# 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 INFORMATION ON HEALTH EFFECTS

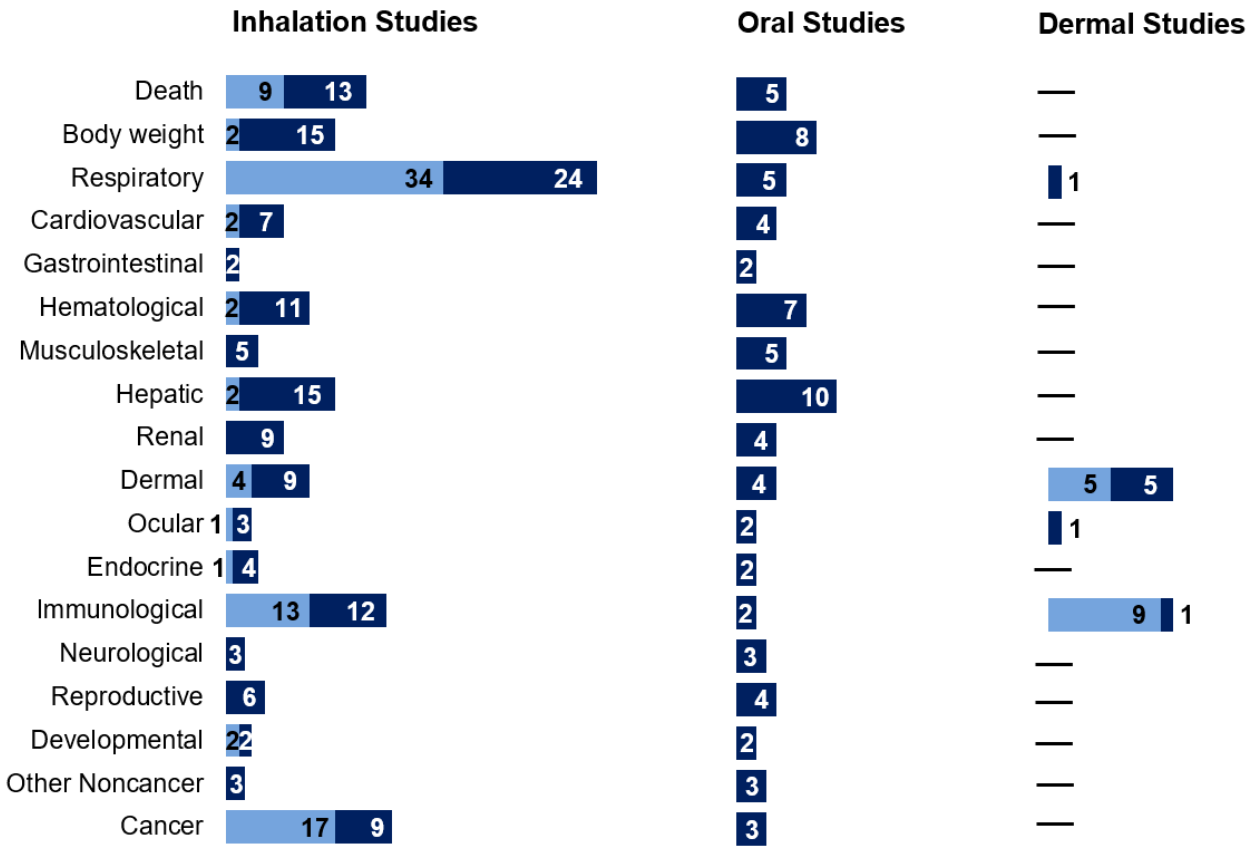
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to beryllium that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of beryllium. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

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-duration 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.

## 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 the studies examined oral exposure in **humans** (versus) **animals**




*Includes studies discussed in Chapter 2; the number of studies include those finding no effect and those that examined multiple endpoints.

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 (beryllium sensitization and CBD); however, the lack of strong, reliable data that quantify 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. $LC_{50}$ values have been reported for a number of beryllium compounds. Systemic effects of acute-, intermediate-, and chronic-duration 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 $LD_{50}$ values have been reported for many of the beryllium compounds. Only one acute-duration oral study has been undertaken to evaluate hematological, hepatic, and neurological effects from beryllium or its compounds; all of 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; Sendelbach and Witschi 1987b; Sendelbach et al. 1989). The heart, liver, kidneys, adrenal glands (Schepers 1964), skin (Stiefel et al. 1980), and 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, an acute-duration inhalation MRL was not derived. No data were located regarding effects in humans after acute-duration oral exposure to beryllium; therefore, the available acute-duration 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 effects of exposure to beryllium and its compounds would be beneficial in identifying an oral and inhalation acute-duration MRL.

No acute-duration 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; 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 beryllium sensitization and CBD after <2 weeks of exposure would be useful for establishing an acute-duration inhalation or 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-duration exposure.

**Intermediate-Duration MRLs.** Several studies indicate that the lung is the main target organ in animals for intermediate-duration 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 an intermediate-duration inhalation or oral MRL. Additional human exposure studies that examine the potential of beryllium to cause beryllium sensitization and CBD after >2 weeks but <1 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-duration 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. 1993a, 1996, 1997; Rossman et al. 1988; Stange et al. 1996b) and animals (Reeves et al. 1967; Vorwald and Reeves 1959; Wagner et al. 1969) after inhalation exposure to beryllium and its compounds. Occupational exposure to soluble and insoluble beryllium compounds caused delayed granulomatous disease of the lung, known as CBD or berylliosis (Cotes et al. 1983; Cullen et al. 1987; Eisenbud and Lisson 1983; Eisenbud et al. 1949; Kreiss et al. 1993a, 1996, 1997; Stange et al. 1996b). Studies by Kreiss et al. (1989), Donovan et al. (2007), and Mroz et al. (2009) suggest that beryllium sensitization does not always result in CBD even with ongoing exposure. It would be beneficial if future

studies addressed beryllium cohorts that have beryllium sensitization but never progress to having CBD even though they are still working in the industry. Longer-duration longitudinal studies are needed to understand the relevance of this observation.

Studies have reported beryllium sensitization and CBD after exposure to beryllium (Madl et al. 2007; Schuler et al. 2012). These studies utilized lapel sampling and adjusted for engineering controls in their study methods. Beryllium sensitization is considered a LOAEL because there is no loss of organ or system function occurring with it. CBD is a SLOAEL, as the respiratory system loses function. SLOAELs are not suitable for MRL derivation. Schuler et al. (2012) identified a LOAEL for beryllium sensitization, which is used to derive the MRL. Beryllium sensitization is reliably confirmed with multiple blood BeLPT tests and an abnormal finding in 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 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 beryllium sensitization and CBD and provide more accurate air concentration measures. Further, it would also be helpful to determine if the community members who get beryllium sensitization or CBD have one of the genetic variants or polymorphisms making them more susceptible to the effects of beryllium exposure.

A well-designed chronic-duration inhalation study in rats and mice that 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-duration oral exposure to beryllium. The Morgareidge et al. (1976) dog study could not be used to derive a chronic-duration 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 chronic-duration oral 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.

## Health Effects.

***Cardiovascular.*** No studies were located regarding cardiovascular effects in humans after oral exposure nor in animals or humans after dermal exposure to beryllium or its compounds. Exposure to beryllium has been associated with an increase in death due to heart disease 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 effects of beryllium or its compounds from oral exposure are few, but available results from an intermediate-duration 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 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 that 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 reported significant alterations in hepatic enzyme levels and lesions (Nirala and Bhadauria 2008; Sharma and Shukla 2000; El-Beshbishy et al. 2012), while others reported no effects 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 (CDC 1983; Cullen et al. 1987; 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. 1988). 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 CBD 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 that epithelial surfaces (e.g., lung, gastrointestinal 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 also to gastrointestinal lesions.

***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- and chronic-duration 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 2,856–7,622 µmol/kg body weight beryllium sulfate via intraperitoneal injection. The study results indicated no alterations to either the nerve tissue or the brain during histological examinations. However, beryllium is not well absorbed by the gastrointestinal tract and is likely to be poorly absorbed 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 and Mathur 1994; Mathur et al. 1987b; 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 tetrahydrate 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 tetrahydrate 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 tetrahydrate 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. 1987b). 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. 1978; 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 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 SNPs associated with beryllium 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 beryllium sensitization 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 beryllium-specific $CD4^+$ T cells primarily occur in the lung, although other organ systems may be involved (Fontenot and Kotzin 2003).

The studies reviewed suggest a need of using beryllium-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 also serve to identify novel pathways

and directions that can be brought back to studies using cells isolated from human subjects. Available data suggest 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 beryllium sensitization 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 Sections 2.5 and 2.19 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 et al. 1974; Foreman et al. 1970; IARC 1980; Martinsen and Thomassen 1986; Xiao-Quan 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. 1988). 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 (LPT) 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-duration exposure to beryllium can result in decreased lung function (Andrews et al. 1969; CDC 1983). This decrease can be measured by spirometry such as $FEV_1$ or FVC (Andrews et al. 1969; Kriebel et al. 1988a, 1988b). 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 BAL are sensitive in confirming CBD in symptomatic individuals (Rossman et al. 1988). The LPT 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). No studies evaluating dermal absorption were located in the literature; dermal absorption is expected to be low as is the case with many metals (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 found 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 and is likely to be poorly absorbed 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 was 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 that 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 tetrahydrate 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. 1987b; 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.

**Environmental Fate.** Limited data on transformation rates and factors influencing transformation of beryllium and beryllium compounds in the environment were located. Reliable data regarding this is important for the assessment of human health and exposure because different beryllium compounds have differing solubilities in water and, therefore, different bioavailability.

**Bioavailability from Environmental Media.** A few studies on the uptake of beryllium in plants and aquatic organisms (see Section 5.4.1) and one *in vitro* study estimating bioavailability for humans were located (Islam et al. 2022). The uptake studies focused on bioaccumulation in biota and not percentage of beryllium bioavailable or environmental media characteristics influencing bioavailability, other than solubility. Because beryllium is ubiquitous at trace levels in the environment, it would be helpful to have

more recent biota uptake studies focusing on bioavailability, and more studies investigating bioavailability for humans exposed to environmental media contaminated with beryllium.

**Food Chain Bioaccumulation.** No studies investigating food chain bioaccumulation were located; one source reported no evidence of bioaccumulation in the food chain of humans (Fishbein 1981). Available studies reported low bioaccumulation in biota (see Section 5.4.1); it would be helpful to have studies examining food chain effects to confirm that biomagnification does not occur. Based on available data, however, there is not a significant concern of bioaccumulation in food chains.

**Exposure Levels in Environmental Media.** Beryllium is fairly well characterized in the ambient environment, including in groundwater used as drinking water sources. No data needs were identified regarding ambient levels; however, more monitoring data from beryllium mining and processing sites and near these sites would be beneficial to estimate exposure for people living in these areas. Available air and groundwater monitoring data located from these sites were limited to small sampling campaigns and may not be the most representative for reliable exposure estimations (ATSDR 2005a, 2006; Sutton et al. 2012). Stack emission monitoring would also be useful. Sediment and soil sampling campaigns from beryllium processing plants and nearby sites were also limited, and monitoring from Superfund sites generally did not include background data for comparison (ATSDR 2000, 2005a; WQP 2022). Reliable data, including consideration of local background levels of beryllium, would be useful in estimating exposure from contaminated sediment and soil.

Additionally, beryllium was frequently detected in indoor ambient air in a limited sampling campaign (Sax et al. 2006); more data investigating this is necessary in order to estimate indoor air exposure levels.

**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.

The most recent general population monitoring studies were conducted in other countries. The last cycle of NHANES that measured urinary beryllium levels was 2010; in this survey, urinary beryllium levels were below the detection limit. Reliable data collected from the general population in the United States is

necessary to estimate exposure levels in the United States, particularly because the United States is the largest producer of beryllium.

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 section above, 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 sections above, there is suggestive data that children can be exposed to beryllium *in utero* or through breast milk. Children may have an increased risk of exposure to beryllium in soil due to increased hand-to-mouth activity.

## 6.3 ONGOING STUDIES

One ongoing study was identified in the National Institute of Health (NIH) RePORTER (2022) database. This study, being conducted by Lisa Maier at National Jewish Health, is evaluating the use of multi-omics to define regulators and drivers of granulomatous inflammation and CBD; the research is funded by the National Institute of Environmental Health Sciences.