sample type	Beryllium Concentration (ppb)
Curative mineral water from Yurtbasi, Elazig, Turkey	0.05
Thermal spring water from Bingol, Turkey	0.51

Sources: Abraham et al. 2014; Kilinc et al. 2010
LOD = Limit of detection, ~0.01 ppb = ~0.01 ng/mL
ND = Not detected

Electronic waste often contains beryllium, and surprisingly dental materials also have minute traces of beryllium. Hibbert et al. (2014) analyzed beryllium in the ash of incinerated e-waste and measured the following mean concentrations (in mg/kg): 0.01 in batteries, 0.1 in screens, 43 in circuit boards, and 44.89 in plastics. In a study to determine chemical elements present in irreversible hydrocolloids, dental impression materials commonly used in Brazil and Europe, beryllium was found in all 8 samples at <0.125 ppb. It was one of the elements with the lowest concentrations (Borges de Olival et al. 2018).

The beryllium concentration in several foods, fruits, and fruit juices from around the world are shown in Table 5-16 and Table 5-17. The median concentration of beryllium in the 38 foods listed in Table 5-16 is 22.5 µg/kg fresh weight (excluding kidney beans) and the range of concentrations is <0.1–2,200 µg/kg fresh weight. The highest concentrations (in µg/kg fresh weight) were reported for kidney beans (2,200), crisp bread (112), garden peas (109), parsley (77), and pears (65). The average concentration of beryllium in fruit and fruit juices, listed in Table 5-17, is 13.0 µg/L, and the concentrations ranged from not detected to 74.9 µg/L.

Table 5-16. Beryllium Content of Various Fresh Foods

	Concentration (µg Be/kg fresh weight)			
Product	Number of samples	Mean	Range	Reference
Bananas, pulp	400	4.2	ND-18	Cowgill 1981
Beans	3	0.07	ND-0.07	Meehan and Smythe 1967
Beans, kidney	-	2,200[a]	-	Awadallah et al. 1986
Cabbage	1	0.2	-	Meehan and Smythe 1967
Cabbage	95	0.091	ND-0.50	Bibak et al. 1999
Cane sugar:				
Brown	-	30	-	Hamilton and Minski 1973
Demerara	-	6	-	Hamilton and Minski 1973
Refined	-	2	-	Hamilton and Minski 1973
Granulated	-	0.2	-	Hamilton and Minski 1973
Carrots, raw	NS	<25	-	Wolnik et al. 1984
Clams, hardshell	31	2±3	-	Capar and Yess 1996
Clams, softshell	10	<2	-	Capar and Yess 1996
Crabs	6	15	10-20	Meehan and Smythe 1967
Coriander	-	34[a]	-	Awadallah et al. 1986
Corn, field	-	<25	-	Wolnik et al. 1984
Dill	-	59[a]	-	Awadallah et al. 1986
Eggplant (aubergine)	-	26[a]	-	Awadallah et al. 1986

Table 5-16. Beryllium Content of Various Fresh Foods

	Concentration (µg Be/kg fresh weight)			
Product	Number of samples	Mean	Range	Reference
Fish, whole:				
Mullet	8	11	1.6-19	Meehan and Smythe 1967
Blackfish	4	11	3.7-18	Meehan and Smythe 1967
Garden pea	-	109[a]	-	Awadallah et al. 1986
Green pepper	-	42[a]	-	Awadallah et al. 1986
Hen eggs, yolk	1	0.2	-	Meehan and Smythe 1967
Hen eggs, yolk, and white	1	0.06	-	Meehan and Smythe 1967
Honey				
Eucaliptus	-	0.18±0.09	-	Bettinelli et al. 2000
Robinia	-	0.38±0.02	-	Bettinelli et al. 2000
Meat	3	4	4-5	Kaiser et al. 1972
Milk	100	0.2	ND-0.7	Meehan and Smythe 1967
Milk	21	<0.01	<0.01	Saribal 2019
Mushrooms	1	1.6	-	Meehan and Smythe 1967
Mushrooms, European wild	1,303	9	<5-36	Seeger et al. 1984
Orange juices	-	<1	-	McHard et al. 1980
Oysters	59	0.6	0.2-5.4	Meehan and Smythe 1967
Oysters, east coast United States	93	<2	-	Capar and Yess 1996
Oysters, west coast United States	40	<2	-	Capar and Yess 1996
Parsley	-	77[a]	-	Awadallah et al. 1986
Peanuts, kernels	2	0.5	0.3-0.8	Meehan and Smythe 1967
Pears	-	65[a]	-	Awadallah et al. 1986
Potatoes	-	59[a]	-	Awadallah et al. 1986
Potatoes	41	0.4–0.6	0.2-1.4	Hofele et al. 1994
Rice	3	4	3-5	Kaiser et al. 1972
Tomatoes	1	0.2	-	Meehan and Smythe 1967
Vegetable marrow, pumpkin	-	20[a]	-	Awadallah et al. 1986

[a]Original data based on dry weight; concentrations are recalculated to fresh weight = concentration * (fresh wt *10)

ND = not detected; - = not specified

Table 5-17. Beryllium Content of Various Fruits and Fruit Juices

Product	Number of samples	Mean (µg/L)	Range
Apple juice	4	22.5	<0.1–43.6
Citrus fruit			
Ruby red grapefruit	1	1.3	—
Lime	1	<0.1	—
Tangerine	1	0.8	—
Grape cultivars	3	4.4	<0.1–7
Lemon products			
CA lemon	1	17.4	—
Bottled lemon	1	17.0	—
Lemonade	1	55.3	—
Orange juice	5	2.8	<0.1–2.8
Papaya (pulp)	3	74.9	64.5–84.1
Pear (pulp)	1	37.3	—
Red currant	1	1.1	—

Table 5-17. Beryllium Content of Various Fruits and Fruit Juices

Product	Number of samples	Mean (µg/L)	Range
Stone fruit (pulp)			
Apricot	1	<0.1	—
Peach	1	<0.1	—
Plum	1	1.6	—
Prune	1	3.6	—
Sour cherry	1	1.5	—
Tomato sauce	2	42.4	39.8–45.0
Tropical fruit			
Banana	1	1.5	—
Kiwi	1	3	—
Mango	1	4.5	—
Pineapple	1	<0.1	—

— = not specified; CA = California
Source: Barnes 1997

More recently, Bocio et al. (2005a) investigated the concentration of beryllium and several other metals in meat, fish and seafood, pulses (edible seeds of the legumes), cereals, vegetables, fruits, tubers, whole milk, yogurt, eggs, and sugar sold in Catalonia, Spain near a hazardous waste incinerator. Beryllium was below the limit of detection (<0.05 µg/g) in all samples.

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

Beryllium concentrations in three species of fish from the Clinch River in Tennessee, adjacent to the U.S. Department of Energy's Oak Ridge Reservation, were 0.63 µg/kg (striped bass), 0.92 µg/kg (white bass), and 0.72 µg/kg (crappie) (Burger and Campbell 2004). Compared to contaminant levels in fish from Poplar Creek, within the boundaries of Oak Ridge Reservation, mean beryllium concentrations are higher in Clinch River but not significantly higher; concentrations in fish from Clinch River were 0.92 µg/kg while concentrations in fish from Poplar Creek were 0.88 µg/kg (Burger and Campbell 2004).

Beryllium has been detected in orchard leaves and in various trees and shrubs in the United States at concentrations of 26 and <1 µg/kg, respectively (IARC 1980). The beryllium concentrations varied with

the plant species and the degree of water contamination in their respective environments (Sarosiek and Kosiba 1993). Beryllium levels were below detection limits (not specified) in vegetation in the immediate vicinity of a municipal solid waste incinerator near Catalonia, Spain (Meneses et al. 1999).

A study by Fresquez et al. (2013) analyzed 50 cigarette brands available in Atlanta, Georgia and found that the mean concentration of beryllium ranged from 0.015 to 0.049 µg/g. A smoker who smokes 20 cigarettes per day is projected to be exposed to 1.5 µg of beryllium per day (Svilar et al. 2013). In a review focusing on cigarettes from the United States, yields of 0–0.0005 µg Be per cigarette have been reported in 4 of 12 studies of smoke measurements; however, 8 of 12 studies failed to detect beryllium at any concentration (Smith et al. 1997).

The beryllium concentration in coal ash is on average 46 mg/kg in the United States (Stadnichenko et al. 1961). Beryllium concentrations in U.S. coal range from 0.18 to 3.17 mg/kg depending on the state and coal type, but concentrations typically range from 1.46 to 1.52 mg/kg (Taylor et al. 2003). In the Czech Republic, beryllium content in the ash of Czech coal ranged from 0 to 1,507 ppm (0 to 1,507 mg/kg) depending on the basin (Pesek et al. 2005). Beryllium concentrations in ammonia, nitrate, and phosphorus fertilizers used in agriculture ranged from <0.2 to 13.5 µg/g (Raven and Loeppert 1997).

5.6 GENERAL POPULATION EXPOSURE

The general population is exposed to trace amounts of beryllium by inhalation of air and ingestion of drinking water and food. The general population may be exposed to beryllium because of coal incineration. If the average concentration of beryllium in air is assumed to be <0.03 ng Be/m^3 (Section 5.5.1), and a normal U.S. adult inhales approximately 20 m^3 of air per day, then the inhalation exposure for a U.S. adult would be approximately <0.6 ng Be/day. This value may be somewhat higher for persons living near sources of beryllium emission.

Graphite furnace atomic absorption spectrometry (GFAAS) was utilized to detect beryllium in the blood and serum of 10 individuals from the general population of Montreal, Canada. The average concentration of beryllium was 0.63±0.08 µg/L in the blood and 0.43±0.03 µg/L in serum. Slightly higher levels appeared in the blood and serum of smokers as compared to nonsmokers (Stephan et al. 2008). Three studies of general adult populations measured median beryllium concentrations in whole blood ranging from 0.01 to <0.03 µg/L (Cesbron et al. 2013; Goulle et al. 2005; Nisse et al. 2017).

Bjorklund et al. (2012) studied beryllium and other metals in human breast milk from 60 samples. Beryllium levels ranging from below the instrumentation detection limit (0.48 ng/L; 50% of samples) to

22 ng/L (2 ng/L median) were reported from new mothers in Sweden from 2002 to 2009 (samples obtained 2–3 weeks postpartum). Hinwood et al. (2015) reported that median beryllium concentrations in pregnant women in Australia were <50 ng//L in blood (n=172) and urine (n=173). Ninety-two percent and 82% of blood and urine samples were below the detection limit (not specified). Concentrations ranged from less than <50 to 59 ng/L in blood and less than <50 to 91 ng/L in urine.

Because beryllium absorption mainly occurs via inhalation and leads to an accumulation of beryllium in the upper respiratory tract and lungs, Nogaj et al. (2014) measured the concentration of beryllium in the pharyngeal tonsils of 379 children (176 girls, 203 boys) between the ages of 2 and 17 years (median 6.0 years) living in southern Poland. The average concentration found in pharyngeal tonsil samples was 16 ng/g with a range of 1 to 58 ng/g. The mean concentration of beryllium was higher ($p<0.05$) in girls than in boys, and concentrations also varied significantly by location. Higher mean concentrations were also found in children living in polluted areas with industrial activity. However, Bocio et al. (2005b) determined human tissue beryllium concentrations were below detection limits (50 ng/g) for residents living near an incinerator.

The mean concentration of beryllium in urine of about 500 nonoccupationally exposed individuals in the United States according to the 3rd National Health and Nutrition Examination Survey (NHANES) was 0.22 µg/g of creatinine (Paschal et al. 1998). Other studies reported mean urinary beryllium concentrations ranging from <0.03 to 0.4 µg/L for persons not occupationally exposed (Apostoli and Schaller 2001). In the last cycle of NHANES that measured urinary beryllium, all values that were not missing were below the lower detection limit of 0.072 µg/L (CDC 2011). Urinary beryllium hasn't been analyzed by NHANES in the last several cycles of the survey.

In a study of 982 adult men and 1,018 adult women in northern France, beryllium was found in 57% of blood samples and 58% of urine samples (Nisse et al. 2017). The mean concentration of beryllium in blood was 0.02 µg/L. There was no difference in mean concentration between males and females, and there was also no difference between survey participants who were smokers, former smokers, or non-smokers. The mean concentration of beryllium in urine was 0.04 µg/L.

A study on preliminary results of environmental exposure to metals in Italy measured the serum metal levels of beryllium in subjects from Umbria and Calabria. The mean concentrations in Umbria and Calabria were 0.06 and 0.05 µg/L, respectively (Bocca et al. 2010).

In a study on mothers' and neonates' exposure to metals in China, beryllium was found in maternal and umbilical cord samples at 0.03 µg/L (Guan et al. 2010). Guan et al. (2010) also found that mothers 35 years or older had significantly higher levels of beryllium than younger mothers. Higher levels of

beryllium were also found in mothers who had a history of stillbirth. Guan et al. (2010) also investigated the relationships between maternal beryllium levels and other factors like history of spontaneous abortion, exposure to harmful occupational factors, residence proximity to a major transportation route, residence proximity to an industrial chimney, and exposure to second-hand smoke during pregnancy, but they did not find significant positive associations between any of these factors and maternal beryllium levels.

Reliable data regarding the daily exposure rate to beryllium from food consumption are lacking. Few studies have measured levels in food abroad (Pearson and Ashmore 2020; Saribal 2020). In New Zealand, beryllium was detected in several white wine samples, and to a lesser extent in varying food products ranging from 0.001 mg/kg in soya milk to 0.022 mg/kg in salad dressing (Pearson and Ashmore 2020). In over 20 milk samples in Turkey, beryllium was below the detection limit of 0.01 ng/mL (Saribal 2020). 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 a value for beryllium content of a total diet sample of 0.0001 µg/g food and a daily consumption of 1,200 g of food (EPA 1987). It is believed by Vaessen and Szteke. (2000) that the amount of beryllium in food was underestimated in the EPA (1987) health assessment. However, Bocio et al. (2005a) determined meat, seafood, cereals, seeds, vegetables, pulses (edible seeds of legumes), fruits, milk, dairy products, eggs, and sugar were below detection limits (0.05 µg/g) near an incinerator in Spain. In another study examining the trace element concentrations of food samples via hospital diets in Japan, the average daily intake of beryllium was determined to be 84.4 µg/day (Muto et al. 1994). Other investigators have reported the total daily intake of beryllium in the range of 5–100 µg/day (Vaessen and Szteke 2000).

Beryllium workers may bring home beryllium and expose the general population in this manner. Workers who do not shower or change clothing prior to leaving work could expose their family and others to beryllium. Fabrics experimentally exposed at a beryllium production worksite contained up to 2.8 mg Be/m^2 (NIOSH 1995). Resuspended beryllium dust concentrations in air from unwashed clothing can reach levels of 0.64 µg/m^3. The shaking of contaminated clothes can administer an inhalation dose of approximately 17 µg beryllium (NIOSH 1995). In another study, beryllium concentrations in machine shop workers' personal vehicles were measured. The highest concentrations of beryllium were measured on the driver's floor of the workers' vehicles at 19 µg/Be/ft^2 (Sanderson 1999).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Several populations are at high risk for beryllium exposure. Individuals with the highest risk include people who are occupationally exposed to beryllium from manufacturing, fabricating, or reclaiming industries. A National Occupational Exposure Survey conducted by NIOSH during 1981–1983 estimated

that 13,938 workers were potentially exposed to beryllium, 4,350 to beryllium oxide, and 1,740 to beryllium copper in the workplace (NIOSH 2002).

People who work in industries where beryllium is present have a greater probability of inhalation exposure than nonoccupational groups. The estimated time-weighted average (TWA for 8-hour day) beryllium exposure levels for some workers in a plant that extracted and produced beryllium metal were >50 μg/m^3 during the mid-1960s. Beryllium exposure levels were >30 μg/m^3 during the mid-1970s. After 1977, this plant complied with the previous OSHA maximum TWA concentration of 2 μg/m^3 (Kriebel et al. 1988a), which has since been updated. The TWA personal air concentration for beryllium in a precious metal refinery in 1983 ranged from 0.22 to 42.3 μg/m^3 (Cullen et al. 1987). The Rocky Flats Environmental Technology Site in Colorado reported mean concentrations of beryllium from area and breathing zone monitors as 0.16 and 1.04 μg/m^3, respectively (Stange et al. 1996a). At the Cardiff Atomic Weapons Establishment in the United Kingdom, annual mean area and personal sampling concentration ranges of beryllium were from 0.02–0.32 and 0.09–0.72 μg/m^3, respectively, over the period from 1961 to 1997 (Johnson et al. 2001). OSHA changed the beryllium maximum 8-hour TWA permissible exposure limit to 0.2 μg/m^3 in 2019.

Morton et al. (2011) compared levels of beryllium in urine samples of an occupationally exposed group of workers, employed in an aluminum smelter facility where beryllium exists as an impurity of the bauxite ore, to a group of non-occupationally exposed individuals. The mean and 90th percentiles of beryllium in the urine for workers at the aluminum smelter were 19.5 and 42.0 ng/L, respectively, while the mean and 90th percentile of the control group was 11.6 and 20.0 ng/L, respectively. Horng et al. (2002) compared urine concentrations of beryllium in steel production workers and steel quality control workers to a control group. The mean concentrations of beryllium in production workers and quality control workers were 1.58 and 1.39 μg/L respectively, while the mean in controls was 0.83 μg/L. The mean concentrations in production workers and quality control workers were both significantly higher than in the controls. The beryllium concentration exceeded 2 μg/L in 2 production workers, which is considered above normal.

Martin and Lariviere (2014) concluded after a review of the literature that although there is significant exposure to beryllium in the aluminum smelting industry, BeS is rare. From January 2004 to April 2005, blood samples of 359 former workers at American Beryllium in Tallevast, Florida, household members, and residents showed that 348 individuals were not beryllium sensitive, three were abnormal, five were borderline, one was uninterpretable, and two tests could not be analyzed (ATSDR 2005b). Skalny et al. (2018) assessed the hair metal levels in aluminum plant workers and concluded that beryllium was not one of the metals to which workers had an increased risk of exposure. However, Godderis et al. (2005)

concluded that exposure in an aluminum cast-house appeared to be acceptable (did not exceed the TLV-TWA defined by ACGIH), but exposure to beryllium due to aluminum recycling requires more attention. Hulo et al. (2016) found that beryllium levels in exhaled breath condensate were higher in aluminum potroom workers and exposed subjects at a primary aluminum production plant than in controls.

There have been no reports of diseases attributable to beryllium exposure as a result of beryllium ore mining operations (Eisenbud and Lisson 1983; EPA 1987). 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. Granero and Domingo (2002) estimated that adults in Alcala de Henares, Spain, an area with industrial activity and heavy traffic, are exposed to $2.7x10^{-9}$ mg/kg day by inhalation while children are exposed to $6.3x10^{-9}$ mg/kg day. No new cases of beryllium disease in people living near beryllium-processing industries have been reported in the past several years, probably because the past exposures were relatively high compared to present levels of beryllium in the ambient and workplace air (EPA 1987; NIOSH 1995). 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.

Beryllium exposures may be higher in areas with naturally high beryllium soil levels, and near beryllium processing sites, electric power plants, and waste sites containing beryllium. At waste sites, beryllium that is found in excess of natural background levels is most likely to be in soil. The National Emission Standard for Hazardous Air Pollutants (NESHAPS) restricts the amount of beryllium emitted into the environment by industries that process beryllium ores, metals, oxides, alloys, or wastes. The NESHAPS can be met by complying with either a 10 g per 24-hour emission limit or by meeting an ambient air concentration of 0.01 $\mu g/m^3$ of air averaged over a 30-day period (EPA 1982). Machine shops machining alloys containing <5% beryllium by weight are excluded from regulation under the NESHAPS emission standard (40 CFR Part 61, subpart C 61.30(b) 2001).

Occupationally exposed workers who carry beryllium dust on their clothes, shoes, or skin from the workplace to their home may increase the risk of beryllium exposure to their family members and themselves (Taylor et al. 2003). In a report to Congress by NIOSH, several historical cases of home contamination by beryllium were reported (NIOSH 1995). The most recent case was in 1992. The majority of these cases were from the contamination of machinist workers' clothing with beryllium dust (NIOSH 1995). Permissible exposure limits have been significantly reduced since the 1990s so it is unclear whether today's 'take home' amounts would be considered a high beryllium exposure.

Furthermore, beryllium industries are required to provide showers and launder employee's work clothes in an effort to reduce the potential for ‘take home’ beryllium exposures (29 CFR 1910.1024).

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 (Stark et al. 2014) and can develop CBD (Kotloff et al. 1993; Fireman et al. 2006). Additionally, individuals may be exposed to high levels of beryllium from implanted dental prostheses (EPA 1987; Taylor et al. 2003). Not all dental alloys contain beryllium, however beryllium is still present in dental alloys in the United States (OSHA 2002). The highest concentration of beryllium released from base metal alloy used as dental crowns measured in an artificial oral environment was 8 µg/day per crown (Tai et al. 1992). The mantles of some lanterns used by campers contain approximately 600 µg of beryllium, and most of the beryllium becomes airborne during the first 15 minutes when a new mantle is used (Fishbein 1981). Therefore, people who camp outdoors and use these mantles are possibly exposed to higher than normal levels of beryllium.

The mean concentration of beryllium in cigarettes available in the U.S. ranged from 0.015 to 0.049 µg/g (Fresquez et al. 2013). It is estimated that smoking 20 cigarettes per day could expose an individual to 1.5 µg of beryllium per day (Svilar et al. 2013). In a study based in Romania, beryllium was detected more frequently in e-cigarette users (21% of those sampled) than cigarette smokers (2% of those sampled), although the median blood concentration of beryllium in non-smokers (0.75 ng/mL, detected in 5% of 58 people sampled) was higher than in cigarette smokers (0.26 ng/mL) or e-cigarette users (0.30 ng/mL) (Badea et al. 2018). Nevertheless, smokers may have a higher probability of exposure to beryllium than the nonsmoking population.

CHAPTER 6. ADEQUACY OF THE DATABASE

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

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk 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.

6.1 EXISTING INFORMATION ON HEALTH EFFECTS

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to beryllium that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of beryllium. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to beryllium are summarized in Figure 6-1. The purpose of this figure is to illustrate the existing information concerning the health effects of beryllium. As shown in Figure 6-1, information on the health effects in humans exposed to beryllium is available primarily for exposure via inhalation. Human exposure and its related health effects are largely limited to occupational studies, and BeS and CBD resulting from inhalation exposures are the most sensitive endpoints.

No studies were located regarding neurological, reproductive, or genotoxic effects in humans following inhalation exposure to beryllium or its compounds. Human studies regarding death were limited to chronic inhalation exposure. Most of the human data concerns respiratory effects and lung cancer as a result of occupational exposure to beryllium or its compounds. Data indicate that beryllium induces immune responses in the lung and skin. No studies were located regarding any effects in humans following oral exposure to beryllium. Further study is needed to understand the immune component of effects observed in animals.

The organs or systems adversely affected in humans after exposure to beryllium include primarily the lungs but the liver, kidneys, adrenals, and hematopoietic tissues have been reported as target organs.

Information on the adverse health effects of beryllium has been presented for occupational exposures primarily of chronic duration and discussed in detail in Chapter 2 and summarized in Table 2-5. In short, results from occupational epidemiological studies indicate exposure can result in respiratory diseases (BeS and CBD) however, the lack of strong, reliable data that quantifies individual worker exposure limits conclusive interpretation of these results.

Several studies have evaluated the health effects of beryllium exposure in animals for the inhalation route. LC50 values have been reported for a number of beryllium compounds. Systemic effects of acute, intermediate, and chronic exposure via inhalation include respiratory, cardiovascular, hematological, hepatic, and renal 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 LD50 values have been reported for many of the beryllium compounds. Only one acute oral study has been undertaken to evaluate hematological, hepatic, and neurological effects from beryllium or its compounds; all these systems were reported to have LOAELs. Gastrointestinal, hematological, musculoskeletal, and reproductive effects due to ingestion of beryllium are reported in the available literature.

Dermal studies reported immunological and dermal effects. Since beryllium is a T-cell activator, exposure can cause immunological effects on the skin. One dermal study indicated a respiratory effect and another study found no ocular effects. No dermal studies were located regarding any other health effects.

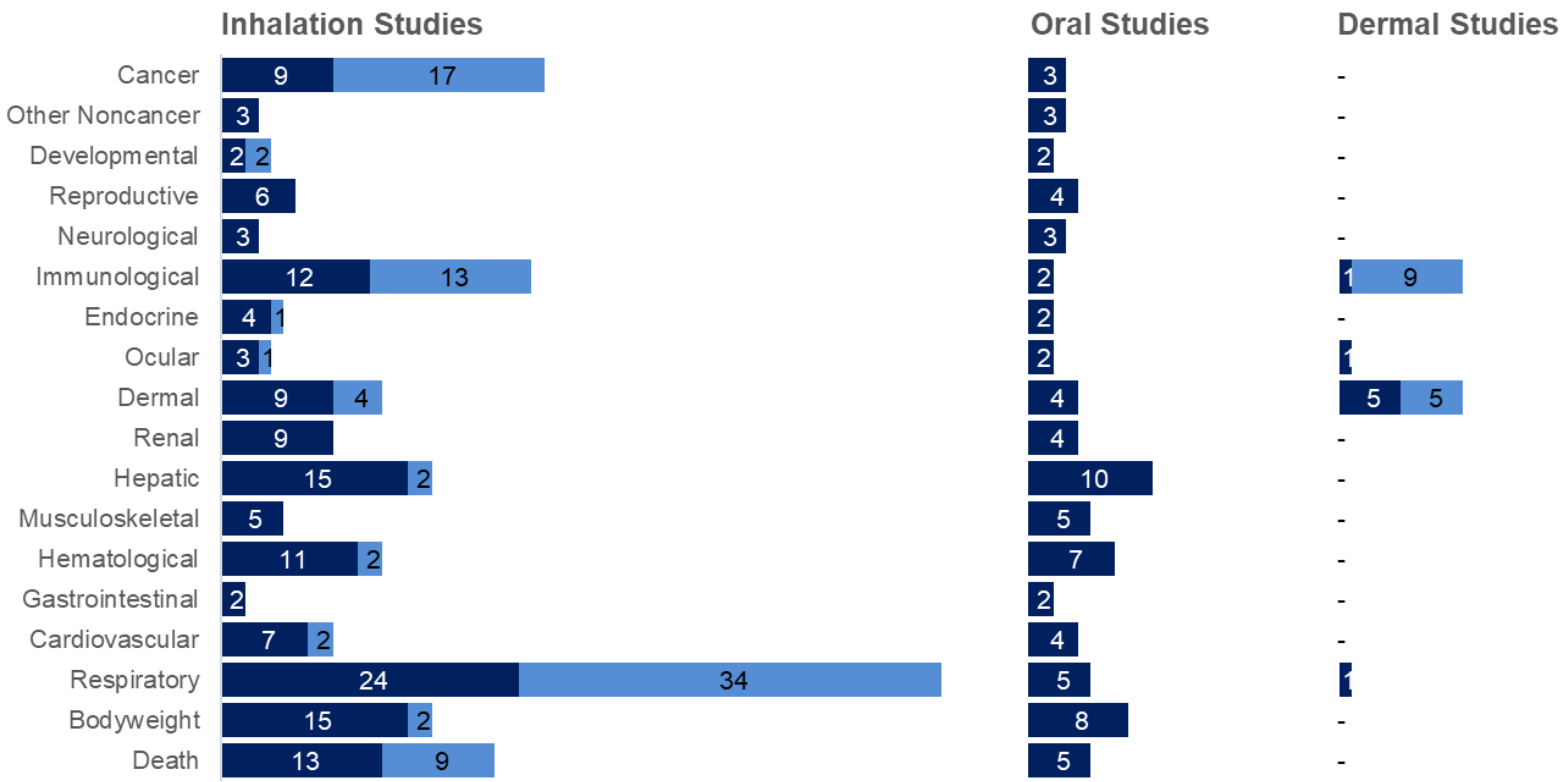
6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figure 6-1 should not be interpreted as a “data need.” A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Acute-Duration MRLs. The lung is the main target organ of inhaled beryllium and its compounds in humans (Eisenbud et al. 1948; VanOrdstrand et al. 1945) and animals (Haley et al. 1989; Hart et al. 1984; Robinson et al. 1968; Sanders et al. 1975; Schepers 1964; Sendebach and Witschi 1987b; Sendebach et al. 1980, 1989). The heart, liver, kidneys, adrenal glands (Schepers 1965), skin (Stiefel et al. 1980), and the

Figure 6-1. Summary of Existing Health Effects Studies on Beryllium by Route and Endpoint*

Potential respiratory, cancerous, and immunological effects were the most studied endpoints
The majority of these studies examined inhalation exposure in **humans** (versus **animals**)



*Includes studies discussed in Chapter 2, the number of studies includes those finding no effect and those that examined multiple endpoints.

hematopoietic tissues (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 CBD 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).

Suitable animal data were not found to derive an acute-duration inhalation MRL. No human acute-duration studies were identified; thus, a provisional acute-duration inhalation MRL was not identified. No data were located regarding effects in humans after acute oral exposure to beryllium, therefore, the available acute oral database was inadequate for deriving an MRL. Most of the available data on the acute-duration toxicity of ingested beryllium are from lethality studies in rats and mice. Human studies focusing on the acute effect of exposure to beryllium and its compounds would be beneficial in identifying an oral and inhalation acute duration MRL.

No acute oral MRL was derived because the effects found in a single study (El-Beshbishy et al. 2012) have not been substantiated in other acute oral studies (Ashby et al. 1990; Lanchow University 1980); Strupp 2011a). Beryllium compounds are poorly absorbed from the gastrointestinal tract (Furchner et al. 1973; Le Fevre and Joel 1986; Morgareidge et al. 1975; Reeves 1965). However, what is absorbed is distributed throughout the body. In one study, Fahmy et al. (2008) evaluated the genotoxic potential of ingested beryllium, which included an evaluation of abnormal sperm. A LOAEL was identified; however, sperm abnormalities are considered a serious LOAEL, which precludes the use of this study for an MRL.

Additional human exposure studies that examine the potential of beryllium to cause BeS and CBD after a <2 weeks of exposure would be useful for establishing a provisional acute-duration inhalation and acute-duration oral MRL. The information regarding beryllium toxicity is useful to the general population and to populations residing at or near hazardous waste sites and beryllium processing plants that might be subject to acute exposure.

Intermediate-Duration MRLs. 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; Wagner et al. 1969). No studies were located regarding effects in humans after intermediate-duration inhalation exposure to beryllium or its compounds. Derivation of an intermediate-duration inhalation MRL is precluded because there are no human intermediate-duration studies. Animal studies are a poor substitute because they are limited and don’t fully mimic CBD in humans.

There are limited data on the toxicity of ingested beryllium following intermediate-duration exposure. No studies were located evaluating oral exposure in humans. The available animal data suggest that the gastrointestinal tract and musculoskeletal system are impacted by ingestion of beryllium (Guyatt et al. 1933; Jacobson 1933; Kay and Skill 1934; Morgareidge et al. 1976). Ulcers appeared in dogs exposed to extremely high oral doses of beryllium; these appeared within weeks 26-33 of exposure and resulted in a discontinuation of the dose group. Rickets are a critical effect following ingestion of beryllium carbonate. However, the rickets do not appear to be due to a direct effect of beryllium on the bone. Rather, the rickets are due to a phosphorus deficiency, which results from the binding of beryllium to dietary phosphorus in the gut. These studies are quite dated, therefore, studies that confirm this mechanism and/or demonstrate rickets with other forms of beryllium may be beneficial.

The available data are insufficient for derivation of a provisional intermediate-duration inhalation or oral MRL. Additional human exposure studies that examine the potential of beryllium to cause BeS and CBD after >2 weeks but less than a year of exposure would be useful for establishing an intermediate-duration inhalation MRL. Additional oral studies involving low concentration beryllium exposure would be useful for identifying critical targets of toxicity and establishing dose-response relationships.

Chronic-Duration MRLs. Health effects in humans and animals after chronic exposure to beryllium and its compounds are reported in the available literature. Lungs are the main target organ in humans (Andrews et al. 1969; Cullen et al. 1987; Eisenbud and Lisson 1983; Hardy and Tabershaw 1946; Kreiss et al. 1993, 1996, 1997; Rossman et al. 1988; Stange et al. 1996b) and animals (Reeves et al. 1967; Vorwald and Reeves 1959; Wagner et al. 1969) after inhalation exposure to beryllium and its compounds. Occupational exposure to soluble and insoluble beryllium compounds caused delayed granulomatous disease of the lung, known as CBD or berylliosis (Cotes et al. 1983; Cullen et al. 1987; Eisenbud and Lisson 1983; Eisenbud et al. 1949; Kreiss et al. 1993, 1996, 1997; Stange et al. 1996b). Studies by Kreiss et al. 1989, Donovan et al. 2007, and Mroz et al. 1999 suggest that BeS does not always result in CBD even with on-going exposure. It would be beneficial if future studies would address beryllium cohorts that have BeS but never progress to having CBD though they are still working in the industry. Longer duration longitudinal studies are needed to understand the relevance of this observation.

More recent occupational studies have reported BeS and CBD after exposure to beryllium (Madl et al. 2007; Schuler et al. 2012). These studies utilize lapel sampling and adjust for engineering controls in their study methods. BeS is considered a LOAEL because there is no loss of organ or system function occurring with it. CBD is a serious LOAEL as the respiratory system loses function. Serious LOAELs are not suitable for MRL derivation. Schuler et al. (2012) identified a LOAEL for BeS, and it is used to

derive the MRL. BeS is reliably confirmed with multiple blood BeLPT tests and confirmed with an abnormal finding in bronchoalveolar lavage (BAL) BeLPT.

Maier et al. (2008), Chesner (1950), Dattoli et al. (1964), Eisenbud et al. (1949), Lieben and Metzner (1959), and Lieben and Williams (1969) studied communities living near beryllium manufacturing facilities and in families of workers who wore contaminated clothing home. However these studies are based on 1950s data (and later) and are not current with the EPA emission standards. Additionally, many of the studies suffer from poor beryllium measurements or estimates. Updated community studies are needed that investigate the prevalence of BeS and CBD and provide more accurate air concentration measures. Further, it would also be helpful to determine if the community members that get BeS and CBD have one of the genetic variants or polymorphisms making them more susceptible to the effects of beryllium exposure.

A well-designed chronic inhalation study in rats and mice which includes lower doses of exposure would fill database gaps and mitigate uncertainties associated with the current body of literature. However, none of the current animal models adequately reproduce features of CBD observed in humans. Therefore, community level studies near facilities using or producing beryllium with well measured air concentrations would be helpful.

Data were not located regarding effects in humans after chronic oral exposure to beryllium. The Morgareidge et al. (1976) dog study could not be used to derive a chronic MRL as gastrointestinal incidence data do not show a statistically significant effect nor a clear dose-response relationship when the highest dose is excluded. It would be very helpful to have additional oral chronic studies undertaken to substantiate that the gastrointestinal tract is a critical target organ. It would also help establish whether the ulcers seen in dogs are problematic in other species.

Data regarding the effects of chronic dermal exposure to beryllium were limited to findings of dermatitis in occupationally exposed individuals (Curtis 1951; VanOrdstrand 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 mice (Huang et al. 1992) exposed to beryllium oxide intratracheally, have been performed to identify an appropriate model to elucidate the pathogenesis of CBD in humans. However, an animal model that exactly mimics CBD or the key precursor pathway in humans has not been found. This information would be useful to the general population and to populations residing at or near hazardous waste sites that may contain beryllium and beryllium compounds.

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; Sanderson et al. 2001a; Steenland and Ward 1991; Wagoner et al. 1980; Ward et al. 1992). However, the quality of some of these studies has been severely criticized (EPA 1987). A number of retrospective cohort mortality studies examining workers at beryllium processing facilities have been conducted and are summarized in Table 2-4. These studies were funded either by the beryllium industry (Boffetta et al. 2014, 2016; Levy et al. 2002, 2009; Mosquin and Rothman 2017) or the National Institute for Occupational Safety and Health (Bayliss et al. 1971; Sanderson et al. 2001a, 2001b; Schubauer-Berigan et al. 2008, 2011a, 2011b, 2017; Wagoner et al. 1980; Ward et al. 1992). Animal studies indicate increases in lung cancer due to inhalation exposure to beryllium or its soluble and insoluble compounds (Nickell-Brady et al. 1994; Reeves et al. 1967; Vorwald 1968; Vorwald and Reeves 1959; Wagner et al. 1969), but these studies are also flawed. Nevertheless, these data and studies conducted by intratracheal, intravenous, and intramedullary routes taken as a whole support the carcinogenic potential of beryllium, and inhaled beryllium is considered a human carcinogen (IARC 2001; NTP1999, 2002). EPA considers beryllium to be a probable human carcinogen (B1) (IRIS 2002) for the inhalation exposure route and I (Inadequate Information) for the oral route of Exposure (EPA, 1992).

Health Effects.

Cardiovascular. No studies were located regarding cardiovascular effects in humans after oral exposure nor in animals and humans after dermal exposure to beryllium or its compounds. Exposure to beryllium has been associated with an increase in death due to heart attacks among workers in a beryllium plant, however, cardiac effects may be due to a response to impaired lung function. Animal studies suggest that observed effects such as heart enlargement may be a compensatory response due to lung fibrosis caused by inhalation exposure. No adverse effects were reported from oral exposure to beryllium. Additional inhalation studies examining the effects of beryllium or its compounds with a focus on cardiovascular endpoints would be useful in clarifying the potential effects of beryllium on the cardiovascular system.

Gastrointestinal. No studies were located regarding gastrointestinal effects in humans or animals after inhalation or dermal exposure to beryllium or its compounds. Studies on the effect of beryllium or its compounds from oral exposure are few, but available results from an intermediate study revealed the presence of inflammatory lesions in the small intestine, stomach, and large intestine of dogs (Morgareidge et al. 1976). However, contrary to this observation, no abnormalities of the gastrointestinal system were seen in rats (Morgareidge et al. 1975). Additional studies examining the effects of beryllium or its compounds with a focus on gastrointestinal endpoints would be helpful in clarifying the potential effects on the gastrointestinal system.

Hepatic. Human studies on the hepatic effects are limited to occupational studies, which report conflicting effects on hepatic endpoints. Workers exposed to beryllium chloride showed no increase in biochemical indices during a 10-month follow-up (Zorn et al. 1986) and an autopsy revealed hepatic necrosis in a worker who was exposed to beryllium from a plant that manufactured fluorescent lamps (Hardy and Tabershaw 1946). Available animal studies indicate there are few hepatic effects after inhalation exposure to beryllium and its compounds, except at lethal doses. However, the relationship between beryllium and its compounds after oral exposure is unclear as some studies report significant alterations in hepatic enzyme levels and lesions (Nirala and Bhadauria 2008; Sharma and Shukla 2000; El-Beshbishy et al. 2001), while others report no effect and no histological damage (Morgareidge et al. 1976; Schroeder and Mitchener 1975b). More oral studies for hepatic effects are needed to elucidate the potential adverse effects of beryllium and its compounds in humans.

Endocrine. Evidence of the effects of beryllium and its compounds on the endocrine system has been observed. In both humans and animals, histological examinations after exposure to beryllium or its compounds via inhalation revealed adverse effects including marked hyperemia and vacuolization in the adrenal glands in humans (Hardy and Tabershaw 1946), or hypoplasia and hypotrophy of the adrenal glands in monkeys (Schepers 1964). However, there is limited information on the potential endocrine effects following oral or dermal exposure to beryllium. Additional oral or dermal studies would be useful to elucidate the effects of beryllium on the endocrine system.

Immunological. 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 CBD 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 would aid in the identification and treatment of patients with CBD. In addition, identification of potential differences in allelic phenotypes between people with chronic beryllium and people exposed to beryllium but without CBD might help identify potentially susceptible populations based on genetic differences. Dermal beryllium exposure caused by occupational exposure could potentially have systemic effects in humans and needs to extensively be examined (Anderson and Meade 2014). Additionally, the EPA Office of Water Scientists indicate epithelial surfaces (e.g., lung, GI tract) appear to have allergenic responses to beryllium exposure and suggest researching

whether the FCGR3A gene (as discussed in section 3.2) is linked not only to lung effects but GI lesions as well.

Neurological. No studies were located regarding neurotoxicity in humans after inhalation, oral, or dermal exposure to beryllium or its compounds. Available neurotoxicity studies are limited to a few on acute or chronic exposures to beryllium (Drobyshev et al. 2019; Morgareidge et al. 1975, 1976). Histological examination of rats and dogs chronically exposed to beryllium sulfate in drinking water did not reveal any abnormalities in nerve tissues (Morgareidge et al. 1975, 1976). Drobyshev et al. (2019) reported a slight dose-response correlation (R^2=0.27) between beryllium in the brain among male rats exposed once to doses of 2,856 to 7,622 µmol/kg-bw beryllium sulfate via intraperitoneal injection. Study results indicate no alterations to either the nerve tissue or brain during histological examinations. However, 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.

Reproductive. No studies were located regarding the reproductive effects in humans after exposure to beryllium or its compounds by any route. Findings from animal studies are inconsistent in their effects on the reproductive system. Decrease in fetal weight, reduced number of implementation sites, reduced litter size, occurrence of resorption of the fetus, sperm abnormalities, damage to the testicular tissues and reduced testes- to-body weight ratio were observed in animals exposed to beryllium (Drobyshev et al. 2019; Fahmy et al. 2008; Mathur et al. 1987b; Mathur and Mathur 1994; Morgareidge et al. 1975; Sharma et al. 2002). However, a chronic duration study that allowed continuous mating did not find any adverse reproductive effects in dogs exposed to beryllium sulfate in the diet (Morgareidge et al. 1976). The findings reported by Morgareidge et al. (1976) provided few study details and should be interpreted cautiously. 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).

There are insufficient data in humans and animals to indicate whether beryllium affects reproductive health following exposure. No studies were located regarding reproductive effects in animals after dermal or inhalation exposures to beryllium or its compounds, and pharmacokinetic data do not exist to support the potential for reproductive effects across the three main routes of exposure. Therefore, additional inhalation, oral, and dermal studies for reproductive effects are needed to further evaluate the potential adverse reproductive effects in humans from exposure to beryllium. Additional inhalation studies should

examine reproductive organs in order to determine whether the potential for reproductive effects due to beryllium exposure exists.

Developmental. Studies of developmental effects from beryllium in humans are limited to a cross-sectional study and a case study after occupational exposure to beryllium or its compounds (Crinnion and Tran 2010, Shirai et al. 2010). Due to the limited number of available studies and study design concerns, these studies cannot be used to draw conclusions about the developmental effects of beryllium in humans.

There is limited information on beryllium's potential to induce developmental effects in animals following oral exposure. No developmental effects were observed in the offspring of dogs chronically exposed to beryllium sulfate in the diet (Morgareidge et al. 1976). However, the utility of this study in establishing the potential for developmental toxicity of ingested beryllium is limited by its nonconventional study design. No inhalation or dermal exposure studies that examined developmental toxicity in animals were identified. Rats injected intravenously with beryllium nitrate during gestation delivered pups that died soon after birth (Mathur et al. 1987). Other studies in which beryllium salts were injected into pregnant mice indicated that beryllium could penetrate the placenta and reach the fetus resulting in behavioral abnormalities in the offspring (Bencko et al. 1979; Tsujii and Hoshishima 1979).

There is insufficient information to support pharmacokinetic extrapolation of the results across the major routes of exposure to beryllium or its compounds from animals to humans. Additional inhalation and dermal studies in mice and other species are needed to evaluate the potential developmental risks to humans.

Cancer. Human cancer studies involving exposure to beryllium or its compounds have been widely contested, as evidenced by several reanalyses of key cancer studies that were used to support IARC's conclusion that beryllium is a human carcinogen (Sanderson et al. 2001b; Schubauer-Berigan et al. 2008; Steenland and Ward 1991; Ward et al. 1992). More recently, Boffetta et al. (2014, 2016) suggested that exposure to insoluble forms of beryllium is not associated with an increased risk of cancer. Schubauer-Berigan et al. (2017), however, found that exposure-response coefficients were higher for a cohort exposed to low levels of insoluble beryllium when compared to a cohort that included higher levels of exposure to soluble forms of Beryllium. Additional studies examining the association and mechanism of action of soluble and insoluble forms of beryllium may be helpful in elucidating whether either form behaves differently to increase the risk of cancer.

Genotoxicity. Genotoxicity data regarding exposure to beryllium or its compounds yield inconsistent results. 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 1979) outcomes for the same compounds. The results for chromosomal aberrations induced by beryllium in mammalian cell cultures are also inconsistent (Ashby et al. 1990; Brooks et al. 1989; Hsie et al. 1979; Larramendy et al. 1981; Miyaki et al. 1979; Williams et al. 1989). Additional research 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. Studies regarding the *in vivo* genotoxic potential of beryllium in animals, particularly by the inhalation route, would be helpful.

Mechanisms of Action. Despite the recent advances in our understanding of the immunopathogenesis of CBD, a number of questions remain unanswered. Few studies have addressed molecular mechanisms of beryllium toxicity and carcinogenicity aside from the single-nucleotide polymorphisms (SNPs) associated with Be susceptibility (Chen et al. 2019). Although, several recent studies using BAL fluid from individuals with CBD provide information on some of the components of the toxic sequence, the specific mechanism has not been fully elucidated. Elucidation of the MHC-bound peptides involved in presentation should provide insight into how beryllium interacts with the MHC/peptide complex and is recognized by the TCR. In CBD, the environment is interacting with genetic susceptibility, but aspects of the beryllium particulates involved in pathogenicity and the nature of non-MHC genetic contributions require elucidation. Studies are also needed to understand why only certain individuals with BeS progress to CBD. For example, finding out whether the number of beryllium-specific T cells or some characteristic of these cells is involved in progression to disease will lead to tools to identify individuals at greatest risk. Granulomas in CBD characterized by noncaseating granulomatous inflammation and alveolitis composed of Be-specific CD4+ T cells primarily occur in the lung, although other organ systems may be involved (Fontenot 2003).

The studies reviewed suggest a need of using Be-stimulated cell systems as hypothesis generating models to identify key pathways for the direct effects of beryllium on various specific cell classes. These types of studies not only avoid the need for cells and tissues obtained directly from human patients with beryllium disease, but they could serve to identify novel pathways and directions that can be brought back to studies using cells isolated from human subjects. Available data suggests the needs of developing the HLA–DP2–transgenic murine model of CBD to address many of the unanswered questions that have been difficult to address given the rarity of the disease. The murine model will enhance the ability of investigators to study the interplay of innate and adaptive immunity in the establishment of CBD (Fontenot 2018). Lastly, the mechanism for BeS proposed by penetration of poorly soluble particles of beryllium through intact skin is not fully understood.

Epidemiology 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). The available epidemiology studies described in the Respiratory and Cancer Section of Chapter 2 evaluated the health effects of workers exposed to beryllium and its compounds in various occupational settings and several reanalyses have been conducted to account for study design limitations. However, a common limitation of occupational studies is the lack of direct, specific exposure information, and the need to use available historical data (e.g., personnel, industrial hygiene records, etc.) to construct job-exposure-matrices to estimate exposure or the likely occurrence of exposure. The accuracy of the exposure estimates depends on several factors including accounting for technological changes and engineering controls and the comprehensiveness and completeness of documentation in the work environment. Therefore, additional studies that are longitudinal, have precise exposure measurements and evaluate the exposure-response relationship of beryllium would be helpful. Studies conducted in people residing around beryllium processing facilities would be useful to further understand risk outside of the occupational setting.

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; IARC 1980; Martinsen and Thomassen 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 from the lung tissue of individuals with CBD (Kanarek et al. 1973) and in the skin of some beryllium sensitive individuals however not all sensitized individuals develop granulomas (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 CBD (Williams and Kelland 1986). A lymphocyte proliferation test has also been used to identify workers with CBD; positive test results rarely occur in workers who are not exposed to beryllium or its compounds (Stokes and Rossman 1991). While the BeLPT documents exposure to beryllium, the test does not quantitate the exposure.

Chronic exposure to beryllium can result in decreased lung function (Andrews et al. 1969; Johnson 1983). This decrease can be measured by spirometry such as forced expiratory volume in 1 second or forced vital capacity (Andrews et al. 1969; Kriebel et al. 1988a, 1998b). Measurements of lung function cannot distinguish between CBD and sarcoidosis or any other lung condition when 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 CBD in symptomatic individuals (Rossman et al. 1988). The lymphocyte proliferation test also distinguishes between CBD and sarcoidosis. A less invasive and more reliable method of determining individual 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 1967; Stiefel et al. 1980; Zorn et al. 1986), but the available information is insufficient 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 most 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 expected to be low as is the case with many metals, and no evidence of absorption was identified in the literature (Damian 2011). However, skin contact with insoluble forms of beryllium may result in sensitization in humans and animals (Tinkle et al. 2003). Studies regarding the rate and extent of beryllium absorption via the lungs and skin 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 plentiful (Finch et al. 1990; Rhoads and Sanders 1985; Sanders et al. 1975; Stiefel et al. 1980; Stokinger et al. 1950; Wagner et al. 1969; Muller et al. 2010; 2011; IRSST 2012)). The target organs for absorption identified in these studies were the lung, lymph nodes, kidneys, 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 1967). 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).

Beryllium is not biotransformed in the body. Studies involving the conversion of soluble beryllium compounds to insoluble compounds would be useful to determine the residence time of the compounds in the gastrointestinal tract. Studies investigating the binding of beryllium to proteins or nucleic acids would be useful in determining the antigenic forms of beryllium, as well as a possible mechanism for genotoxicity. Information regarding the clearance of beryllium from serum in humans (Stiefel et al. 1980; Zorn et al. 1986) and animals (Finch et al. 1990; Rhoads and Sanders 1985; Sanders et al. 1975; Stiefel et al. 1980) 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). One study compared the lung deposition of different sizes of beryllium dusts in humans and mice and noticed difference across species (IRSST, 2012). This could be due to a variety of species differences including posture. No other studies were located comparing the differences in inhalation exposures among species with respect to absorption or excretion. Beryllium is not well absorbed by the gastrointestinal tract or after dermal exposure. Additional comparative toxicokinetics studies regarding distribution, absorption, and excretion of inhaled beryllium could be used to study ABD and CBD, with the help of in vitro, organ on chip models using human lines.

Children's Susceptibility. No information on the toxicity of beryllium in children has been located. Studies that examine sensitive endpoints such as the lung, immune, and gastrointestinal effects in young animals would be useful for assessing whether children will be unusually susceptible to beryllium toxicity. The available animal data are inconclusive to determine whether the developing organism is sensitive to beryllium toxicity. A reported human case study by Crinnion and Tran (2010) suggests exposure to beryllium may be transferred to the infant in-utero or through lactation; animal studies by Sharma et al. (2002) observed beryllium crossing the placental barrier and accumulating in the offspring. As discussed in Chapter 2 the only available oral study did not find developmental effects in the offspring of dogs chronically exposed to beryllium sulfate in the diet (Morgareidge et al. 1976). However, injection studies have found developmental effects (fetal/ neonatal mortality, internal abnormalities, and behavioral effects) (Bencko et al. 1979; Mathur et al. 1987; Tsujii and Hoshishima 1979). Data needs relating to developmental effects are discussed in detail in the Developmental Toxicity subsection above. There are some data to suggest that beryllium can cross the placenta and be transferred to an infant via breast milk (Krachler et al. 1999a). The available toxicokinetic data did not evaluate the potential differences between adults and children. Toxicokinetic studies examining how aging can influence the absorption, distribution, and excretion of beryllium would be useful in assessing children's susceptibility to beryllium toxicity. There are no data to determine whether there are age-specific biomarkers of exposure or effects or any interactions with other chemicals that would be specific for children. Research in adults on methods for reducing beryllium toxic effects or body burdens would also be applicable to children.

Physical and Chemical Properties. No data needs were identified regarding physical and chemical properties of beryllium.

Production, Import/Export, Use, Release, and Disposal. Continued monitoring of beryllium production, import/export, use, release, and disposal would be helpful in identifying sources of emerging and potential human exposure. Additional data on environmental releases of beryllium from anthropogenic sources such as combustion of coal and fuel oil, the incineration of municipal solid waste, the production, use, and recycling of beryllium and industrial effluent waste would be helpful for determining potential contributions to human exposure.

Exposure Levels in Humans. The available data on exposure to beryllium from food consumption is limited to estimates based on the value of beryllium content from a total diet sample of 0.1 ng per g food and daily food consumption of 1,200 g. Reliable data regarding the daily exposure rate to beryllium from food consumption are lacking. Studies evaluating daily exposure to beryllium from food consumption would be helpful in filling this data gap and better characterizing beryllium exposure in humans.

At waste sites, beryllium that is found in excess of natural background levels is most likely to be in soil and that presents a special hazard for young children. Children may be particularly susceptible because of their behaviors and lifestyle. Children crawl, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Continued monitoring of beryllium exposure particularly among populations and residents near waste sites and in rural areas are needed to identify potential exposure to humans and related adverse health effects.

Individuals occupationally exposed to beryllium are at highest risk of exposure to beryllium. As discussed in the Epidemiology and Human Dosimetry Studies sub-section, longitudinal studies with strong study design and precise exposure data are needed to evaluate the human health effects of beryllium exposure.

Exposures of Children. As discussed in the Developmental and Children Susceptibility sub-sections of this chapter, there is suggestive data that children can be exposed to beryllium in-utero or through breast milk. Additional studies evaluating the reproductive and developmental exposures to beryllium is needed to better assess the relationship between beryllium exposures in children and potential adverse health effects. Furthermore, studies focusing on the toxicokinetic of adsorption, distribution, and excretion of beryllium in children would be useful in assessing children's susceptibility to beryllium toxicity.

6.3 ONGOING STUDIES

Ongoing studies on beryllium are outlined in Table 6-1. Note that the studies listed below are funded by the National Institutes of Health (NIH) and do not include ongoing studies that are funded by other sources. Information in this table is current as of July 2019, and studies resulting from this research may continue to be published.

Table 6-1. Ongoing Studies on Beryllium

Investigator	Affiliation	Research Description	Sponsor
Barski, A	Cincinnati Children's Hospital Medical Center	Study examining the epigenetic regulation and programming of T-cells to better understand and develop treatment for immunological and infectious diseases.	NIGMS
Dai, S	University of Colorado Denver	Mechanisms of action study examining human T cell hypersensitivity to beryllium and nickel metal ions.	NIEHS
Dai, S	University of Colorado Denver	Molecular of action study of heavy metals in autoimmunity.	NIEHS
Fontenot, AP	University of Colorado Denver	A molecular study examining the interaction between antigen-specific effector and regulatory T-cells in beryllium-induced disease.	NIEHS
Fontenot, AP	University of Colorado Denver	Immunological study examining HLA-DP2 expressing antigen-presenting cells before and after beryllium exposure.	NHLBI
Li, L	National Jewish Health	A molecular mechanism study evaluating the role of the alveolar macrophages in chronic beryllium disease to improve understanding of factors involved in CBD development.	NIEHS
Maier, L	National Jewish Health	A case-control study examining the epigenetic alterations that impact gene transcription and immune cell differentiation of chronic beryllium disease development.	NIEHS
Mckee, A	University of Colorado Denver	A mouse study examining the innate and adaptive immune effects of beryllium on pulmonary dendritic cell function in chronic beryllium disease.	NHLBI
Yalin, A	Colorado State University	A study developing a portable direct-read instrument able to read size and composition of large inhalable particles such as metals.	NIOSH

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding beryllium in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on MRLs for beryllium.

Table 7-1. Regulations and Guidelines Applicable to Beryllium

Agency	Description	Information	Reference
	Air		
EPA	RfC[a]	$2x10^{-5}$ mg/m^3	IRIS 1998
WHO	Air quality guidelines	No data	WHO 2010
EPA	Ambient Air	0.01 µg/m^3 (30-day average)	EPA 1973
	Water & Food		
EPA	Drinking water standards		EPA 2018b
	1-day health advisory for a 10-kg child	30 mg/L	
	10-day health advisory for a 10-kg child	30 mg/L	
	DWEL[b]	0.07 mg/L	
	National primary drinking water regulations		EPA 2009
	MCL	0.004 mg/L	
	MCLG (Public health goal)	0.004 mg/L	
	RfD[c]	$2x10^{-3}$ mg/kg/day	EPA 2018b
WHO	Disinfection by-products-drinking-water	Not established	WHO 2017
FDA	EAFUS	No data	FDA 2019
	Cancer		
HHS	Carcinogenicity classification	Known to be human carcinogens	NTP 2016
EPA	Carcinogenicity classification (Inhalation)	B1[d]	IRIS 1998
	Carcinogenicity classification (oral)	I	EPA (1991)
IARC	Carcinogenicity classification	Group 1[e]	IARC 2012
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards and construction	0.2 µg/m^3	OSHA 2018c 29CFR1910.1024
	STEL (15 minutes)	2 µg/m^3	OSHA 2018c 29CFR1910.1024
	Acceptable ceiling concentration-beryllium and beryllium compounds	5 µg/m^3	OSHA 2018b 29CFR1910.1000 Table Z-2
	Acceptable maximum peak above the acceptable ceiling concentration for an 8-hour shift for a max duration of 30 minutes-beryllium and beryllium compounds	25 µg/m^3	OSHA 2018b 29CFR1910.1000 Table Z-2

Table 7-1. Regulations and Guidelines Applicable to Beryllium

NIOSH	REL (up to 10-hour TWA)	0.5 µg/m^3	NIOSH 2019
ACGIH	TLV (9-hour TWA)	0.005 µg/m3	OSHA 2018a
	Emergency Criteria		
AIHA	ERPGs		AIHA 2016
	ERPG-1	NA[f]	
	ERPG-2	25 µg/m^3	
	ERPG-3	100 µg/m^3	
EPA	AEGLS-air	No data	AEGLs 2018
DOE	PACs-air		DOE 2018
	Beryllium		
	PAC-1	0.0023 mg/m^3	
	PAC-2	0.025 mg/m^3	
	PAC-3	0.1 mg/m^3	
	Beryllium chloride		
	PAC-1	0.02 mg/m^3	
	PAC-2	0.22 mg/m^3	
	PAC-3	0.89 mg/m^3	
	Beryllium fluoride		
	PAC-1	0.012 mg/m^3	
	PAC-2	0.13 mg/m^3	
	PAC-3	0.52 mg/m^3	
	Beryllium hydroxide		
	PAC-1	0.011 mg/m^3	
	PAC-2	0.12 mg/m^3	
	PAC-3	0.48 mg/m^3	
	Beryllium nitrate		
	PAC-1	0.047 mg/m^3	
	PAC-2	0.52 mg/m^3	
	PAC-3	2.1 mg/m^3	
	Beryllium oxide		
	PAC-1	0.0063 mg/m^3	
	PAC-2	0.069 mg/m^3	
	PAC-3	0.28 mg/m^3	

[a]RfC: The RfC is based on a LOAEL of 2.0x10^{-4} mg/m^3 for sensitization and progression to chronic beryllium disease identified in the co-principal studies by Kreiss et al. (1996) and Eisenbud et al. (1949).
[b]DWEL: A lifetime exposure concentration protective of adverse, non-cancer health effects that assumes all of the exposure to a contaminant is from a drinking water source.
[c]RfD: The RfD is based on a BMD_{10} of 0.46 mg/kg-day for small intestinal lesions identified in a dog dietary study by Morgareidge et al. (1976).
[d]B1: probable human carcinogen. Despite being classified a B1 carcinogen for the inhalation route, beryllium is regulated by EPA as a noncarcinogen because of a classification of Inadequate information (I) for the oral exposure route.
[f]I: Inadequate information
[f]Group 1: carcinogenic to humans

AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; CFR = Code of Federal Regulations; HHS = Department of Health and Human Services; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; GRAS = Generally Recognized As Safe; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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Zorn H, Stiefel T, Porcher H. 1986. Clinical and analytical follow-up of 25 persons exposed accidentally to beryllium. Toxicol Environ Chem 12(3-4):163-171. https://doi.org/10.1080/02772248609357156.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public.

They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s): Beryllium and Compounds
CAS number(s): 7440-41-7
Date: January 2022
Profile status: Draft for Public Comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of a provisional acute-duration inhalation MRL.

Rationale for Not Deriving an MRL: There are insufficient data for derivation of a provisional acute-duration inhalation MRL. The animal studies identify serious LOAELs which are not suitable for deriving MRLs, the lowest LOAEL was 0.184 mg/m^3 (Schepers 1964). This was a serious LOAEL, as 2/3 of the monkeys died at this dose.

Agency Contacts (Chemical Manager): Rae T. Benedict, PhD

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s): Beryllium and Compounds
CAS number(s): 7440-41-7
Date: January 2022
Profile status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of a provisional intermediate-duration inhalation MRL. Derivation of an intermediate-duration inhalation MRL is precluded because there are no human intermediate-duration studies. The Lowest LOAEL is a serious LOAEL for metaplasia and granulomas of lung at 0.035 mg/m^3 (Schepers 1957) in rats. Less serious LOAELs identified in Muller et al. (2011) are not suitable for setting an MRL since each study only tested one concentration level and none had identified a NOAEL for any of the endpoints examined including respiratory and immunological. Thus, making it inappropriate to derive an MRL from animal data.

Rationale for Not Deriving an MRL: There are insufficient data for derivation of a provisional intermediate-duration inhalation MRL.

Agency Contacts (Chemical Manager): Rae T. Benedict, PhD

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s): Beryllium and Compounds
CAS number(s): 7440-41-7
Date: January 2022
Profile status: Draft for Public Comment
Route: Inhalation
Duration: Chronic
Provisional MRL: 0.001 µg/m^3 (0.0036 ppb)
Critical Effect: Beryllium Sensitization
Reference: Schuler et al. 2012
Point of Departure: LOAEL of 0.04 µg/m^3
Uncertainty Factor: 30 (10 for use of a LOAEL and 3 for human variability)
LSE Graph Key: 22
Species: Human

MRL Summary: A provisional chronic-duration inhalation MRL of 0.001 µg/m^3 was derived for beryllium based on evidence of beryllium sensitization in humans following occupational exposures to beryllium for up to six years (Schuler et al. 2012). The provisional MRL is based on a LOAEL of 0.04 µg/m^3 for beryllium sensitization and a total uncertainty factor of 30 (10 for use of a LOAEL and 3 for human variability due to subpopulation of genetically susceptible workers).

Selection of the Critical Effect: The long-term studies that evaluated inhalation exposure to beryllium are primarily occupational epidemiology studies. Madl et al. (2007) examined exposure-response relationships for beryllium sensitization and chronic beryllium disease (CBD) in workers exposed to beryllium. Results showed, that within a given year of their work history, beryllium-sensitized and CBD workers were exposed to beryllium concentrations greater than 0.2 µg/m^3 (95th percentile). However, the average of the non-process area samples for the 17.6 year period was 0.04 µg/m^3 (Table A-1). Two earlier studies, Cullen et al. (1987) and Kreiss et al. (1996) also observed health effects (BeS) at 1.2 and 0.55 µg/m^3. These studies are not included in the LSE tables as the exposure measurements are not sufficient for inclusion (they are summarized in Chapter 2). Schuler et al. (2012) evaluated exposure-response relationships for beryllium sensitization and chronic beryllium disease in workers with 6 or less years of beryllium exposure. The authors reported no cases of beryllium sensitization among workers with average respirable concentrations of <0.04 µg/m^3 and observed cases of chronic beryllium disease among workers with respirable cumulative concentrations of <0.33 µg/m^3-year. Sensitization prevalence was 9.8% and CBD prevalence was 2.3%.

Table A-1. Summary of Relevant NOAEL and LOAEL Values Considered for Derivation of a Chronic Inhalation MRL for Beryllium

Species	Exposure Duration	NOAEL µg/m^3	LOAEL µg/m^3	Effect[b]	Reference/ Chemical Form
Respiratory					
Humans	Occupational, average 17.6 years		0.04[a]	Chronic beryllium disease (CBD) diagnosed	Madl et al. 2007 beryllium metal
Humans	Occupational, average 12.6 years		1.2[a]	Breathing difficulties, scarring of the lung	Cullen et al. 1987 beryllium alloy
Humans	Occupational, average 12.6 years		0.52 [a]	CBD	Cullen et al. 1987 beryllium alloy
Humans	Occupational, NS		0.2[a] [c]	BeS and CBD diagnosed (Median concentration among BeS and CBD)	Kreiss et al. 1996 beryllium oxide
Humans	Occupational, ≤6 years (median of 1.75 years)		0. 17[a]	CBD case observed with average exposure concentration	Schuler et al. 2012 beryllium metal, oxide, and beryllium-copper alloy
Immunotoxicity					
Humans	Occupational average 17.6 years		0.4	BeS diagnosed (95th percentile of exposure concentration, among BeS and CBD workers)	Madl et al. 2007 beryllium metal
Humans	Occupational average 12.6 years		0. 52	Increased T-cell activity	Cullen et al. 1987 beryllium alloy
Humans	Occupational ≤6 years (median of 1.75 years)		0. 04	BeS case observed with average exposure	Schuler et al. 2012 beryllium metal, oxide, and beryllium-copper alloy

[a]Denotes a serious lowest observed adverse effect level (SLOAEL)
[b]Unless otherwise noted, effects were observed at average exposure levels
[c]Denotes exposure converted into Be fraction by applying a ratio conversion factor (i.e., beryllium oxide is comprised 36.03% of beryllium and multiplied by exposure)

Selection of the Critical Effect and Principal Study: Schuler et al. (2012) is chosen as the principal study and beryllium sensitization is the critical effect. The selection was made because Schuler et al. (2012) established the lowest LOAEL (at 0.04 µg/m^3) that did not cause a serious LOAEL and the study measured respirable air concentrations which are important for deposition of beryllium into the lungs through breathing.

Summary of the Principal Study:

Schuler CR, Virji MA, Deubner DC, Stanton ML, Stefaniak AB, Day GA, Park JY, Kent MS, Sparks R, Kathleen K 2012 Sensitization and chronic beryllium disease at a primary manufacturing facility, part 3: exposure–response among short-term workers Scand J Work Environ Health 2012;38(3):270-281

The study population consisted of workers who were employed in 1999. The study population was limited to those workers who were not employed at the facility before January 1993 and had no known previous work beryllium exposure. The participation rate was almost 91% with 264 out of 291 eligible. Workers completed a work history questionnaire and were evaluated for beryllium sensitization and chronic beryllium disease. Individual estimates of average, cumulative, and highest job exposures for total, respirable, and submicron beryllium mass concentrations were developed from the work history of each participant where:

- Average Exposure (µg/m^3) = time-weighted average annual exposure of all jobs in the employee's work history;
- Cumulative Exposure (µg/m^3/year) = exposure levels for each job worked, multiplied by number of years at that job, summed over all jobs in the work history; and
- Highest Job Exposure (µg/m^3) = exposure level for each participant's single job with the highest mean exposure.

Of the 264 participants, 26 were diagnosed with beryllium sensitization and six of those with chronic beryllium disease. Individuals were considered sensitized if they had ≥2 abnormal BeLPT during the 1999 survey, or if they had abnormal test results in the pre-1999 testing. An increase in sensitization prevalence was reported as exposure quartile increased. For average respirable beryllium, the quartiles included (<0.06, 0.06-0.42, 0.43-1.02, and 1.03-3.56 µg/m^3. Among the quartiles, based on a Cochran-Armitage test for trend (exact) P was less than 0.05 for total mass of beryllium and between 0.05 and 0.1 for respirable beryllium. Beryllium sensitization was observed when respirable beryllium concentrations were 0.04 µg/m^3 for average and highest job categories.

Selection of the Point of Departure for the MRL: The provisional chronic-duration inhalation MRL for beryllium was calculated using the reported LOAEL of 0.04 µg/m^3.

Adjustment for Intermittent Exposure: *Not applicable*

Human Equivalent Concentration: *Not applicable*

Uncertainty Factors: The NOAEL was divided by 30:

- 10 for use of a LOAEL
- 3 for human variability as study included sensitive population of genetically susceptible workers that could develop beryllium sensitization and chronic beryllium disease.

Provisional MRL = LOAEL ÷ (UF_1 x UF_2)

0.04 µg /m^3 ÷ (10 x 3) = 0.001 µg/m^3 (0.000001 mg/ m^3, 0.0036 ppb)

Other Additional Studies or Pertinent Information that Lend Support to this MRL:

A case control study and community study support the MRL. Confirming the LOAEL value of 0.04 µg/m^3 , Viet et al. (2000) assessed exposure-response relationships in a case control study of workers at the Rocky Flats nuclear production facility. BeS cases were classified if either two BeLPT results were positive, either by two consecutive draws or two different lab analyses of the same draw. BeS cases were observed at 0.036 µg beryllium/m^3 with CBD occurring at mean exposure levels of 0.07 µg/m^3. Furthermore, the derived MRL of 0.001 µg/m^3, a value likely to be without appreciable risk of adverse health effects, is below the concentrations found to have an effect in a community study by Maier et al. (2008). Maier et al. (2008) studied a community that lived near a beryllium manufacturing facility. This study found that beryllium exposures were 0.0155 to 0.028 µg/m^3 based on ambient air sampling in 1958. CBD was found in residents that resided around the plant (within 1.5 miles) who were not workers at the plant or family members of workers (Maier et al. 2008).

Agency Contacts (Chemical Managers): Rae T. Benedict, PhD

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s): Beryllium and Compounds
CAS number(s): 7440-41-7
Date: January 2022
Profile status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of a provisional acute-duration oral MRL.

Rationale for Not Deriving an MRL: The available data on the acute-duration toxicity of ingested beryllium are from lethality studies in rats and mice, and several older studies lacked control groups (these are no longer presented on the LSE table). Ashby et al. (1990) identified a serious LOAEL (death) at 140 mg/kg/day. El-Beshbishy et al. (2012) identified less serious LOAELs at 9.8 mg/kg/day at several endpoints, however since this study one tested one dose level and identified no NOAELs, these endpoints are not suitable for deriving a provisional acute-duration oral MRL.

Agency Contacts (Chemical Manager): Rae T. Benedict, PhD

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s): Beryllium and Compounds
CAS number(s): 7440-41-7
Date: January 2022
Profile status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of a provisional intermediate-duration oral MRL.

Rationale for Not Deriving an MRL: The available data from intermediate-duration studies have identified several effects including hematological (hypoplasia of bone marrow), gastrointestinal, and musculoskeletal (rickets) endpoints as critical targets of beryllium toxicity (Morgareidge et al. 1976; Guyatt et al. 1933; Jacobson 1933; Kay and Skill 1934). The hematological findings by Morgareidge et al. 1976 also reported death (2/10) at the same dose of 12 mg/kg/day, so it is not possible to derive an MRL based on that dose. The gastrointestinal effects have never been substantiated. The musculoskeletal effect of rickets is not considered a direct effect from Be exposure. Rather, the rickets are due to a phosphorus deficiency, which is hypothesized to result from the precipitation of beryllium with dietary phosphorus in the acidic environment of the digestive tract (Kay and Skill, 1934). Additionally, these effects have only been observed following exposure to beryllium carbonate.

Agency Contacts (Chemical Manager): Rae T. Benedict, PhD

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s): Beryllium and Compounds
CAS number(s): 7440-41-7
Date: January 2022
Profile status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL.

Rationale for Not Deriving an MRL: No adverse effects were observed in rats exposed to 31 mg/kg/day beryllium sulfate in the diet (Morgareidge et al. 1975). Schroeder and Mitchener (1975a,b) exposed rats (females 0.7 and males 0.6 mg/kg/day) and mice (1 mg/kg/day) to beryllium sulfate in drinking water without observing significant adverse effects. Morgareidge et al. (1976) conducted a chronic dog feeding study in which groups of five male and five female dogs were exposed to beryllium sulfate in the diet for 143–172 weeks. The highest dose group (500 ppm or 12 mg beryllium/kg/day for males and 17 mg beryllium/kg/day for females) was discontinued between 26 and 33 weeks due to high morbidity and mortality, resulting in an intermediate rather than a chronic duration for this portion of the study. Findings for the highest dose group have been categorized in the profile as intermediate instead of chronic exposure duration effects. Of the remaining dose groups, ulcerative lesions were observed in 1 of 10 dogs exposed to 50 ppm (1 mg beryllium/kg/day). No gastrointestinal effects were observed at the lower dose levels. After a portion of the study was re-categorized as intermediate due to the early deaths, there is no longer a statistically significant health effect nor a clear dose-response relationship for the chronic duration portion of the Morgareidge et al. (1976) study. Therefore, it is not suitable for developing a provisional chronic duration oral MRL.

Agency Contacts (Chemical Manager): Rae T. Benedict, PhD

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR BERYLLIUM

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to beryllium.

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for beryllium. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of beryllium have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of beryllium are presented in Table B-1.

B.1 LITERATURE SEARCH AND SCREEN

Table B-1. Inclusion Criteria for the Literature Search and Screen

Health Effects
Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models

Table B-1. Inclusion Criteria for the Literature Search and Screen

Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the existing toxicological profile for beryllium (ATSDR 2002); thus, the literature search was restricted to studies published between 2000 to 2019. The following main databases were searched in May 2019:

- Science Direct
- Toxline
- PubMed
- Medline

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for beryllium. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to beryllium were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed 05/2019	(Beryllium-9[Title/Abstract] OR glucinium[Title/Abstract] OR glucinum[Title/Abstract] OR "Beryllium metallic"[Title/Abstract] OR Beryllium[Title/Abstract] OR "Beryllium dust"[Title/Abstract] OR "Beryllium metal"[Title/Abstract] OR "Beryllium, metal powder"[Title/Abstract] OR "Beryllium (metal) "[Title/Abstract]) OR 7440-41-7[EC/RN Number]) OR "beryllium"[MeSH Terms]) OR "beryllium"[Supplementary Concept] Filters: Publication date from 2000/01/01
Toxline 05/2019	(Beryllium-9 OR glucinium OR glucinum OR "Beryllium metallic" OR Beryllium OR "Beryllium dust" OR "Beryllium metal" OR "Beryllium, metal powder" OR "Beryllium (metal)" OR 7440-41-7)
Science Direct 05/2019	TI/AB (beryllium OR 7440-41-7 OR beryllium-9 OR "beryllium metallic" OR glucinium OR "beryllium metal")
Medline 05/2019	MH "Beryllium" OR AB (Beryllium-9 OR glucinium OR glucinum OR "Beryllium metallic" OR Beryllium OR "Beryllium dust" OR "Beryllium metal" OR "Beryllium, metal powder") OR AB "Beryllium (metal) " OR RN 7440-41-7

[a]Several versions of the TSCATS database were searched, as needed, by CASRN including TSCATS1 via Toxline (no date limit), TSCATS2 via https://yosemite.epa.gov/oppts/epatscat8.nsf/ReportSearch?OpenForm (date restricted by EPA receipt date), and TSCATS via CDAT (date restricted by 'Mail Received Date Range'), as well as google for recent TSCA submissions.

The May 2019 results were:
• Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 4,590
• Number of records identified from other strategies: 1
• Total number of records to undergo literature screening: 4,591

B.1.2 Literature Screening

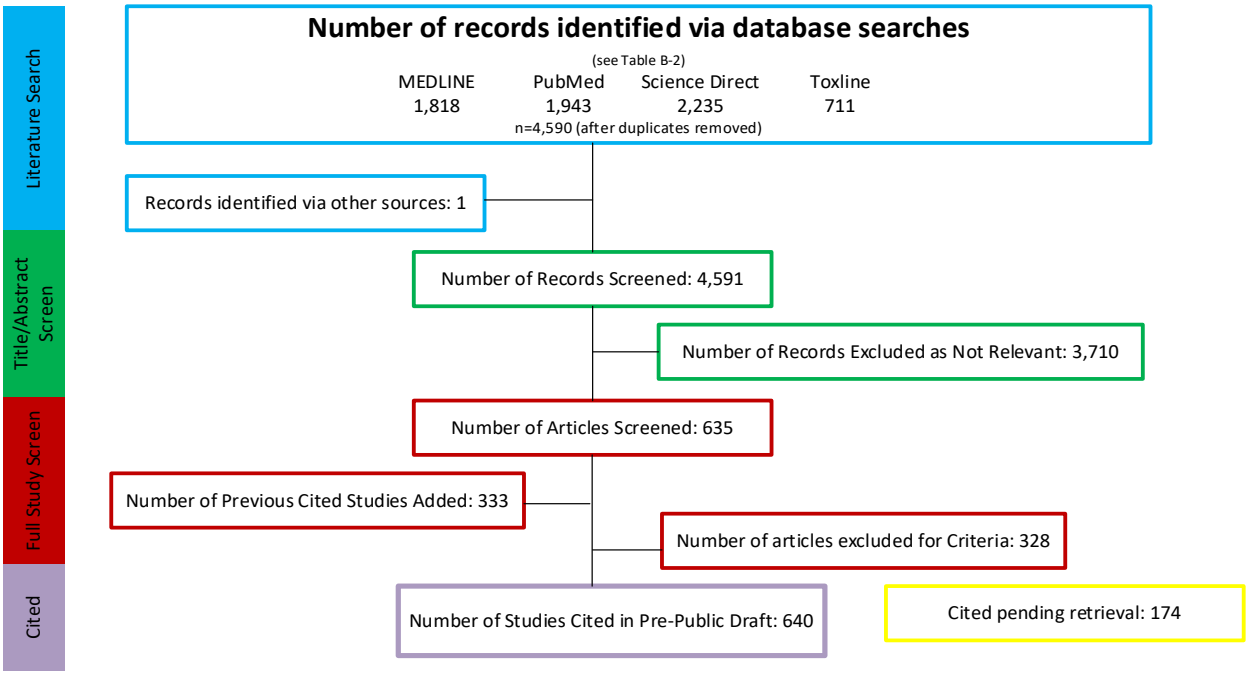
A two-step process was used to screen the literature search to identify relevant studies on beryllium:
• Title and abstract screen
• Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.
• Number of titles and abstracts screened: 4,591
• Number of studies considered relevant and moved to the next step: 635

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.
• Number of studies undergoing full text review: 635
• Number of studies cited in the pre-public draft of the toxicological profile: 640
• Total number of studies cited in the profile: 640

Present a summary of the results of the literature search and screening in Figure B-1.

Figure B-1. May 2019 Literature Search Results and Screen for Beryllium



APPENDIX C. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints 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?

Minimal Risk Levels (MRLs)

Where sufficient toxicological information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. 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. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page C-5)

1) **Route of exposure.** One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

2) **Exposure period.** Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

3) **Figure key.** 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 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

4) **Species (strain) No./group.** The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

5) **Exposure parameters/doses.** The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a more

complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

6) **Parameters monitored.** This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), urinalysis (UR), and water intake (WI).

7) **Endpoint.** This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

8) **NOAEL**. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

9) **LOAEL.** A LOAEL is the lowest dose used in the study that caused an adverse 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 endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

10) **Reference.** The complete reference citation is provided in Chapter 8 of the profile.

11) **Footnotes.** Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page C-6)

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

13) **Exposure period.** The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

14) **Endpoint.** These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

15) **Levels of exposure.** Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m3 or ppm and oral exposure is reported in mg/kg/day.

16) **LOAEL**. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

17) **CEL**. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

18) **Key to LSE figure.** The key provides the abbreviations and symbols used in the figure.

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

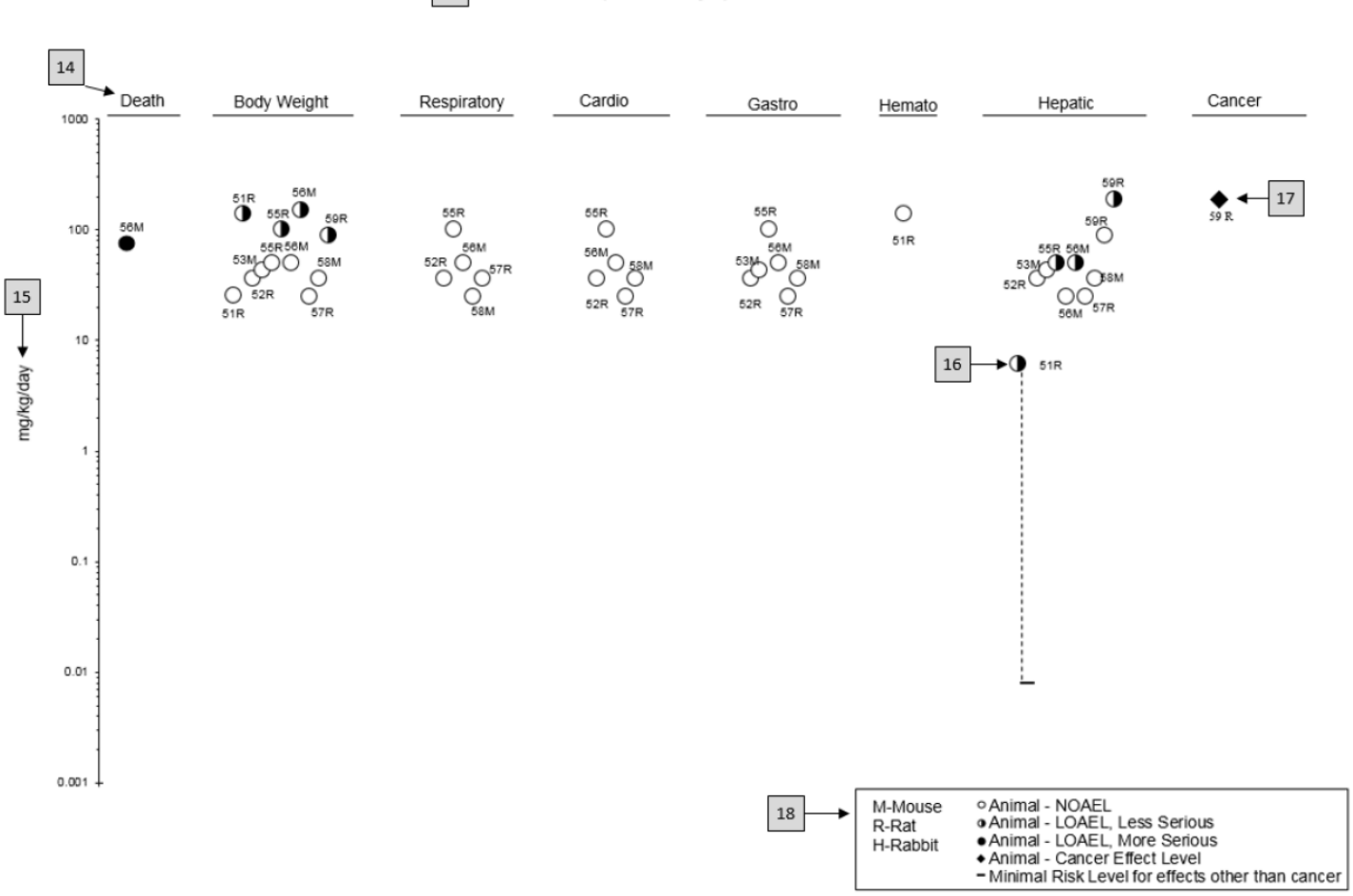
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

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

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:
Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

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

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

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

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

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

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX E. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Allele—One of two or more versions of a gene. An individual inherits two alleles for each gene, one from each parent. If the two alleles are the same, the individual is homozygous for that gene. If the alleles are different, the individual is heterozygous. Though the term allele was originally used to describe variation among genes, it now also refers to variation among non-coding DNA sequences.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

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 effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and 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)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

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

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

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

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ABD	Acute beryllium disease
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BeLPT	Beryllium lymphocyte proliferation test
BeS	Beryllium sensitization
BMD/C	benchmark dose or benchmark concentration
BMDx	dose that produces a X% change in response rate of an adverse effect
BMDLx	95% lower confidence limit on the BMDx
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CBD	Chronic beryllium disease
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency

ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard

NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SLOAEL	serious lowest-observed-adverse-effect level
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory

TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
µg	microgram
µm	micrometer
µM	micromole
q1*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result