

## 2. RELEVANCE TO PUBLIC HEALTH

### 2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO BERYLLIUM IN THE UNITED STATES

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

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

### 2.2 SUMMARY OF HEALTH EFFECTS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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**2.3 MINIMAL RISK LEVELS***Inhalation MRLs*

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

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

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

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

***Oral MRLs***

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

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

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

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