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

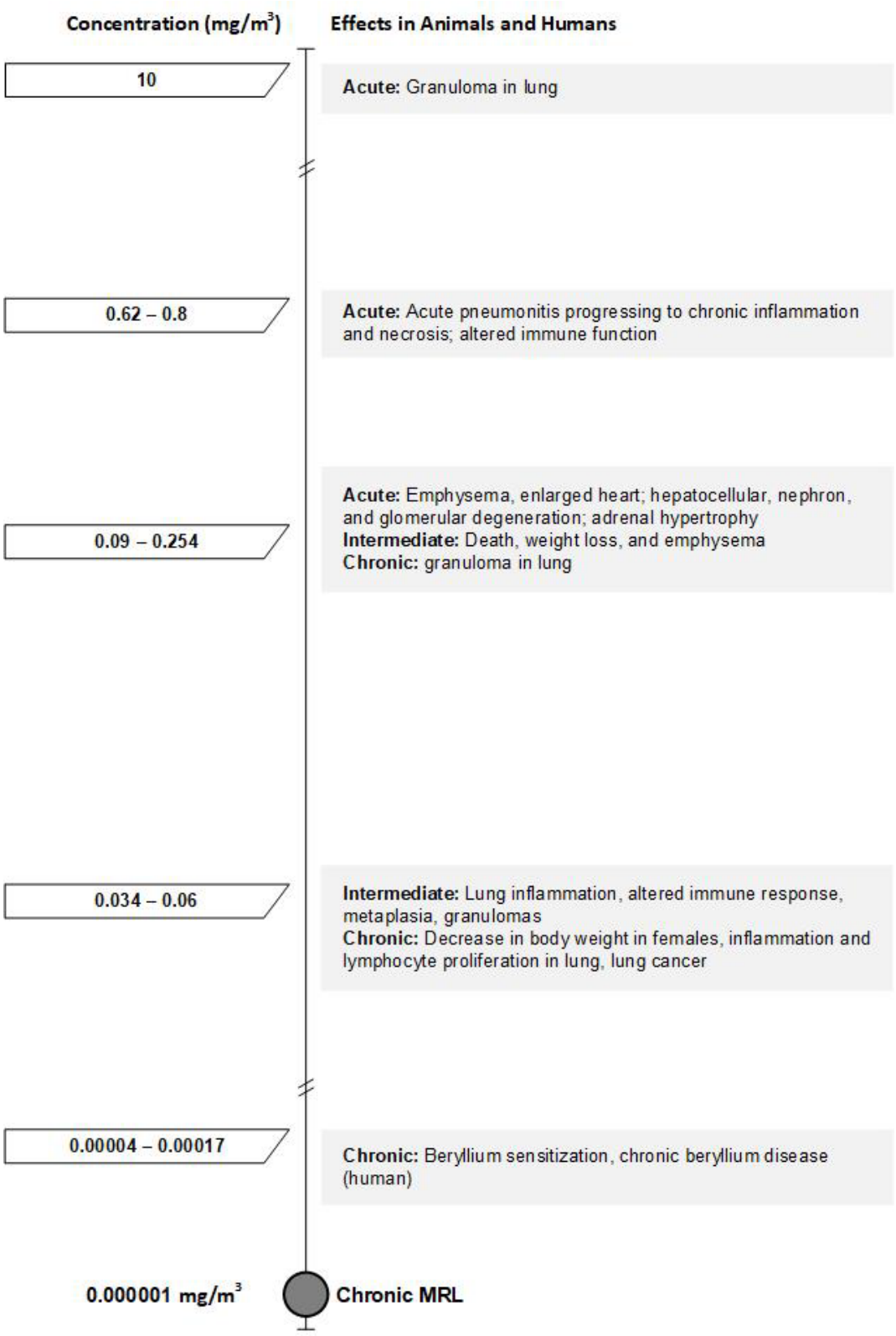
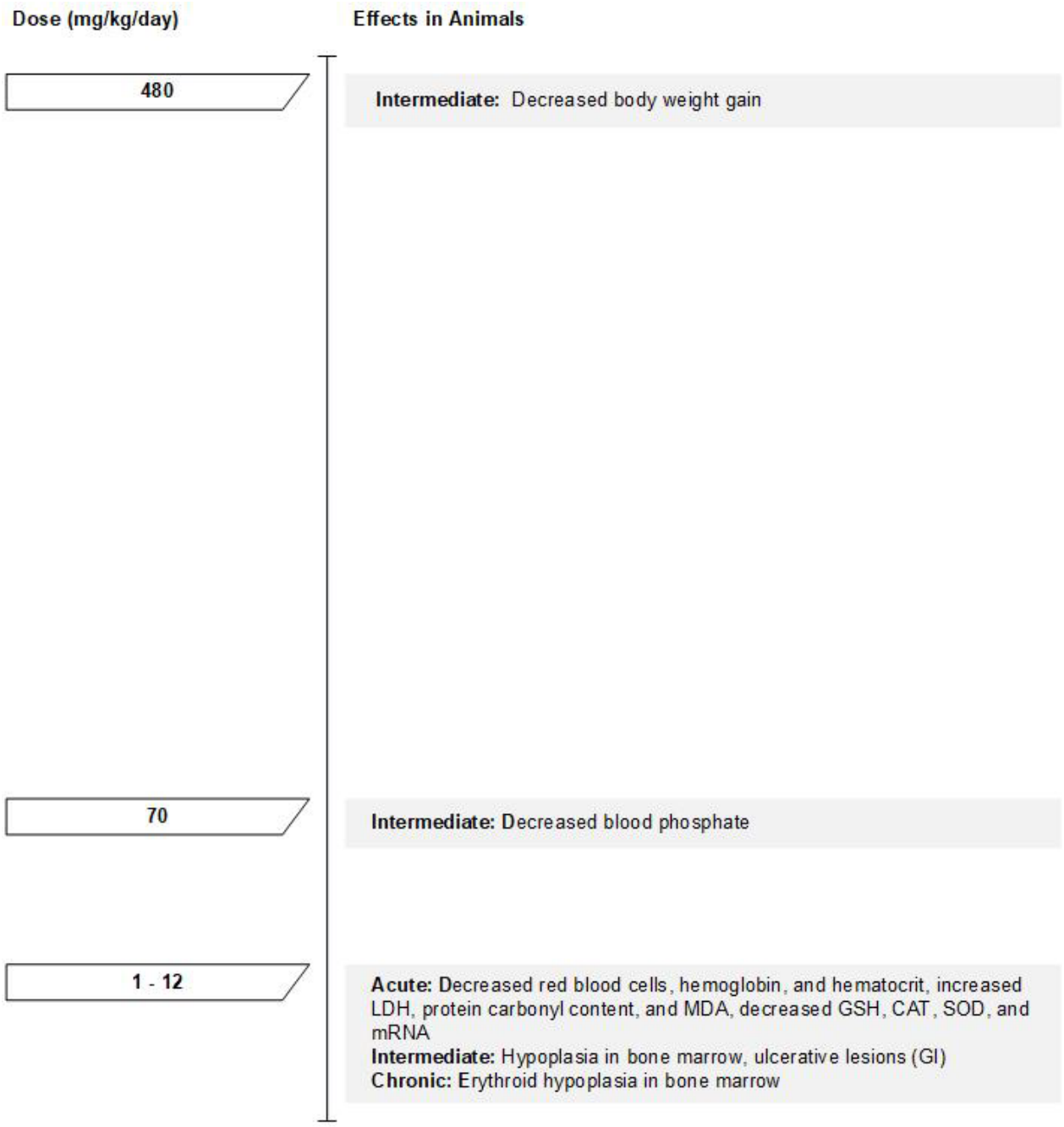


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Beryllium



1.3 MINIMAL RISK LEVELS (MRLS)

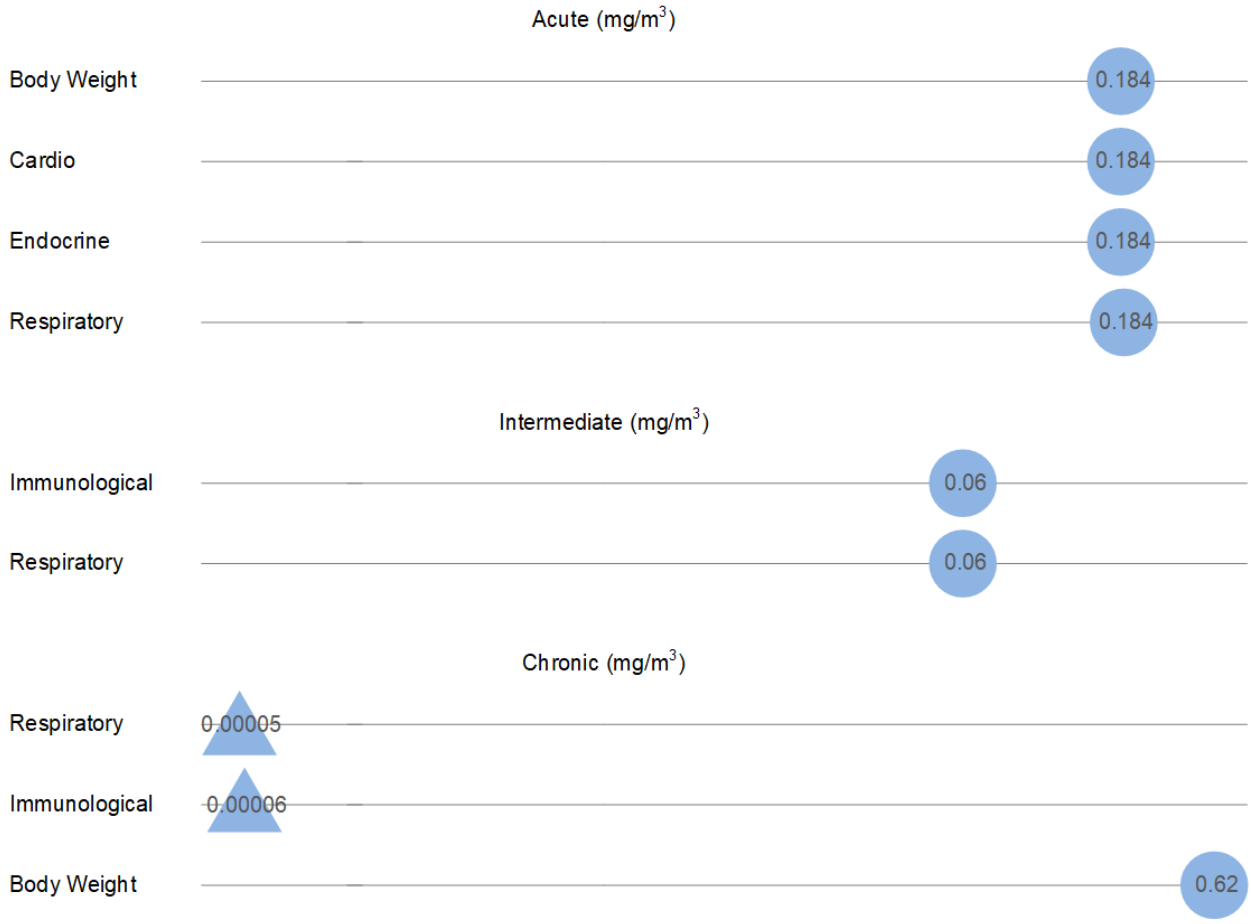
Based on the available human and animal data, the respiratory tract is the critical target of beryllium after inhalation exposures. However, except for the chronic duration, available data were deemed insufficient for deriving inhalation MRLs. The existing animal database is inadequate for developing 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.

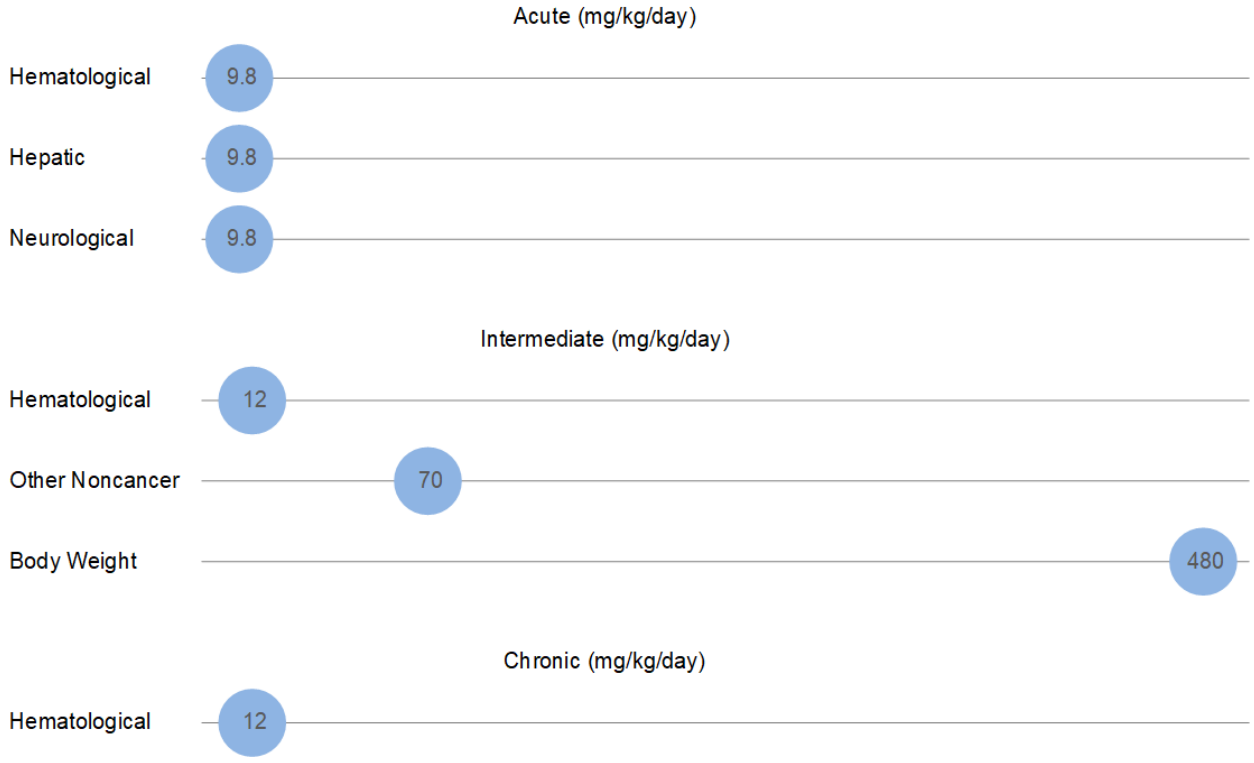


Table 1-1. Provisional Minimal Risk Levels (MRLs) for Beryllium[a]

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