ADDENDUM TO THE TOXICOLOGICAL PROFILE FOR BERYLLIUM

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ADDENDUM for BERYLLIUM
Supplement to the 2002 Toxicological Profile for Beryllium

Background Statement

This addendum to the Toxicological Profile for Beryllium supplements the profile that was released in 2002.

Toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). CERCLA mandates that the Administrator of ATSDR prepare toxicological profiles on substances on the CERCLA Priority List of Hazardous Substances. CERCLA further states that the Administrator will "establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" [Title 42, Chapter 103, Subchapter I, § 9604 (i)(1)(B)].

The purpose of this addendum is to provide to the public and federal, state, and local agencies a non-peer reviewed supplement of the scientific data that were published in the open peer-reviewed literature since the release of the profile in 2002.

Chapter numbers in this addendum coincide with the Toxicological Profile for Beryllium (2002). This document should be used in conjunction with the profile. It does not replace it.

3. HEALTH EFFECTS

3.1 INTRODUCTION

A number of epidemiology studies of current and former workers have expanded the knowledge base on beryllium sensitization and chronic beryllium disease (CBD). These studies have examined the prevalence of beryllium sensitization among workers in various industries and the relationship between duration of employment and prevalence of beryllium sensitization. The epidemiology studies also examined the progression of beryllium sensitization to CBD among workers with or without continued beryllium exposure and the worsening of symptoms in individuals with CBD. Several epidemiology studies examined the carcinogenicity of beryllium; most of these studies involved a re-evaluation of studies discussed in the beryllium toxicological profile (2002). A series of animal studies examined differences in the respiratory and immunological effects between several beryllium compounds and particle sizes; these studies also examined possible toxicokinetic differences. New information on the oral toxicity of beryllium is limited to an animal study examining male reproductive toxicity; dermal exposure studies are limited to human and animal studies evaluating the immune response.

Studies published since the toxicological profile have also provided additional information on the mechanisms of beryllium toxicity and have examined the sensitivity and specificity of the beryllium lymphocyte proliferation test which is used to diagnose beryllium sensitivity. A number of studies have looked at the possible associations between specific human leukocyte antigen genotypes or other types of polymorphisms and the susceptibility to beryllium sensitization and/or CBD.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

3.2.1 Inhalation Exposure

3.2.1.2 Systemic Effects

Respiratory Effects. Cummings et al. (2009) described two cases of acute beryllium disease in workers exposed to relatively low concentrations of soluble beryllium (e.g., beryllium fluoride). Both men worked in a metal production department involved in the operation of a reduction furnace. Most of the air samples contained <10 µg/m^3 beryllium and none exceeded 100 µg/m^3. Several months after exposure to soluble beryllium began, the workers complained of shortness of breath, chest pain, and non-productive cough. Pulmonary function tests showed decreases in forced vital capacity (FVC) and carbon

monoxide diffusing capacity (DL_{CO}); however, chest radiographs were normal. A worsening of respiratory symptoms and further decreases in FVC and DL_{CO} were noted with continued exposure, and chest radiographs were still normal. 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 which involved exposure to less soluble and insoluble beryllium compounds; the investigators did not note whether respiratory symptoms redeveloped in this worker. Eighteen months after initiation of exposure, both subjects were asymptomatic but chest radiographs and biopsies revealed non-caseating granulomas. Based on these two cases and a re-examination of historical data, Cummings et al. (2009) suggested that acute beryllium disease may be part of the continuum of CBD and that acute beryllium disease may be due to an immunological response to beryllium rather than an irritation response.

A number of studies have evaluated the prevalence of beryllium sensitization among workers at several types of facilities; 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. A summary of these studies are presented in Table 3-1. A relatively low prevalence of beryllium sensitization was found among workers at nuclear facilities (a weapons assembly site and at the Nevada Test Site) or construction workers at nuclear weapons facilities; the prevalences ranged from 1.3 to 2.3% (Mikulski et al. 2011a, 2011b; Rodrigues et al. 2008; Sackett et al. 2004; Welch et al. 2004, 2013). The increased risk of sensitization in a group of approximately 1,000 workers was 3.83 (95% confidence interval [CI] 1.04–14.03) after adjusting for age and smoking (Mikulski et al. 2011a). Another study found significantly higher employment duration among sensitized workers (Rodrigues et al. 2008). Although none of the studies provided exposure monitoring data, Rodrigues et al. (2008) noted that the risk of sensitization was significantly higher in workers involved in clean-up (odds ratio [OR] 2.68; 95%CI 1.10–6.19) or working in a building where beryllium was machined (OR 2.52; 95%CI 1.02–6.19). A similar rate of beryllium sensitization (1.1%) was found in beryllium alloy workers (Stanton et al. 2006). Beryllium can be a component of bauxite, which is the principal source of aluminum; two studies of workers at aluminum smelters reported beryllium sensitization, although the rates were very low (0.27 and 0.28%) (Nilsen et al. 2010; Taiwo et al. 2008). Nilsen et al. (2010) reported that the concentrations of respirable beryllium in two areas of the facility were 86 and 216 ng/m^3.

Table 3-1. 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			
Mikulski et al. 2011a	1,004 former workers (831 males, 173 females) at a nuclear weapons assembly site; mean employment duration was 11.2 years Workers divided into three exposure categories: virtually no exposure; rare exposure (including bystander or indirect exposure); and occasional exposure (including bystander and indirect exposure)	Beryllium sensitization 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 1.09–18.31) 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
Mikulski et al. 2011b	570 former workers at a nuclear weapons assembly site Workers divided into the same exposure categories as Mikulksi et al. (2011a)	Beryllium sensitization 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 Nonsignificant increase in sensitization in workers in occasional exposure group (OR 2.64; 95% CI 0.23–29.94) No abnormal lung function in sensitized workers
Rodrigues et al. 2008	1,786 former workers at Nevada Test Site Subcohort of 1,503 former workers, excludes females and participants with missing data Exposure potential classified by job histories and job tasks	Beryllium sensitization 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 subcohort, sensitized workers had significantly higher employment duration; 3% increased risk for developing sensitization for each additional year worked Significant higher risk of sensitization in workers involved in clean-up and working in building where beryllium was machined—OR 2.68 (95% CI 1.10–6.19) and 2.52 (95% CI 1.02–6.19) No significant difference between sensitized and nonsensitized workers (after adjusting for smoking) in lung function or chest radiographs

Table 3-1. 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 clean-up (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	Beryllium sensitization 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 significantly 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
Welch et al. 2004	3,842 former construction workers at three nuclear weapons facilities	Beryllium sensitization criteria 3; repeat sampling to confirm abnormal or borderline response with a split test CBD testing (chest radiograph, chest CT scan, lung function testes, pulmonary exercise study, and bronchoscopy with lavage and/or biopsy) in beryllium-sensitized workers	1.4% confirmed beryllium sensitization with two abnormal tests Five confirmed CBD cases (15% of beryllium sensitized workers)
Welch et al. 2013	13,810 former construction workers at nuclear weapons facilities	Beryllium sensitization 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 testes, pulmonary exercise study, and bronchoscopy with lavage and/or biopsy) in beryllium-sensitized workers	1.4% confirmed beryllium sensitization 15% of sensitized workers diagnosed with CBD

Table 3-1. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
		CBD diagnosis criteria 2	
Arjomandi et al. 2010	50 current and former workers with beryllium sensitization working at a nuclear weapons research and development facility	CBD testing physical examination, chest imaging (typically radiograph and HRCT), lung function testing, and fiberoptic bronchoscopy with BAL and transbronchial biopsies	12.5% diagnosed with CBD
		CBD diagnosis criteria 3	
Aluminum smelter			
Nilsen et al. 2010	362 workers at aluminum smelter in Norway; 31 non-exposed subjects not living near the facility	Beryllium sensitization criteria 4; repeat samples to confirm abnormal response or uninterpretable	0.28% were confirmed sensitized No signs of lung disorders
	216 ng/m^3 (respirable beryllium) in prebake room 86 ng/m^3 (respirable beryllium) in Soederberg pot room	Chest radiography and high-resolution computer tomography; lung function test (spirometry, lung volumes, carbon monoxide diffusion capacity, airway resistance)	
Taiwo et al. 2008	734 workers at aluminum smelters TWA mean 0.22 µg/m^3 (0.002–13.00 µg/m^3)	Beryllium sensitization criteria 4; repeat samples to confirm one abnormal result or borderline or uninterpretable results	0.27% were confirmed beryllium sensitized; mean beryllium exposure levels were 0.04 and 0.16 µg/m^3 in two sensitized workers
		Sensitized participants underwent CBD testing of BAL and transbronchial biopsies	Both sensitized workers were diagnosed with CBD
		CBD diagnosis criteria 1	

Table 3-1. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Beryllium oxide ceramics			
Schuler et al. 2008	136 beryllium oxide ceramics workers employed in 1992; 115 workers followed through 2003 (includes current and former workers)	Beryllium sensitization 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 production			
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	Beryllium sensitization 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 significant trend for increased beryllium sensitization prevalence and exposure levels were 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 respirable average beryllium concentration and 1.18 (95% CI 0.95–1.49) for cumulative respirable beryllium 27% of sensitized workers diagnosed with CBD (2.3% of all workers diagnosed with CBD)

Table 3-1. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
			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 average respirable beryllium concentration and 1.68 (95% CI 1.02–3.28) for cumulative respirable beryllium concentration
Rosenman et al. 2005, 2006	577 former employees at a beryllium processing facility in Pennsylvania operating from 1957 to 1978	Beryllium sensitization criteria 5; repeat sampling to confirm initial abnormal result; if the results were negative on repeat test, test was repeated 1 year later 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 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 Mean average exposures were estimated as 1.6 and 1.6 µg/m^3 for workers with beryllium sensitization and definite/probable CBD, respectively. The respective estimated cumulative exposures were 100 and 181 µg-years/m^3. In the remaining workers, the estimated mean average and cumulative exposures were 1.6 µg/m^3 and 209 µg-years/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 (pre-program group) and 290 starting employed in 2000 or later after exposure controls were put into place (program group)	Beryllium sensitization criteria 6; repeat sampling to confirm initial abnormal, borderline, or uninterpretable results	8.9% confirmed beryllium sensitization in pre-program group and 3.1% confirmed beryllium sensitization in the program group

Table 3-1. 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. 2005	144 workers at a copper-beryllium alloy facility 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	Beryllium sensitization criteria 4; split analyzed at two laboratories; follow-up samples to confirm initial abnormal, borderline, or uninterpretable results CBD diagnosis criteria 4	10/144 (7%) of workers diagnosed with beryllium sensitization. Prevalence higher in workers in rod and wire production area was not statistically significant. Workers were more likely to report incidents that may have resulted in high beryllium exposures. 6/144 (4%) diagnosed with CBD; prevalence of CBD significantly higher among workers in the rod and wire production area No significant increases in respiratory symptoms in beryllium-sensitized workers
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	Beryllium sensitization 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, 19, and 38%); 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 3-1. 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			
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)	Beryllium sensitization 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 sensitization and CBD may have had unrecognized exposures that occurred during loading and unloading beryllium-contaminated trailer vans or from handling dusty aluminum-beryllium ingots

[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 = bronchioalveolar lavage; BeLPT = beryllium lymphocyte proliferation test; CBD = chronic beryllium disease; CI = confidence interval; CT = computed tomography; EKG = electrocardiogram; FVC = forced vital capacity; FEV_1 = forced expiratory volume at 1 second; HRCT = high-resolution computed tomographic scanning; LOD = level of detection; OR = odds ratio; TWA = time-weighted average

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; Schuler et al. 2005, 2008, 2012). A study examining the relationship between employment duration and prevalence found that the highest rates were in workers exposed for <1 year; 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 (Donovan et al. 2007). 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) and a study of beryllium production workers found higher prevalences in workers exposed for <4 months (16.7%) or 4–8 months (15.0%) compared to 9.8% overall (Schuler et al. 2012). The Donovan et al. (2007) study also showed a reversion of beryllium sensitization; 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. Several studies provided some estimates of exposure levels associated with beryllium sensitization. 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) estimated that the mean average exposures for workers at a beryllium processing facility with beryllium sensitization was 1.6 μg/m^3; air levels were estimated using a daily weighted average for a specific job and the amount of time spent at that job. 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.

Studies at several types of beryllium facilities have also reported cases of CBD; see Table 3-1 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 bronchioalveolar 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 beryllium oxide ceramic workers, CBD was diagnosed in 13% of all workers with an overall mean time

between hire and CBD diagnosis of 11 years (Schuler et al. 2008). In workers at nuclear facilities, 10.5–15% of the beryllium sensitized workers were diagnosed with CBD (Arjomandi et al. 2010; Sackett et al. 2004; Welch et al. 2004, 2013). Although the incidence of beryllium sensitization is low among aluminum smelter workers and beryllium alloy workers, two studies reported that 100% of the beryllium-sensitized workers were diagnosed with CBD (Stanton et al. 2006; Taiwo et al. 2008); it should be noted that both studies combined only found beryllium sensitization in 3 of 822 workers. The prevalence of CBD was highest among beryllium production workers, particularly among machinists. The prevalence ranged from 4 to 11% (Rosenman et al. 2005; Schuler et al. 2008, 2005). Among beryllium production workers, CBD was diagnosed in 27–64.3% of the workers with beryllium sensitization (Rosenman et al. 2005; Schuler et al. 2005, 2008, 2012).

Studies by Newman et al. (2005) and Mroz et al. (2009) followed beryllium-sensitized and CBD subjects over time. In the Newman et al. (2005) 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 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 follow-up, 19% at 4 years of follow-up, and 37% at 6 years follow-up. Several studies have examined the progression of beryllium sensitization to CBD and the worsening of CBD. In a follow-up study, Mroz et al. (2009) examined 229 subjects diagnosed with beryllium sensitization and 171 subjects with CBD; the subjects were evaluated between 1982 and 2002. Among subjects who never smoked, there was a significantly greater decline in lung function and higher levels of BAL fluid markers in the CBD subjects compared to the 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). Among the CBD subjects, 19.3% progressed to needing oral immunosuppressive therapy.

Muller and associates have conducted a study in mice exposed to fine or total respirable aerosols of several beryllium compounds. The study results have been presented in several published papers (Muller et al. 2010, 2011; Salehi et al. 2008) and in an unpublished report (IRSST 2012); although the results appear to be the same, there are differences in the number of animals tested. Salehi et al. (2008) examined the effect of particle size on the pulmonary toxicity of beryllium metal. Groups of 35 C3H/HeJ male mice were nose-only exposed to 250 $\mu g/m^3$ beryllium metal as fine particles (mass median aerodynamic diameter [MMAD] of 1.5±0.15 μm) or inhalable particles (MMAD of 4.1±0.60 μm)

6 hours/day, 5 days/week for 3 weeks; a control group of 35 mice were similarly exposed to filtered air. One week after exposure termination, 30 animals/group were sacrificed; the 5 animals in the fine particle group were sacrificed 3 weeks after exposure termination. Lung inflammation was significantly higher among mice exposed to the fine particles, as compared to the inhalable particles; the inflammation scores were 2.5±0.51 (mild to moderate inflammation) and 1.9±0.56 (mild inflammation), respectively. Lung inflammation was higher in the fine particle group sacrificed at the end of the recovery period compared to those sacrificed at exposure termination, but the difference was not statistically significant. Beryllium exposure also resulted in perivascular and peribronchial mononuclear cell infiltration in the lungs; in the beryllium fine particle group, mononuclear cell infiltration was larger at the end of the recovery period than at the end of exposure. Analysis of bronchioalveolar lavage fluid showed that beryllium-exposed mice secreted significantly more interleukin (IL)-12, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α compared to controls.

In studies by Muller et al. (2010, 2011; data also reported in IRSST 2012), groups of 40 male C3H/HeJ mice were nose-only exposed to filtered air, 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) 6 hours/day, 5 days/week for 3 weeks; the beryllium concentration for the three beryllium groups was 250 µg/m^3. The mice (35/group) were sacrificed 1 week after exposure termination and histological examinations of the lungs were conducted; the remaining 5 animals/group were sacrificed after a 3-week recovery period. One week post-exposure, lung inflammation was observed in the three beryllium groups; although differences in the severity of the lung inflammation were observed between the groups, the authors did not provide a statistical analysis of these data. The histological scores for lung inflammation in the 1- and 3-week recovery groups are presented in Table 3-2. The severity of the lung inflammation was significantly greater in the mice sacrificed 3 weeks after exposure termination compared to those sacrificed 1 week after exposure termination. The highest beryllium lung burdens were found in the mice exposed to beryllium oxide (see Section 3.4.2.1 for additional information).

Table 3-2. Lung Inflammation Severity Scores in Mice exposed to Beryllium Metal, Beryllium Oxide, or Beryllium Aluminum

	No inflammation	Mild inflammation	Moderate inflammation
Sacrificed 1 week post-exposure			
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%

Table 3-2. Lung Inflammation Severity Scores in Mice exposed to Beryllium Metal, Beryllium Oxide, or Beryllium Aluminum

	No inflammation	Mild inflammation	Moderate inflammation
Sacrificed 3 weeks post-exposure			
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. 2010, 2011; IRSST 2012

IRSST (2012) also nose-only exposed groups of 35 C3H/HeJ mice to HEPA filtered air (same control group as fine particle study described above), beryllium metal (MMAD of 4.1±0.71 µm), or beryllium aluminum (MMAD 6.5±1.96 µm) 6 hours/day, 5 days/week for 3 weeks; the study also assessed a beryllium oxide group, but the particle size was similar to fine particle study and the data were collapsed with the other fine particle group. The study also involved exposure to fine particles and these data were reported in the Muller et al. (2010, 2011) papers, as well as in the IRSST (2012) paper. The target beryllium concentration was 250 µg/m^3. The mice (30/group) were sacrificed 1 week after exposure termination and histological examinations of the lungs were conducted; the remaining 5 animals/group were sacrificed after a 3-week recovery period. Lung inflammation was observed in both beryllium groups (see Table 3-3). Comparing these results to those obtained in mice exposed to fine particles (IRSST 2012; Muller et al. 2010) suggests that exposure to fine particles resulted in more severe lung damage than exposure to larger particles.

Table 3-3. Lung Inflammation Severity Scores in Mice exposed to Beryllium Metal or Beryllium Aluminum

	No inflammation	Mild inflammation	Moderate inflammation
Sacrificed 1 week post-exposure			
Controls	95.5%	4.5%	0%
Beryllium metal	22.7%	68.2%	9.1%
Beryllium aluminum	61.1%	38.9%	0%
Sacrificed 3 weeks post-exposure			
Controls	91.7%	8.3%	0%
Beryllium aluminum	0%	100%	0%

Source: IRSST 2012

Dermal Effects. In the two cases reported by Cummings et al. (2009), both workers reported a rash and skin ulcers on their wrists and forearms within 2 weeks of beginning work in the metal production operation and exposure to soluble beryllium compounds, particularly beryllium fluoride.

3.2.1.3 Immunological and Lymphoreticular Effects

In the Salehi et al. (2008) 3-week mouse study discussed in the Respiratory Effects section, significantly higher CD4 and CD8 counts were observed in splenic mononuclear cells in mice exposed to fine or inhalable beryllium metal particles than in the control group; a lower percentage of CD19 (a marker for B cells) was also observed in the beryllium-exposed groups. Other changes in splenic lymphocytes in the beryllium groups included increased in expression of cytotoxic $CD8^+$ T cells and $CD4^+$ T helper cells and an increase in IFN-γ. Significant differences in the results of beryllium lymphocyte proliferation testing were found between the beryllium-exposed mice and controls and between the mice exposed to fine beryllium particles and those exposed to inhalable beryllium particles.

In the IRSST (2012) and Muller et al. (2011) studies discussed in the Respiratory Effects section, a 3-week nose-only exposure to beryllium metal, beryllium oxide, or beryllium aluminum resulted in significant increases in the expression of IFN-γ, $CD4^+$, and $CD8^+$ and a decrease in CD19 expression in splenic mononuclear cells. With the exception of IFN-γ, which was greater in beryllium-oxide-exposed mice compared to beryllium-metal-exposed mice, there were no differences between the beryllium groups. Some cytokine levels were significantly altered in the BAL fluid, as compared to controls; these alterations consisted of an increase in IFN-γ levels in the beryllium aluminum and beryllium oxide groups, increases in IL-12 levels in the beryllium metal and beryllium oxide groups, increases in IL-2 levels in the beryllium aluminum group and decreases in IL-4 levels in all beryllium groups. As reported in IRSST (2012), significantly higher percentage of $CD4^+$ spleen lymphocytes and lower percentage of CD19 spleen lymphocytes were observed in the beryllium oxide group as compared to the beryllium metal and beryllium aluminum groups. In the BAL fluid, levels of IL-4 and TNF-α were significantly higher in the beryllium metal group compared to the other two beryllium groups, and IL-12 and INF-γ were significantly higher in the beryllium oxide groups compared to the other two beryllium groups. IRSST (2012) compared the phenotypes of spleen lymphocytes in mice exposed to 250 $\mu g/m^3$ fine and larger beryllium metal or beryllium aluminum particles 6 hours/day, 5 days/week for 3 weeks. 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.

3.2.1.7 Cancer

Several papers have been published evaluating the carcinogenicity of beryllium in beryllium workers. Most of the papers were re-evaluations of the Ward et al. (1992) cohort study and Sanderson et al. (2001a) nested case-control study conducted by NIOSH. In a study sponsored by Brush Wellman, Levy et al. (2009) re-evaluated the lung cancer mortality data from the Ward et al. (1992) study of beryllium workers from eight beryllium worker cohorts. In contrast to the approach used in the Ward et al. (1992) study, which calculated standardized mortality ratios, Levy et al. (2009) calculated hazard ratios using Cox proportional regression analysis. Cox proportional hazard analysis models were also used to examine potential confounders. Unlike the Ward et al. (1992) study, Levy et al. (2009) did not find significant differences in hazard ratios between the exposed cohorts and the reference cohorts. Additionally, no significant differences in the hazard ratios between the different dates of hires (which are considered a surrogate for exposure concentration) were found.

Levy et al. (2007b) also re-analyzed the data from the nested case-control study by Sanderson et al. (2001a). As discussed in the toxicological profile for beryllium (Agency for Toxic Substances and Disease Registry 2002), Sanderson et al. (2001a) found significant associations between lung cancer mortality and three exposure metrics (cumulative exposure, average exposure, and maximum exposure). Levy et al. (2007b) 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. (2007b) did not find significant associations between lung cancer mortality and any of the exposure metrics. Levy et al. (2007b) also noted that the mean ages at death, first employed, and termination were significantly higher in the controls, as compared to the cases.

The National Institute of Occupational Safety and Health (NIOSH) (Schubauer-Berigan et al. 2008) re-evaluated the data from Sanderson et al. (2001a) study to evaluate whether adjusting for age-at-hire and birth year (which would 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 significantly 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.

In a follow-up to the Ward et al. (1992) study, Schubauer-Berigan et al. (2011a) examined lung cancer mortality in 9,199 workers at seven beryllium facilities in the United Sates who were employed for at least 2 days between 1940 and 1969; the workers were followed through 2005. Beryllium exposure was assessed in four of the facilities (5,436 workers) 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 standardized mortality ratios (SMRs) were found for lung cancer in workers at two of the facilities (SMR 1.45; 95% CI 1.17–1.78 at Lorain facility and SMR 1.20; 95% CI 1.04–1.37 at Reading facility) and all facilities combined (SMR 1.17; 95% CI 1.08–1.28). At some facilities, the mortality rate was 64% higher than the U.S. population. In the subcohort of workers in the facilities with monitoring data, the lung cancer rates were significantly higher than the U.S. population for cumulative beryllium exposure of ≥10,300 μg/m^3-days; no significant increase in standardized rate ratios (SRRs) was observed when compared to the referent population (workers exposed to <1 μg/m^3). No significant dose-related trend between cumulative exposure levels and SRRs were found; however, a significant dose-related trend was observed when short-term workers (<1 year) were excluded. Significant increases in SMRs and SRRs were found in workers with maximum beryllium exposure levels of ≥10 μg/m^3 (the referent group for the SRR was workers with maximum beryllium exposures of <10 μg/m^3; there was little variation in the rates when short-term workers or professional workers were excluded. Adjusting for a smoking bias factor did not substantially alter the results. A significant increase in the SRR was observed for nervous system cancer among workers with an employment duration of ≥10 years and a 10-year lag (referent group was workers employed for <1 year); however, this was not significantly different from the U.S. population. When workers employed for <1 year were excluded, no relationship between nervous system cancer and cumulative or maximum beryllium exposure were found. Significant associations (increased SMR and SRR values) between beryllium exposure and urinary tract cancer were observed in workers with maximum beryllium exposures of ≥10 μg/m^3.

Bofetta et al. (2014) 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; all worked at least 1 day prior to 12/31/2009 and the earliest date of hire ranged from 1947 to 1980. 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 significant increases in deaths from all cancer types, lung cancer, and nonmalignant respiratory disease even when the workers were divided by latency and/or start date. A significant increase in deaths from uterine cancer (SMR 302.3; 95% CI 121.5–622.9) 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.

3.2.2 Oral Exposure

3.2.2.5 Reproductive Effects

Groups of five male white Swiss mice were administered 0, 93, 75, 187.50, or 375 mg/kg beryllium chloride via gavage for 5 days; animals were sacrificed 35 days after the first dose (Fahmy et al. 2008). At all doses tested, there were significant increases in the percentage of abnormal sperm.

3.2.3 Dermal Exposure

3.2.3.3 Immunological and Lymphoreticular Effects

Skin patch testing in three individuals with CBD resulted in strongly positive reactions that were characterized by erythema, induration, 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 skin biopsy obtained 2–5 weeks postexposure showed granuloma formation; the spongiosis and edema were resolved.

Toledo et al. (2011) reported 12 cases of positive results of skin patch testing with beryllium chloride (two of these cases were also reported by Lucas Costa et al. 2008). Of the 62 patients tested with a metal series, 12 had positive patch test reactions to beryllium chloride. The reactions were observed at the day 4 reading (2 days post-exposure) in three of the subjects, between days 7 and 10 in six subjects, and between days 10 and 20 in three subjects. Only one of the subjects with a positive reaction had occupational exposure to beryllium.

In a study by Tinkle et al. (2003), 0.5 M beryllium sulfate was placed on the dorsal side of the ears of groups 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, the 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.

3.3 GENOTOXICITY

Three studies have evaluated the genotoxicity of beryllium. In an *in vitro* assay, beryllium sulfate was negative (with or without metabolic activation) in the Umu test which evaluates single-strand DNA gaps or DNA fragments in *Salmonella typhimurium* (Yamamoto et al. 2002). In mice administered a single dose of ≥187.5 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 (Fahmy et al. 2008). Repeated exposure for 1, 2, or 3 weeks resulted in significant increases in chromosomal aberrations in bone marrow and spermatocytes at ≥93.75 mg/kg/day (Fahmy et al. 2008). The investigators noted that the percentage of induced chromosomal aberrations was dose- and duration-related. Significant increases in DNA strand breaks were observed in the bone marrow of mice administered ≥11.5 mg/kg/day beryllium chloride via gavage for 7 days (Attia et al. 2013); exposure to 5.75 mg/kg/day did not result in significant alterations.

3.4 TOXICOKINETICS

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

Beryllium tissue burdens were examined in mice exposed to 0 or 250 µg/m^3 beryllium as 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) 6 hours/day, 5 days/week for 3 weeks and sacrificed 1 week after exposure termination (IRSST 2012; Muller et al. 2010, 2011). 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 beryllium aluminum group as compared to the other beryllium groups. No differences in beryllium spleen, liver, kidney, or blood levels were found between the beryllium metal and beryllium oxide groups. Beryllium concentrations in the lungs were significantly different in the three beryllium groups; the highest concentration was found in the beryllium oxide group and the lowest concentration was found in the beryllium aluminum group. The lung burden was approximately 7.5 times higher in the beryllium oxide group than in the beryllium metal group and approximately 6 times higher in the beryllium metal group than in the beryllium aluminum group.

When mice were exposed (6 hours/day, 5 days/week for 3 weeks) to 250 µg/m^3 of larger particles of beryllium metal (MMAD of 4.1±0.71 µm) or beryllium aluminum (MMAD 6.5±1.96 µm), much lower concentrations of beryllium were found in the lung (IRSST 2012). The lung beryllium concentrations were approximately 12,000 and 2,000 ng/g in mice exposed to fine beryllium metal (MMAD 1.50±0.12 µm) and larger particle beryllium metal, respectively. For beryllium aluminum, the lung concentrations were 2,000 and 7,500 ng/g, respectively. Beryllium concentrations in the blood, kidneys, liver, and spleen were also higher in the mice exposed to fine particles of beryllium metal or beryllium aluminum than in the mice exposed to larger beryllium particles; statistical comparisons between the fine and larger particle burdens were not made for these tissues.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

In the Muller et al. (2010) study discussed in Section 3.4.2.1, increased levels of beryllium were found in the 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.

3.5 MECHANISMS OF ACTION

3.5.2 Mechanisms of Toxicity

A large number of studies have examined the mechanisms of beryllium toxicity; most of the studies focused on CBD. Several recent papers have extensively reviewed these mechanistic data (Amicosante and Fontenot 2006; Dai et al. 2013; Falta et al. 2010; Sawyer and Maier 2011). The following discussion is taken from these reviews with data from the primary studies added to supplement the reviews; 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. Beryllium in the lungs binds to the major histocompatibility complex (MHC) class II molecule; the binding occurs on the glutamic acid at position 69 of the human leukocyte antigen (HLA)-DP or at position 71 of the HLA-DR (Falta et al. 2010). This antigen-presenting complex (APC) is then

recognized by T cell antigen receptors (TCRs). Recent evidence suggests that the binding of beryllium to HLA-DP results in surface changes to the MHC, which interacts with the TCRs and that the TCRs do not directly interact with beryllium (Clayton et al. 2014). The TCR-activated beryllium-specific $CD4^+$ T cells clonally proliferate and secrete Type 1 helper T (Th1) cytokines—IL-2, IFN-γ, and TNF-α; the release of Th2 type cytokines have not been detected in CBD. The release of Th1-type cytokines results in macrophage activation, accumulation, and aggregation, and the development of granulomatous inflammation. $CD4^+$ T cells from the lungs of individuals with active CBD display a phenotype consistent with their differentiation into T effector memory cells that is persistent in the lungs for prolonged periods and demonstrate oligoclonal expansion of TCRs that are specific to beryllium and are compartmentalized in the lungs (Clayton et al. 2014).

There is evidence to suggest beryllium-specific $CD4^+$ T cells can also be activated independent of the B7/CD28 pathway normally provided by APCs. Two distinctive subsets of beryllium-specific T effector memory cells have been identified in the BAL fluid of CBD patients: cells that express the co-stimulatory molecule CD28 and cells that are CD28 negative. Beryllium-specific $CD28^+$ $CD4^+$ T cells in the blood are sequestered in the CBD lung where CD28 expression is down-regulated. The loss of CD28 expression correlates with increased IFN-γ expression and a decrease in IL-2 secretion (Chain et al. 2013). The $CD28^-$ $CD4^+$ T cells express HLA-DP and LFA-1 co-stimulatory surface molecules and are able to present beryllium-antigen to other T cells; thus, T cell activation and proliferation can occur in the absence of APCs. APCs appear to play an initial role in establishing sensitization and in responding to re-exposure to beryllium.

Available data suggest that beryllium increases oxidative stress in the CBD lung by directly elevating the production of reactive oxygen species (ROS) and depleting thiol antioxidants such as glutathione and cysteine. The beryllium-induced increase in ROS induced macrophage apoptosis via the activation of caspases (3-, 8-, and 9-). Unlike the macrophages, CBD BAL lymphocytes do not appear to undergo apoptosis.

Based on these mechanistic data, Sawyer and Maier (2011) proposed a pathogenic mechanism for the development of lung inflammation and granuloma formation in CBD that occur during beryllium exposure and after termination of beryllium exposure. Upon exposure, macrophages and dentritic cells in the skin and respiratory tract endocytose beryllium. HLA-DP-beryllium antigen complexes (in association with co-stimulatory molecules) are generated in response to the dissolved intracellular beryllium particles. In regional lymph nodes, the APCs activate naïve T cells via a mechanism dependent

on B7/CD28 co-stimulation. The activated naïve T cells proliferate and oligclonally expand their TCRs 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. The next step involves the down-regulation of CD28 expression and up-regulation of HLA-DP and LFA-1 expression in the beryllium-specific $CD4^+$ T cells, giving them the ability to self-present the beryllium antigen within the granuloma. Even after termination of beryllium exposure, persistent levels of beryllium are present in CBD lung granulomas. This beryllium is endocytosed by granuloma macrophages, which then undergo ROS and caspases mediated apoptosis. These apoptotic macrophages are endocytosed by other healthy macrophages resulting in a release of beryllium in a manner that promotes presentation to beryllium-specific $CD28^-$ $CD4^+$ T cells. The activated $CD4^+$ T cells proliferate and increase the production of cytokines; the cytokines in turn maintain the chronic inflammation by promoting the entry of blood mononuclear phagocytes and beryllium-specific $CD4^+$ T effector memory cells into the granuloma.

Mack et al. (2010, 2014) suggested an additional mechanism for the continued lung damage after termination of beryllium exposure. These studies found a correlation between the percentage of $CD4^+$ regulatory T cells expressing forkhead box P3 (FoxP3) in the BAL fluid and CBD disease severity. Based on these findings, the investigators suggested that the dysfunction of FoxP3-expressing $CD4^+$ regulatory T cells allowed for the development and perpetuation of an exaggerated immune response in the lungs.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Beryllium

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 $\mu g/m^3$ 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. Mice were sacrificed 1 week after exposure; a subgroup of five mice exposed to fine beryllium was sacrificed 3 weeks after exposure termination. Beryllium levels in washed hair were significantly higher in both groups of beryllium-exposed mice sacrificed 1 week post 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 post 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. As with the hair, the 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.

3.8.2 Biomarkers Used to Characterize Effects Caused by Beryllium

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. Additionally, 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 false positive rates in the four laboratories conducting the BeLPT ranged from 0.00 to 3.35%, with an average false positive rate of 1.09%. 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. 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 0.683. Test specificity, the proportion of normal tests in all patients who do not have CBD, was 0.969. 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 as beryllium sensitization were diagnosed with CBD. 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. (2008) also 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%.

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 results were found. When three borderline results were found, the positive predictive values were 83.7 and 98.3% at 1 and 10% population prevalences. When the results were one abnormal, one borderline, and one normal, the positive predictive values were 55.7 and 93.2% at 1 and 10% prevalences.

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.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

As discussed in the beryllium toxicological profile (Agency for Toxic Substances and Disease Registry (ATSDR 2002), a number of independent studies have established an increased susceptibility to beryllium sensitization and/or CBD among individuals carrying the human leukocyte antigen (HLA) DPB1 allele with a glutamic acid at position 69 of the β chain (HLA DPB Glu69). 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; 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-DBP1 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 significantly higher prevalences of HLA-DPB Glu69 homozygotes and heterozygotes among subjects with beryllium sensitization or CBD as compared to beryllium-exposed nonsensitized subjects (see Table 3-4); 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 nonsensitized 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 nonsensitized 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 3-5. 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.

Table 3-4. Risk of Beryllium Sensitization and CBD by HLA-DPB1 Glu69 Genotype in Beryllium Workers

Genotype	Odds ratio (95% CI)
Beryllium sensitization	
Homozygote	3.54 (1.29–9.51)
Heterozygote	3.28 (1.63–6.64)

Table 3-4. Risk of Beryllium Sensitization and CBD by HLA-DPB1 Glu69 Genotype in Beryllium Workers

Genotype	Odds ratio (95% CI)
CBD	
Homozygote	2.90 (1.16–7.14)
Heterozygote	6.88 (3.53–13.55)

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

Source: Rosenman et al. 2011

Table 3-5. Risk of Beryllium Sensitization 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 Glu69 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)

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

Source: Van Dyke et al. 2011b

Two studies conducted by Van Dyke (2011a, 2011b) examined the relationship between beryllium exposure and the HLA-DPB1 Glu69 genotype for beryllium sensitization or CBD. The OR for beryllium sensitization and CBD (combined) among HLA-DPB1 Glu69 carriers with beryllium exposure >0.1 $\mu g/m^3$ was 24.1 (95% CI 4.77–122). Among workers with a lifetime weighted average beryllium exposure of 2 $\mu g/m^3$, 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). No relationship between beryllium sensitization and beryllium exposure matrices were found.

Studies have also examined the frequencies of other HLA genotypes among those who were DPB1 Glu69 negative. Rosenman et al. (2011) found that among the CBD and beryllium-sensitized workers who were

DPB1 Glu69 negative, 100% were positive for DRB E71, compared to 19.2% in controls. The HLA-DPB1 Glu69 and HLA-DRB 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-DRB1*13 carriers; the prevalence in the non-sensitized workers was 15.7%, and no association was found for beryllium sensitization. Another study (Amicosante et al. 2005) found that HLA-DRP 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-DRP Phe47.

Several studies have examined whether other polymorphisms are also associated with CBD or beryllium sensitization. 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. In contrast, McCanlies et al. (2007) did not find significant associations between TNF-α-308*02 or TNF-α-238*02 carriage 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. However, Sato et al. (2007a) and Maier et al. (2001) did find relationships between TNF-α promoter polymorphisms and CBD disease severity.

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 by CCR5 polymorphism in a combined group of beryllium-sensitized and CBD subjects, associations were found between BAL lymphocyte percentages and specific 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). No differences in GCL polymorphisms were found between the controls and beryllium-sensitized subjects. 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 nonsensitized subjects.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

3.11.2 Reducing Body Burden

Johri et al. (2004) evaluated the effectiveness of three chelating agents—glutathione, 2,3-dimercapto propane sulfonic acid with sodium selenite, and D-penicillamine with sodium selenite—in reducing the beryllium body burden following an intramuscular dose with 50 mg/kg beryllium nitrate in rats. The chelating agents were administered for 3 days and the animals were sacrificed 1, 3, or 7 days later. As compared to the control group exposed to beryllium without a chelating agent, beryllium levels in the liver, kidneys, lungs, and uterus were significantly lower in the three groups receiving chelation agents and sacrificed on post-treatment day 7. The D-penicillamine with sodium selenite was the most effective in decreasing tissue beryllium levels. Higher beryllium levels were observed in in the lungs in the chelation groups as compared to the beryllium-exposed control group at sacrificed on post treatment day 1.

A series of studies conducted by Nirala and associates examined the potential of several agents on renal and hepatic toxicity in rats following a 28-day intraperitoneal exposure to beryllium nitrate. Post-beryllium administration of gallic acid (Nirala et al. 2008c; Zhao et al. 2007), propolis (Nirala et al. 2008a, 2008b, 2008c), tiron (sodium-4,5-dihydroxy-1,3-disulfonate; tiferron) (Nirala et al. 2007, 2008a, 2008b, 2009), piperine (Nirala 2007, 2008a; Zhao et al. 2007), or calcium trisodium diethylene triamine pentaacetic acid (Nirala et al. 2009) resulted in significant decreases in serum clinical chemistry parameters indicative of liver and/or kidney damage; many of these compounds also resulted in significant decreases in blood, liver, and kidney beryllium levels (Nirala et al. 2007, 2008b, 2008c). Co-administration with an adjuvant such as α-tocopherol (Nirala et al. 2007, 2009) or piperine (Nirala et al. 2007; Zhao et al. 2007) further increased the effectiveness of the therapeutic agent.

3.12 ADEQUACY OF THE DATABASE

3.12.3 Ongoing Studies

The ongoing studies on the toxicology and toxicokinetics of beryllium were listed in National Institutes of Health (NIH) Research Portfolio Online Reporting Tools (RePORTER 2014):

- Investigation by Brian Day of National Jewish Health, Denver Colorado (sponsored by the National Institute of Environmental Health Sciences [NIEHS]; project completion date: 2015) aims to examine the mechanisms by which beryllium stimulates oxidative stress in beryllium-specific CD4+ T cells by altering thiol redox status, the balance between histone acetyltransferase and histone deacetyltransferase activities that modulates inflammation and steroid sensitivity in CBD, and mechanistic approaches to treat CBD.

- Investigation by Andrew P. Fontenot of the University of Colorado, Denver (sponsored by NIEHS; project completion date: 2015) aims to elucidate the role of naturally-occurring Foxp3-expressing T regulatory cells in the progression of beryllium sensitization to CBD, to evaluate whether CD4+T cells can serve as a biomarker of disease progression and severity, and to evaluate the effects of anti-TNF-α-amAb (infliximab) on the frequency and function of beryllium-responsive CD4+T cells and naturally occurring regulatory CD4+T cells in blood and BAL of CBD patients.

- Another investigation conducted by Andrew P. Fontenot (sponsored by the National Heart, Lung, and Blood Institute; project completion date: 2018) aims to identify additional beryllium-dependent peptides which form the T-cell receptor ligand expressed on CD4+T cells in CBD patients. An additional aim of the investigation is to determine whether tetramers of the beryllium-dependent ligands can be used as biomarkers of disease progression and severity.

- A third investigation conducted by Andrew P. Fontenot (sponsored by the National Heart, Lung, and Blood Institute; project completion date: 2014) aims to develop a humanized HLA-DP2 transgenic mouse model of beryllium-induced disease.

- An investigation by Lisa A. Maier of the University of Colorado, Denver (sponsored by NIEHS; project completion date: 2015) aims to use a genome wide association study to identify genetic regions that confer risk of beryllium sensitization and CBD.

- An investigation by Lee S. Newman of the University of Colorado, Denver (sponsored by NIEHS; project completion date: 2015) aims to characterize the beryllium antigen responsible for CD4+ T cell activation.

4. CHEMICAL AND PHYSICAL INFORMATION

4.2 PHYSICAL AND CHEMICAL PROPERTIES

The vapor pressure for beryllium chloride is 1 mm Hg at 291°C (sublimes) (HSDB 2014a).

The water solubility for beryllium sulfate is 41.3 g/100 g water at 25°C. Beryllium sulfate is insoluble in alcohol (HSDB 2014b).

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

The United States is one of three countries that produce beryllium products from beryllium ores. In addition, the United States is the leading manufacturer of beryllium metals, alloys, and oxides (Welch 2012). U.S. production of beryllium was reported as 175, 120, 180, 235, and 200 metric tons in 2008, 2009, 2010, 2011, and 2012, respectively (USGS 2013). Tables 5-1 and 5-2 lists the facilities in each state that manufacture or process beryllium and beryllium compounds, respectively; the intended use, and the range of maximum amounts that are stored on site are also presented in these tables. The data, which are derived from the Toxics Release Inventory (TRI13 2014), only include certain types of facilities that were required to report; therefore, this is not an exhaustive list.

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	2, 12, 13, 14
GA	2	0	99,999	8, 14
ID	1	10,000	99,999	12
IL	3	0	99,999	8
IN	1	0	99	2, 3, 8, 11
KS	1	1,000	9,999	8
LA	2	0	999,999	1, 3, 8, 12
NC	2	0	99,999	1, 5, 14
NY	1	Not available	Not available	Not available
OH	2	10,000	99,999	7
OR	1	10,000	99,999	12
PA	1	10,000	99,999	1, 3, 9
TN	1	10,000	99,999	7, 8
TX	1	100	999	12
VA	1	10,000	99,999	9

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

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacturing Aid
12. Ancillary/Other Uses
13. Manufacturing Impurity
14. Process Impurity

Source: TRI13 2014 (Data are from 2013)

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AZ	1	1,000	9,999	1, 3, 4, 5, 9, 13
CA	1	10,000	99,999	8
FL	3	100	99,999	1, 3, 4, 5, 9, 12, 13, 14
GA	1	10,000	99,999	1, 3, 4, 5, 9, 13, 14
IL	3	100	99,999	1, 5, 7, 12
IN	7	0	99,999	1, 5, 7, 9, 12, 13, 14
KS	1	1,000	9,999	14
KY	5	10,000	99,999	1, 5, 9, 12, 13
MI	1	10,000	99,999	1, 5, 9, 13, 14
MO	1	10,000	99,999	8, 14
MT	1	10,000	99,999	1, 5, 12, 14
NC	3	1,000	99,999	1, 5, 9, 12, 14
NM	3	100	999,999	1, 3, 4, 5, 9, 12, 13, 14
OH	6	100	999,999	1, 3, 4, 5, 7, 9, 12, 13, 14
PA	3	1,000	99,999	1, 4, 5, 7, 8, 9, 13
SC	1	1,000	9,999	1, 3, 4, 5, 9, 13
TN	1	10,000	99,999	1, 5, 12
TX	6	0	99,999	1, 2, 3, 4, 5, 8, 9, 11, 12, 13, 14
UT	2	10,000	999,999	1, 4, 6, 12
WI	1	10,000	99,999	8
WV	2	10,000	99,999	1, 3, 4, 5, 9, 12, 13

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

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacturing Aid
12. Ancillary/Other Uses
13. Manufacturing Impurity
14. Process Impurity

Source: TRI13 2014 (Data are from 2013)

5.2 IMPORT/EXPORT

Approximately 70, 24, 271, 92, and 16 metric tons of beryllium were imported into the United States in 2008, 2009, 2010, 2011, and 2012, respectively (USGS 2013). These figures includes estimated beryllium content of imported ores and concentrates, oxide and hydroxide, unwrought metal (including powders), beryllium articles, waste and scrap, and beryllium-copper master alloy. In 2007, U.S. exports of beryllium-containing ores were 150 metric tons of beryllium metal equivalents (Welch 2012). Approximately 112, 23, 39, 21, and 63 metric tons of beryllium were exported in 2008, 2009, 2010, 2011,

and 2012, respectively (USGS 2013). These figures include estimated beryllium content of exported unwrought metal (including powders), beryllium articles, and waste and scrap.

5.3 USE

Using sales estimates to forecast apparent uses, approximately 42% of beryllium was used in consumer electronics and telecommunications items, 11% was estimated to be in defense-related applications, 11% was estimated to be in industrial components and commercial aerospace applications, 8% was estimated to be in energy applications, and the balance was used in appliances, automotive electronics, medical devices, and other applications (USGS 2013).

6. POTENTIAL FOR HUMAN EXPOSURE

6.2 RELEASES TO THE ENVIRONMENT

Data from the TRI on facilities that release beryllium and beryllium compounds in 2012 are shown in Tables 6-1 and 6-2, respectively (TRI13 2014).

Table 6-1. 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
CA	1	0	0	0	0	0	0	0	0
GA	2	27	0	0	2	0	27	2	29
ID	1	2	0	0	12,240	0	12,242	0	12,242
IL	3	0	0	0	0	0	0	0	0
IN	1	0	0	0	0	0	0	0	0
KS	1	5	0	0	0	0	5	0	5
LA	2	133	0	0	0	0	133	0	133
NC	2	55	0	0	0	0	55	0	55
NY	1	NA	NA	NA	NA	NA	NA	NA	NA
OH	2	6,800	0	0	0	0	6,800	0	6,800
OR	1	0	0	0	16,571	0	16,571	0	16,571
PA	1	1	16	0	0	895	17	895	912
TN	1	1	5	0	47	0	1	52	53

Table 6-1. 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
TX	1	0	0	0	499	0	499	0	499
VA	1	0	0	0	0	0	0	0	0
Total	21	7,024	21	0	29,359	895	36,349	950	37,299

[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 are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment0(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II0V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off0site, including to POTWs.

NA = not available; RF = reporting facilities; UI = underground injection

Source: TRI13 2014 (Data are from 2013)

Table 6-2. 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
AZ	1	19	0	0	6,022	0	6,041	0	6,041
CA	1	0	0	0	0	0	0	N/A	0
FL	3	60	0	0	2,596	0	2,293	363	2,656
GA	1	45	0	0	10,000	0	10,045	0	10,045
IL	3	45	12	0	37,378	0	34,240	3,195	37,435
IN	7	100	42	0	51,632	16	41,949	9,841	51,790
KS	1	6	0	0	2	0	8	0	8
KY	5	390	22	0	59,772	0	60,184	0	60,184
MI	1	19	31	0	6,203	0	6,250	3	6,253
MO	1	0	0	0	0	0	0	0	0
MT	1	20	0	0	7,910	50	7,930	50	7,980

Table 6-2. 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
NC	3	52	12	0	15,720	0	15,784	0	15,784
NM	3	32	0	0	27,185	0	27,210	7	27,217
OH	6	299	26	556	79,549	12,152	71,773	20,809	92,582
PA	3	70	1	0	10,219	0	71	10,219	10,290
SC	1	6	12	0	1,409	0	1,427	0	1,427
TN	1	11	0	0	6,147	0	6,158	0	6,158
TX	6	67	0	0	56,130	0	56,197	0	56,197
UT	2	27	0	0	77,273	273	11,214	66,359	77,573
WI	1	0	0	0	0	0	0	N/A	0
WV	2	51	0	0	24,775	0	13,826	11,000	24,826
Total	53	1,319	158	556	479,922	12,491	372,599	121,846	494,446

[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 are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI13 2014 (Data are from 2013)

6.2.1 Air

The estimated releases of 7,024 pounds of beryllium to the atmosphere from 21 domestic manufacturing and processing facilities in 2013, accounted for about 18.8% of the total estimated environmental releases from facilities required to report to the TRI (TRI13 2014). These releases are summarized in Table 6-1. Estimated releases of 1,319 pounds of beryllium compounds to the atmosphere from 53 domestic manufacturing and processing facilities in 2013, accounted for about 0.3% of the estimated total environmental releases from facilities required to report to the TRI (TRI13 2014). These releases are summarized in Table 6-2.

6.2.2 Water

Estimated releases of 21 pounds of beryllium to surface water from 21 domestic manufacturing and processing facilities in 2013, accounted for about 0.05% of the estimated total environmental releases from facilities required to report to the TRI (TRI13 2014). These releases are summarized in Table 6-1. Estimated releases of 158 pounds of beryllium compounds to the surface water from 53 domestic manufacturing and processing facilities in 2013, accounted for about 0.03% of the estimated total environmental releases from facilities required to report to the TRI (TRI13 2014). These releases are summarized in Table 6-2.

6.2.3 Soil

Estimated releases of 29,359 pounds of beryllium to land from 21 domestic manufacturing and processing facilities in 2013, accounted for about 79% of the estimated total environmental releases from facilities required to report to the TRI (TRI13 2014). These releases are summarized in Table 6-1. Estimated releases of 479,922 pounds of beryllium compounds to land from 53 domestic manufacturing and processing facilities in 2013, accounted for about 97% of the estimated total environmental releases from facilities required to report to the TRI (TRI13 2014). These releases are summarized in Table 6-2.

6.3 ENVIRONMENTAL FATE

6.3.1 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 be present in the 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).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

6.4.1 Air

Since beryllium was 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 is lower.

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).

6.4.2 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).

Beryllium was present in 14 samples from wells in the glacial aquifer system of the Northern United States out of 847 samples analyzed. Only one of the samples contained beryllium concentrations at ≥1 µg/L (USGS 2009). The U.S. Geological Survey's (USGS) National Water-Quality Assessment Program is a comprehensive study of trace elements detected in groundwater across the United States 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). Beryllium levels based on the type of aquifer unit are presented in Table 6-3. Very few detections exceeded the beryllium maximum contaminant level (MCL) of 4 µg/L.

Table 6-3. Beryllium Levels (µg/L) in Groundwater Across the United States Sampled by the National Water-Quality Assessment Program 1992–2003

	Concentration percentile (µg/L)								
Number of samples	Maximum	99th	95th	90th	75th	50th	25th	10th	Percent exceeding MCL
Unconsolidated sand and gravel aquifers									
1,318	<1	<1	<1	<1	<1	<1	<1	<1	0
Glacial unconsolidated sand and gravel aquifers									
511	1.24	<1	<1	<1	<1	<1	<1	<1	0
Semi-consolidated sand aquifers									
338	16	1.8	<1	<1	<1	<1	<1	<1	0.3
Sandstone aquifers									
258	18	4	<1	<1	<1	<1	<1	<1	0.8

Table 6-3. Beryllium Levels (µg/L) in Groundwater Across the United States Sampled by the National Water-Quality Assessment Program 1992–2003

Number of samples	Concentration percentile (µg/L)								Percent exceeding MCL
	Maximum	99th	95th	90th	75th	50th	25th	10th	
Sandstone and carbonate aquifers									
186	<1	<1	<1	<1	<1	<1	<1	<1	0
Carbonate-rock aquifers									
189	<1	<1	<1	<1	<1	<1	<1	<1	0
Basaltic- and volcanic-rock aquifers									
31	<1	<1	<1	<1	<1	<1	<1	<1	0
Crystalline-rock aquifers									
194	7.5	1.7	<1	<1	<1	<1	<1	<1	0.5

Source: USGS 2011

Leung and Jiao (2006) conducted a study to analyze the influence of urbanization on groundwater. It was found that beryllium was present in higher 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 was 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.

6.4.3 Sediment and Soil

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 A 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 areas (0.62 mg/kg), than in urban areas (0.49 mg/kg) in 2011 (Vilavert et al. 2012).

Beryllium concentrations in the sediment of the coastal Beaufort Sea ranged from 0.3 to 2.3 µg/g (Trefry et al. 2013).

6.4.4 Other Environmental Media

A smoker who intakes 20 cigarettes per day is projected to be exposed to 1.5 µg of beryllium per day (Svilar et al. 2013).

Beryllium was found in the carpets of the LLNL site, after vacuuming, at a concentration of 0.002–0.480 µg/cm^2. Beryllium concentrations in overhead dust were reported to range from 19.4 to 151 µg/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/cm^2 (Sutton et al. 2012).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

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 µg/L in the blood and 0.43 µg/L in serum. Slightly higher levels appeared in the blood and serum of smokers as compared to nonsmokers (Stephan et al. 2008).

6.6 EXPOSURES OF CHILDREN

In a study of beryllium and other metals in human breast milk, beryllium levels ranging from below the instrumentation detection limit of 0.48 ng/L to 22 ng/L (2 ng/L median) were reported in breast milk samples collected from new mothers in Sweden from 2002 to 2009 (samples obtained 2–3 weeks postpartum) (Bjorklund et al. 2012).

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

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 were 11.6 and 20.0 ng/L, respectively.

7. ANALYTICAL METHODS

7.1 BIOLOGICAL SAMPLES

The most frequently used methods for the determination of beryllium in human tissues and urine include fluorescence, gas chromatography, atomic emission, inductively coupled plasma mass spectrometry (ICP-MS), and atomic absorption spectrometry (Stephan et al. 2008).

ICP-MS is a sensitive and reliable method used to quantify beryllium and other metals in urine samples. Samples from a population of occupationally and non-occupationally exposed individuals were collected and stored. Unfrozen samples were digested 1:10 using a diluent consisting of 1% nitric acid before being analyzed using an ICP-MS with direct injection nebulization employing a flow rate of 0.87L/minute. The limit of detection was 6 ng/L (Morton et al. 2011).

ICP-MS was also used to detect beryllium in breast milk. Samples were collected and stored from new mothers 2–3 weeks postpartum. Samples were thawed at room temperature and homogenized using a mechanical shaker. Samples were digested using 2 mL of 65% nitric acid and 3 mL of deionized water and heated to 250°C for 30 minutes. Digested samples were transferred to acid washed polyethylene tubes and diluted with an additional 20 mL of deionized water. Samples were analyzed using an ICP-MS containing a collision/reactor cell system in order to minimize possible interferences. The limit of detection for this particular method was reported as 0.00048 µg/L (Bjorklund et al. 2012).

Zeeman GFAAS was used to detect beryllium levels in blood and serum samples of volunteers (Stephan et al. 2008.). Collected blood samples were diluted 8-fold using Nash reagent (dilution was 5-fold for serum samples) containing 5% (v/v) nitric acid, 5% (v/v) of ammonium hydroxide, 0.2% (v/v) Triton X-100, 0.2% (v/v) antifoam B, and 0.5% (w/v) of ethylenediaminetetraacetic acid (EDTA). Analysis by GFAAS yielded a detection limit of 7 ng/L for blood and 2 ng/L for serum samples.

Zeeman GFAAS was utilized to detect beryllium in undiluted human blood from patients in Saint Petersburg, Russia (Ivanenko et al. 2012). The purpose of this method was for the rapid quantification and clinical diagnosis of acute and chronic metal intoxication without complex sample preparation; therefore, no sample digestion using nitric acid or dilution using deionized water was performed for beryllium analysis. The limit of detection was 0.10 µg/L (Ivanenko et al. 2012).

Inductively coupled plasma-atomic emission spectroscopy (ICP-AES) was used to detect beryllium concentrations in pharyngeal tonsils removed from 379 children. The limit of detection was not quantified. The average concentration of beryllium in the tonsils was 0.016 µg/g (Nogaj et al. 2014).

8. REGULATIONS AND ADVISORIES

Table 8-1. Regulations and Guidelines Applicable to Beryllium and Compounds

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Beryllium and beryllium compounds		IARC 2015
	Carcinogenicity classification	Group 1[a]	
WHO	Air quality guidelines	No data	WHO 2010
	Drinking water quality guidelines	Not established	WHO 2011
NATIONAL			
Regulations and guidelines:			
a. Air			
ACGIH	Beryllium and compounds (as Be)		ACGIH 2014
	TLV (8-hour TWA)	0.00005 mg/m^3 [b,c]	
AIHA	ERPGs		AIHA 2014
	Beryllium		
	ERPG-1	Not appropriate	
	ERPG-2	25 µg/m^3	
	ERPG-3	100 µg/m^3	
DOE	PACs		DOE 2012
	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	0.28 mg/m^3	
	Beryllium fluoride		
	PAC-1	0.012 mg/m^3	
	PAC-2	0.13 mg/m^3	
	PAC-3	0.89 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 oxide		
	PAC-1	0.0063 mg/m^3	
	PAC-2	0.069 mg/m^3	
	PAC-3	0.28 mg/m^3	

Table 8-1. Regulations and Guidelines Applicable to Beryllium and Compounds

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
DOE *(cont.)*	Beryllium nitrate		
	PAC-1	0.047 mg/m^3	
	PAC-2	0.52 mg/m^3	
	PAC-3	2.1 mg/m^3	
EPA	AEGLs	No data	EPA 2014a
EPA	National emission standards for hazardous air pollutants—beryllium emissions to the atmosphere from rocket-motor test sites	Shall not exceed 75 µg minutes/m^3 of air within the limits of 10–60 minutes, accumulated during any 2 consecutive weeks, in any area in which an effect adverse to public health could occur	EPA 2014b 40 CFR 61.42
	National emission standards for hazardous air pollutants – combustion products from the firing of beryllium propellant are collected in a closed tank	Emissions from such tank shall not exceed 2 g/hour and a maximum of 10 g/day	
	National emission standards for beryllium		EPA 2014c 40 CFR 61.32
	Emissions to the atmosphere from stationary sources	Shall not exceed 10 g over a 24-hour period	
	Request approval from the Administrator to meet an ambient concentration limit on beryllium in the vicinity of the stationary source	0.01 µg/m^3, averaged over a 30-day period	
NIOSH	Beryllium and beryllium compounds (as Be)		NIOSH 2015
	REL (10-hour TWA)	0.0005 mg/m^3 [d,e]	
	IDLH	4 mg/m^3 [e]	
OSHA	Beryllium and beryllium compounds (as Be)		
	PEL (8-hour TWA) for general industry	2 µg/m^3	OSHA 2013 29 CFR 1910.1000 Table Z-2
	Acceptable ceiling concentration	5 µg/m^3	
	Acceptable maximum peak above the acceptable ceiling concentration for an 8-hour shift for a maximum duration of 30 minutes	25 µg/m^3	
	PEL (8-hour TWA) for construction	2 µg/m^3	OSHA 2014a 29 CFR 1926.55

Table 8-1. Regulations and Guidelines Applicable to Beryllium and Compounds

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
OSHA *(cont.)*	PEL (8-hour TWA) for shipyard	2 µg/m^3	OSHA 2014b 29 CFR 1915.1000
b. Water			
EPA	Land disposal restrictions; universal treatment standards for beryllium		EPA 2014d 40 CFR 268.48
	Waste water standard	0.82 mg/L	
	Non-waste-water standard	1.22 mg/L TCLP	
	National primary drinking water regulations for beryllium		
	MCLG	0.004 mg/L	EPA 2014e 40 CFR 141.51
	MCL	0.004 mg/L	EPA 2014f 40 CFR 141.62
	Drinking water health advisories for beryllium		EPA 2012
	1-Day (10-kg child)	30 mg/L	
	10-Day (10-kg child)	30 mg/L	
	RfD	0.002 mg/kg/day	
	DWEL	0.07 mg/L	
c. Food			
FDA	Allowable level for beryllium in bottled water	0.004 mg/L	FDA 2014 21 CFR 165.110
d. Other			
ACGIH	Beryllium and compounds (as Be)		ACGIH 2014
	Carcinogenicity classification	A1[f]	
EPA	Beryllium and compounds		IRIS 2005
	Carcinogenicity classification	B1[g]	
	RfC	2x10^{-2} µg/m^3	
	RfD	2x10^{-3} mg/kg/day	
	Health based limits for exclusion of waste-derived residues		EPA 2014g 40 CFR 266, Appendix VII
	TCLP extract concentration limit for beryllium	7x10^{-3} mg/L	
	Designation of hazardous substances and reportable quantities		EPA 2014h 40 CFR 302.4
	Beryllium and beryllium powder	10 pounds[h]	
	Beryllium chloride, beryllium fluoride, and beryllium nitrate	1 pound	

Table 8-1. Regulations and Guidelines Applicable to Beryllium and Compounds

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA *(cont.)*	Standards for management of hazardous waste – Risk specific doses (10^{-5}) for beryllium		EPA 2014i 40 CFR 266, Appendix V
	Unit risk	$2.4x10^{-3}$ $m^3/\mu g$	
	RsD	$4.2x10^{-3}$ $\mu g/m^3$	
	Toxic chemical release reporting; community right-to-know, effective date for reporting—beryllium	01/01/87	EPA 2014j 40 CFR 372.65
DHHS	Beryllium and compounds		NTP 2014
	Carcinogenicity classification	Known to be human carcinogens	

[a]Group 1: carcinogenic to humans.
[b]Inhalable fraction.
[c]Skin and dermal sensitization notations for soluble compounds; respiratory sensitization notation for soluble and insoluble compounds.
[d]Ceiling REL should not be exceeded at any time.
[e]Potential occupational carcinogen as defined by the OSHA carcinogen policy (29 CFR 1990).
[f]A1: confirmed human carcinogen.
[g]B1: probable human carcinogen.
[h]No reporting of releases of this hazardous substance is required if the diameter of the pieces of the solid metal released is larger than 100 micrometers (0.004 inches). No RQ is being assigned to the generic or broad class.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; CFR = Code of Federal Regulations; DHHS = Department of Health and Human Services; DOE = Department of Energy; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure level; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; RsD = risk specific dose; RQ = reportable quantity; STEL = short-term exposure limit; TCLP = toxicity characteristic leaching procedure; TLV = threshold limit value; TWA = time-weighted average

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