BERYLLIUM AND COMPOUNDS

CAS number: 7440-41-7 (elemental beryllium)

Empirical formula: Be (elemental beryllium)

TLV–TWA, 0.00005 mg/m^3 (0.05 µg/m^3), as Be, Inhalable particulate matter

A1 — Confirmed Human Carcinogen

SOLUBLE COMPOUNDS

Dermal Sensitizer (DSEN)

Skin

SOLUBLE AND INSOLUBLE COMPOUNDS

Respiratory Sensitizer (RSEN)

TLV® Recommendation

The critical effects associated with workplace exposure to beryllium are beryllium sensitization (BeS) and chronic beryllium disease (CBD). It is generally accepted that sensitization occurs among a subset of workers but it is not possible to identify this population in advance. Exposure assessment data from plants manufacturing or using beryllium metal, ceramics, or alloys do not provide strong differentiation between workplace exposure concentrations or calculated lifetime weighted (LTW) average exposures for workers who develop sensitization and those who do not.

A growing number of studies are providing information regarding workplace exposure levels that are associated with development of BeS and subclinical or clinical CBD. Reports of Kelleher et al. (2001) and Madl et al. (2007) showed that 10 of 27 beryllium-sensitized individuals in a beryllium machining plant had total LTW average exposures below 0.2 µg Be/m^3. Three of the cases had mean total LTW exposures between 0.05 and 0.1 µg Be/m^3, seven cases between 0.1 and 0.2 µg Be/m^3, and the remaining 17 cases above 0.2 µg Be/m^3. Therefore, a TLV–TWA of 0.05 µg Be/m^3 is expected to be protective of the beryllium-sensitive population because available data indicate very low or no incidences of beryllium sensitization or disease at this level. The studies of Stanton et al. (2006), Schuler et al. (2005) and Rosenman et al. (2005) also support this TLV–TWA. When applying this TLV–TWA, it should be kept in mind that it is based on a long-term average concentration.

Due to the potential for beryllium particles to interact with immune competent cells in the upper respiratory tract, conducting airways, pulmonary region, and GI tract (following particle clearance and swallowing), the TLV–TWA applies to inhaled beryllium particulate matter.

Schuler et al. (2005) suggest that an enhanced risk for BeS and CBD in a beryllium alloy plant was related to the percentage of samples exceeding 0.2 µg Be/m^3 total particulate mass. The exceedance fraction was 25% in job categories having significant increases in BeS and CBD compared to ≤ 7% excursions for job categories with no increased risk. While these full-shift data suggest peak exposures may be important contributors to BeS, they are inadequate to support a STEL. However, in light of this possibility, strict adherence to the guidance on excursions should minimize the risk of BeS.

RSEN and DSEN notations are assigned because of the significant body of evidence showing beryllium exposure by inhalation and dermal routes results in sensitization of lymphocytes in the blood and lung of a percentage of exposed individuals. The immune response to beryllium is cell-mediated, and data suggest that individuals sensitized to beryllium are at risk for development of CBD. There is some evidence in humans indicating that sensitization to beryllium can result from dermal exposure to soluble beryllium compounds (Curtis, 1951). Tinkle et al. (2003) have also demonstrated penetration of insoluble particles into the dermal layer of human cadaver skin and shown that skin contact with poorly soluble compounds could cause sensitization in mice. Further evidence of the importance of dermal exposure comes from recent studies reporting new cases of BeS despite the reduction in airborne levels. Therefore, a Skin notation is also assigned. Industrial hygienists are encouraged to minimize surface contamination with beryllium-containing dust in the workplace. This will help prevent dermal exposure and possible sensi-

tization by this route, possible absorption of beryllium through wounds, and inhalation of beryllium secondary to re-suspension of settled dust.

These efforts to enhance Be exposure controls by reducing or preventing dermal exposure, coupled with administrative and engineering controls (e.g., air showers) to prevent migration of Be particles, have reduced the incidence of BeS to very low levels (Deubner and Kent, 2007). Due to latency, it is too early to draw conclusions on the future incidence of CBD.

There is much controversy over interpretation of the epidemiological evaluations of the carcinogenicity of beryllium. However, there is evidence that high exposure among workers before the 1950s was associated with increased incidences of lung cancer. There is also evidence that beryllium causes cancer in animals. Therefore, an A1, Confirmed Human Carcinogen, notation for beryllium metal and compounds is assigned.

TLV® Basis

Beryllium sensitization; chronic beryllium disease (berylliosis).

Chemical and Physical Properties

Beryllium (atomic number 4, periodic table Group IIA; CAS 7740-41-7) is a gray metal. Major classes of beryllium compounds encountered industrially include beryllium fluoride [7787-49-7], beryllium hydroxide [13327-32-7], and beryllium oxide [1304-56-9]. The major beryllium-containing alloys are beryllium-copper and beryllium-aluminum alloys.

See Table 1.

Major Sources of Exposure

The current estimate is that 134,000 workers in government and private industry are potentially exposed to beryllium in the United States. As of 1996, there were only two beryllium mines in the U.S. with an estimated worker population less than 200 persons (Henneberger et al., 2004). These estimates do not include former beryllium workers in the U.S., or current or former beryllium workers worldwide (Newman et al., 2005a).

Beryllium occurs naturally as the silicate, bertrandite, and the aluminosilicate, beryl. Exposure to bertrandite and beryl dusts occurs during ore crushing and grinding; however, the ores are not considered sources of BeS (Deubner et al., 2001). Exposure to soluble beryllium salts (sulfate, ammonium carbonate, beryllium carbonate, and to a lesser extent, beryllium hydroxide) may occur during extraction of the metals from the ore (Deubner et al., 2001). These salts are considered the main potential source of sensitization during beryllium extraction.

Beryllium hydroxide is the feedstock for production of beryllium oxides, metal, and copper beryllium master alloy (4% beryllium). Beryllium oxide (BeO) is used in ceramics for resistor cores, laser tubes, and circuit chip carriers. Exposure to oxides may occur during production and machining of ceramics.

Metallic beryllium is used for structural materials in the aerospace industry, with wide military applications. Copper beryllium alloys are widely used in the electronics industry. Aluminum beryllium alloys are used in the structural components of aircraft. Inhalation and dermal exposure to pure metal or beryllium alloys may occur during manufacture of the metal or during its machining, grinding, or polishing.

Worldwide beryllium production has decreased steadily from 1998, when an estimated 7230 metric

TABLE 1. Chemical and Physical Properties of Selected Beryllium Compounds[a]

Compound (molecular formula)	Properties				
	Molecular Weight	Specific Gravity (g/cm^3)	Melting Point (°C)	Boiling Point (°C)	General Solubility
Beryllium (Be)	9.01218	1.8477	1287	2500[a]	
Beryllium fluoride (BeF_2)	47.01	1.986	555	1036 (sublimation)	Freely soluble in water, sparingly soluble in alcohol
Beryllium hydroxide (BeH_2O_2)	43.03	1.92	NA[b]	NA	Very slightly soluble in water and dilute alkali
Beryllium oxide (BeO)	25.01	3.01	2530	NA	Very sparingly soluble in water, acids and bases

[a]Extrapolated
[b]NA = not applicable

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tons were produced, to 2000, when production decreased to 3100 metric tons. The largest producers of beryllium are the United States (> 60% of the total) and Russia (U.S. GS, 2006).

The toxicology of beryllium and its compounds have been reviewed by the U.S. Environmental Protection Agency (U.S. EPA, 1998, 2008), the Agency for Toxic Substances and Disease Registry (ATSDR, 2002), and the Health and Safety Executive (HSE, 1992). Borak (2006) provided an excellent chronology of the occupational exposure limits for beryllium and the need for updated guidance. Kreiss et al. (2007) reviewed aspects associated with occupational exposure to beryllium and emphasized the importance of dermal exposure and the need for novel, performance-based approaches for controlling beryllium exposures.

Animal Studies

Acute, Subchronic, and Chronic

Discussions of the toxic effects of inhaled beryllium compounds and metal following single or repeated exposure in animals may have relevance to acute beryllium disease which occurs at high concentrations; however, they are of limited value in the derivation of a TLV–TWA based on BeS and CBD because no studies in animals have directly addressed the adequacy of human workplace exposure concentrations for preventing chronic beryllium-associated diseases. Rather, research in animals during the last 20 years has focused on defining an appropriate animal model for CBD. To date, an animal model with responses including sustained granulomatous lung lesions with a significant lymphocytic component and the presence of *in vitro* beryllium-specific lymphocytic proliferation has not been identified (Finch et al., 1996). Several parallels between murine and human responses to beryllium metal have been observed (Nikula et al., 1997); however, in these studies, animals were exposed only once to relatively high concentrations of beryllium (approximately 20–60 µg/m^3), an exposure scenario that cannot be directly extrapolated to assess the adequacy of current workplace exposure standards. The reader is referred to reviews of animal models of CBD (Finch et al., 1996; Haley et al., 1993).

Because BeS is a Type IV cell-mediated immune response, mechanistic and dose-response data from studies of skin sensitization are relevant (Friedman et al., 1983; Kligman and Basketer, 1995). In the latter case, the dose metric most appropriate is µg/cm^2 due to the importance of the density of antigen presenting cells (Langerhans cells) and T-lymphocytes at the site of contact. The analogous situation is the surface area on which Be particles are deposited in the respiratory tract (or GI tract following clearance and swallowing).

Tinkle et al. (2003) showed that mice could be sensitized following dermal exposure to poorly soluble beryllium particles.

Stefaniak et al. (2006) compared the dissolution rates of BeO particles from a screener operation, finished product BeO powder, finished product Be metal powder and a multi-constituent aerosol from an arc furnace during processing of copper-beryllium alloy. The authors suggested that the dissolution rate may be an important factor in determining the risk of BeS and CBD for different chemical forms of beryllium.

Cancer

A limited number of studies has been conducted in animals to evaluate the carcinogenicity of various forms of inhaled beryllium. The studies are summarized below.

BERYLLIUM ORE

Cancer incidence was not increased in hamsters exposed to 0.21 or 0.62 mg beryllium/m^3 as bertrandite or beryl ore (Wagner et al., 1969). Rats similarly exposed to bertrandite ore did not have a greater incidence of lung cancer than observed in the controls. However, 18 of 19 rats exposed to 0.62 mg Be/m^3 as beryl ore developed bronchial alveolar cell tumors, adenomas, adenocarcinomas, or epidermoid tumors.

METALLIC BERYLLIUM

A single exposure at 410 to 980 mg Be/m^3 for 8 to 48 minutes produced lung tumors 14 months after exposure in 64% of the rats (Nickell-Brady et al., 1994). Single exposures of A/J and C3H/HeJ mice to beryllium metal produced only a weak, or no carcinogenic response (Nikula et al., 1994, 1995).

BERYLLIUM SULFATE

Rats exposed at 0.35 mg Be/m^3 as beryllium sulfate for 180 days had increased lung cancer rates compared to controls (Schepers et al., 1957). Repeated exposure of rats at 0.034 mg Be/m^3 as beryllium sulfate for 13 months produced lung tumors (adenocarcinomas with a predominantly alveolar pattern) in 100% of the rats (Reeves et al., 1967).

BERYLLIUM OXIDE

Primary pulmonary cancer of the bronchiole was observed in rats exposed at 0.006 or 0.0545 mg Be/m^3 as BeO (Vorwald and Reeves, 1959) after a nine-month latency period.

Genotoxicity

IN VIVO

Beryllium sulfate administered to CBA mice by oral gavage at 80% and 50% of the medial lethal dose (2.3 and 1.4 g/kg, respectively) failed to

increase the incidence of micronucleated polychromatic erythrocytes in bone marrow (Ashby et al., 1990). No studies investigating the genotoxicity of beryllium following inhalation or dermal exposure were found.

IN VITRO

Salmonella typhimurium Assays

Beryllium sulfate was not mutagenic in several strains of *S. typhimurium* when the assays were run in the presence (Ashby et al., 1990) or absence (Dunkel et al., 1984) of metabolizing systems. Similar results have been reported for $BeCl_2$ (Ogawa et al., 1987), $Be(NO_3)_2$ and BeO (Kuroda et al., 1991). Thus, the majority of *S. typhimurium* assays suggest that beryllium compounds do not produce mutations in Ames-type assays.

Escherichia coli Assays

Zakour and Glickman (1984) observed that $BeCl_2$ induced *amber* and *ochre* gene mutations by 3-fold over spontaneous mutation levels in an *E. coli* forward mutation assay.

Co-Mutagenesis Assays

Co-mutagenesis by beryllium compounds in *E. coli* has also been explored. UV mutagenicity was not enhanced by up to 2 mM $BeCl_2$ (Rossman and Molina, 1986). In a study of co-mutagenesis with 9-aminoacridine (100 μmoles/plate), $BeCl_2$ (1–2500 μmol/plate) resulted in a positive effect with two *S. typhimurium* strains (Ogawa et al., 1987). Thus, while the evidence for beryllium as a direct-acting mutagen is somewhat weak, it may enhance the mutagenicity of other agents, suggesting a potential pathway for beryllium-induced carcinogenicity.

Recombination Repair Deficient Systems

Early reports to assess genomic DNA damage after beryllium exposure were mixed in the recombination repair deficient (*rec*) assay with *Bacillus subtilis*. Positive results were found using 0.5 μmol $BeSO_4$ in the streak method (Kada et al., 1980; Kanematsu et al., 1980). The more sensitive spore plate method (compared to the streak method) also demonstrated positive results for $BeCl_2$ and $Be(NO_3)_2$ (Kuroda et al., 1991). In contrast, a lack of mutagenicity was observed for $BeCl_2$ in both the *B. subtilis rec* assay (Nishioka, 1975; Kanematsu et al., 1980) and the *Sacharomyces cerevisiae* D3 mitotic recombination assay (Simmon, 1979). Thus, in the recombination repair deficient assay, beryllium appears to be positive depending on the particular test compound, laboratory, or dose.

Mammalian Cell Systems

Unlike the generally negative results in reverse mutation assays in prokaryotes, soluble beryllium compounds can induce forward mutations in mammalian cells. Miyaki et al. (1979) reported that the frequency of 8-azaguanine resistance at the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus was two to six times higher in Chinese hamster V79 cells treated with $BeCl_2$ compared to untreated cells. In two publications, Hsie et al. (1978, 1979) reported that $BeSO_4$ was weakly positive in Chinese hamster ovary cells in the HGPRTase test. Thus, soluble beryllium compounds demonstrate evidence of inducing weak mutagenesis in mammalian cells.

A number of studies have examined the potential for induction of chromosomal aberrations in mammalian cell systems. Chinese hamster ovary (CHO) cell exposure at 0.2 to 1.0 mmol $BeSO_4$ caused only minor changes in chromosomal deletions, exchanges and gaps as examined by standard cytogenetic techniques (Brooks et al., 1989). $BeSO_4$, up to 2.5 mg/ml, was shown to be nonclastogenic in Chinese hamster lung cells (Ashby et al., 1990). In contrast, Larramendy et al. (1981) found that 5 μg $BeSO_4$/ml increased chromosomal aberrations in human lymphocytes by 10-fold, and produced a 21-fold increase in chromosomal aberrations in Syrian hamster cells (HEC) exposed at this same level. HEC cells and cultured human lymphocytes also showed increased sister-chromatid exchange (SCE) after treatment with $BeSO_4$ (Larramendy et al., 1981). Dose-dependent increases in SCE were also observed with both $BeCl_2$ and $Be(NO_3)_2$-exposed V79 cells (Kuroda et al., 1991). Conversely, Anderson (1983) failed to find any significant increase in SCE by $BeSO_4$-treatment of either human lymphocytes or the cultured macrophage cell line P338D1. In the micronucleus assay, at levels of 50 to 80% (2.3–1.5 g/kg, respectively) of its medium lethal dose, $BeSO_4$ failed to induce micronucleated polychromated erythrocytes (MPE) in the bone marrow of mice (Ashby et al., 1990).

Seven to eight days of treatment with 2.5 and 5 μg/ml $BeSO_4$ was found to induce morphological transformation of Syrian hamster secondary embryo cells (SHE) (DiPaolo and Casto, 1979). These investigators also observed that beryllium enhanced the transformation induced by Simian adenovirus SA7, albeit at high concentrations of $BeSO_4$ (50–600 μmol) (Casto et al., 1979). $BeSO_4$ induced morphological transformation of BALB/3T3 mammalian cells at a dose range of 0.2 to 25 μg/ml and in SHE cells at 0.312 to 2.5 μg/ml. In these studies, the carcinogenic potential of the transformed cell lines were not addressed by injection into a suitable host. The transformation potential in BALB/3T3 cells was confirmed, as treatment with concentrations of 50 to 200 μg $BeSO_4$/ml for 72 hours produced 9- to 41-fold increases in transformation efficiency (Keshava et al., 2001). In this study, 100% of all nude mice injected with $BeSO_4$ transformed cells developed fibrosarcomas. In summary, the mammalian trans-

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formation tests provide strong evidence that beryllium can induce malignant changes in the cells.

Reproductive/Developmental Toxicity

Rats fed less than 31 mg Be/kg/day as beryllium sulfate in the diet had no lesions of the prostate, seminal vesicles, epididymis, ovaries, uterus, or oviducts as indicated by histopathology (Morgareidge et al., 1977).

Male and female rats administered 0.6 mg Be/kg once (as BeO) showed no consistent effects on reproductive performance as determined by the average number of pregnancies per female, live pups per litter, dead pups per litter, live pups per female, lactation index, or average weight of live pups per female (Clary et al., 1975).

Fetal mortality and abnormalities have been found following acute or repeated administration of high doses (50 mg/kg) of beryllium by injection or intratracheal instillation in rats (Selivanova and Savinova, 1986; Sharma et al., 2002). The doses and dosing regimens are unlikely to be relevant to human occupational exposure.

Human Studies

Occupational exposure to beryllium and its compounds has been associated with three different clinical syndromes: 1) acute beryllium disease caused by short-term exposures at high concentrations of beryllium; 2) BeS and CBD, immunologically mediated responses occurring after a latent period ranging from a few weeks to many years; and 3) lung cancer.

Acute Beryllium Disease

Acute beryllium disease can affect any level of the respiratory tract causing rhinitis, pharyngitis, tracheobronchitis, and pneumonitis. The acute pneumonitis is potentially the most serious result of acute exposure to very high levels of soluble beryllium salts. It can occur either as a fulminating illness within three days of massive exposure, or after prolonged exposure to lower levels of the compound. The main presenting symptom is shortness of breath. Malaise, anorexia, and weight loss are common findings. Physical examination may reveal cyanosis, tachypnea, tachycardia, and crackling sounds in the lung. Alterations in lung ventilation-perfusion balance may result in hypoxemia and hypercapnea. Chest X-rays may show pulmonary edema or the presence of nodules. Acute beryllium disease may be fatal. Fibrosis may develop among individuals surviving the disease (Vorwald et al., 1966). Individuals who have had acute beryllium disease may also develop chronic disease. Freiman and Hardy (1970) reported that among 124 cases of chronic disease, 11% had documented history of one or two attacks of acute disease prior to the onset of CBD.

Beryllium Sensitization (BeS) and Chronic Beryllium Disease (CBD)

CBD is characterized by a Type IV, cell-mediated delayed hypersensitivity reaction (Newman, 1996). Sensitization to beryllium can be detected in peripheral blood cells by the beryllium-stimulated lymphocyte proliferation test (BeLPT) (Newman, 1996). The test has been used by many investigators to screen workers within the beryllium industry and U.S. Department of Energy Nuclear sites for sensitization to beryllium (Newman et al., 1996; Stange et al., 2001, 2004; Henneberger et al., 2004; Kreiss et al., 1993a, b, 1996, 1997; Kelleher et al., 2001; Welch et al., 2004; Sackett et al., 2004; Schuler et al., 2005).

The utility of the BeLPT test for screening asymptomatic beryllium workers for sensitization has been questioned based on several factors including intra- and inter-laboratory variability in results and its low sensitivity (68%), despite having a high specificity (97%) (Borak et al., 2006). Intra- and inter-laboratory variability have been demonstrated in several studies (Cullen, 2005; Schuler et al., 2005; Stange et al., 2004; Deubner et al., 2001; Kreiss et al., 1997). Donovan et al. (2007) evaluated the performance in the BeLPT test based on results of a long-term surveillance program conducted by the Brush Wellman Co. Ten thousand results from 2400 participants were examined. The results showed that approximately one percent of new employees with no previous history of beryllium exposure had con-firmed positive results from the time of hire. Median time to the first positive results in confirmed positive individuals was five months. Workers sometimes oscillated between positive and negative outcomes upon follow-up assessments. The studies reported no correlation between the time of employment and increased prevalence of confirmed positive BeLPT results. The cumulative incidence of confirmed positive results in subsets of workers that participated in multiple surveys increased over time. Cher et al. (2006) reported laboratory variation that "was beyond what would be expected due to chance alone" and suggested improved quality management among laboratories performing the BeLPT. In contrast, a recently reported survey of the efficacy of the BeLPT test to predict BeS and CBD in over 12,000 workers at 18 U.S. Department of Energy sites found the positive predictive ability of the assay to be comparable to that of other commonly accepted medical screening tests (Stange et al., 2004).

Individuals with positive BeLPT results may choose to undergo medical follow-up to determine if lung lymphocytes obtained by bronchoalveolar lavage proliferate *in vitro* in response to beryllium challenge (i.e., bronchoalveolar lavage cell BeLPT). Biopsies are obtained to examine lung tissue lymphocyte prevalence or granulomas. Increased

numbers of lung lymphocytes or granulomas in the absence of clinical symptoms have been termed subclinical CBD.

Clinical CBD is characterized by dyspnea on exertion, weight loss, nonproductive cough, fatigue, chest pain, anorexia, and weakness. It progresses over a long period with an increase in the severity of the symptoms. Advanced cases display clubbing of the fingers and a combination of fibrosis and active interstitial inflammation. Cor pulmonale can develop and is a cause of death in very advanced cases. The latency period for development of clinical CBD can be more than 20 years.

Only a subset (2%–19%) of beryllium-exposed individuals becomes sensitized to beryllium (Kreiss et al., 1993a, b, 1996, 1997; Newman et al., 2001, 2005b; Kelleher et al., 2001; Maier, 2002; Sackett et al., 2004; Schuler et al., 2005; Stange et al., 2001, 2004). However, even some individuals with minimal exposure to beryllium become sensitized or develop CBD (Newman et al., 2001; Kelleher et al., 2001). Sensitization does not always result in progression to CBD. Up to 50% of workers who were screened displayed sensitization without evidence of disease (Maier, 2002). However, progression from sensitization to disease has been demonstrated (Newman et al., 2001, 2005a, b; Stange et al., 2001; Henneberger et al., 2004). Thus, individuals showing immunological sensitization to beryllium are considered at risk for development of subclinical and clinical CBD.

There appears to be a genetic basis for susceptibility to BeS (Maier, 2002; Wang et al., 2001; Richeldi et al., 1993; McCanlies et al., 2004). Allelic variations in the HLA-DPB1 gene, such as substitution of a glutamic acid at position 69 in exon 2 (Glu69) may predispose individuals to beryllium sensitivity (reviewed in Maier, 2001). McCanlies et al. (2004) reported an odds ratio of 9.4 for the association between CBD and the HLA-DP-Glu26 allele. Other alterations, such as polymorphisms in the TNF-α promoter and TGF-ß may be important in the development of beryllium-specific granulomatous inflammation (Maier, 2001; Gaede et al., 2005). Christiani et al. (2008) discussed the limitations of using these genetic susceptibility factors to evaluate the occupational risks of beryllium exposure, among other workplace substances, and some of the social, ethical, and legal issues surrounding the use of genetic screening.

Curtis (1951) reported cutaneous hypersensitivity in workers with beryllium-induced dermatitis. In this study, 16 "control" individuals not exposed to beryllium were patch-tested with soluble beryllium salts. Eight of the 16 developed dermal hypersensitivity, suggesting that sensitization to beryllium can result from dermal exposure. Tinkle et al. (2003) demonstrated BeS in mice following dermal application of poorly soluble beryllium. The observation of new cases in exposed workers, despite lowering airborne concentrations, also suggests dermal exposure may be an important contributor.

Studies Evaluating the Relationships between Beryllium Exposure and BeS and CBD

Several studies have examined the development of BeS and CBD in beryllium-exposed workers. Many of these studies lack adequate exposure assessment, while early studies identified only workers with CBD and not BeS. Kolanz et al. (2001) reviewed historical and current exposure assessment methods for beryllium and the usefulness of these methods for evaluating risk of developing CBD. Several studies have been published since 2001. The following discussion covers those epidemiology studies that have exposure and health data pertinent to the development of a TLV.

Schuler et al. (2005) conducted a population-based cross-sectional study in a copper-beryllium alloy facility. The median time since hire for study participants was 16 years (range < 1 to 45 years). Of these 153 participants, 11 had beryllium exposure prior to hire. Nine participants were excluded from statistical analyses because of suspect BeLPT results, reducing the number of participants analyzed statistically to 144.

For the purposes of risk factor analysis for CBD, six known cases, one diagnosed in the year prior to the survey, four diagnosed during the survey, and one diagnosed after the survey ended (6/144 = 4%) were included. For the purposes of risk factor analysis for sensitization, the analysis was restricted to the group of sensitized workers consisting of the eight employees with abnormal BeLPT results (four of whom had CBD), together with the two additional workers with CBD diagnosed before and after the screen (10/144 = 7%). Thirteen percent (2/15) of workers with one year or less of reported beryllium exposure were sensitized but did not have CBD.

Among the four plant work categories (production of rod and wire, production of strip metal, production support, and administration), the prevalence of CBD (7%; 6/81 individuals) was significantly higher ($p < 0.05$) for those having ever worked in rod and wire production. Within this job category, the incidences of CBD among those working in the point and chamfer, wire annealing and pickling, and wire drawing subcategories was 21% (3/14 individuals), 10% (4/39) and 10% (4/42), respectively. These incidences were all significantly greater than the corresponding non-exposed control group. In these same subcategories, incidences of beryllium sensitized individuals were 21% (3/14 individuals), 13% (5/40), and 14% (6/44), respectively. Median total beryllium exposures for the point and chamfer, wire annealing and pickling, and wire drawing operations were 0.03 µg Be/m^3 (range, < 0.01–1.58), 0.12 µg Be/m^3 (range, 0.01–7.80), and 0.06 µg Be/m^3 (range, 0.01–0.38). The fraction of

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samples that exceeded 0.2 µg/m^3 were 6%, 54%, and 13% for the point and chamfer, wire annealing and pickling, and wire drawing operations, respectively. For all other operations within the wire and rod production, strip metal production, production support and administration, median total beryllium exposure levels were 0.02 to 0.11 µg/m^3. The upper limit of percentages of samples in these areas exceeding 0.2 µg/m^3 was ≤ 7%.

Overall, the statistically significant incidences of BeS or CBD were associated with job categories where the median exposure concentration ranged from 0.03 to 0.12 µg/m^3 and approximately 25% of the personal sample exposures exceeded 0.2 µg/m^3. By comparison, no statistically significant risk was associated with job categories where median exposure concentrations were 0.02 to 0.11 µg/m^3 and fewer than 7% of samples exceeded 0.2 µg/m^3.

The relationship between exposure to beryllium and the presence of BeS and CBD was examined in a cohort of workers in a beryllium precision machining factory (Kelleher et al., 2001). Work at the plant began in 1969, and involved the use of beryllium metal, oxide, and alloys. The initial screening of workers (n = 235) was conducted from 1995 to 1997. Follow-up screens were conducted on 187 of the original 235 individuals at two-year intervals following the initial screen. The group had been employed at the machining plant for an average 11.7 years (range, 1 month to 29 years). Sixty of the 235 had been employed at the plant less than one year at the time of their initial blood screens.

Fifteen of the 235 individuals in the initial screen had confirmed abnormal blood BeLPT results. Follow-up surveillance two years later identified five additional individuals with abnormal BeLPTs, and the second follow-up surveillance conducted in 1999 identified two additional individuals with abnormal BeLPT. Of the 22 individuals with abnormal BeLPT, 19 underwent clinical surveillance. Thirteen of the 19 were diagnosed with CBD, two had probable CBD, and four were diagnosed as beryllium sensitized. Four of the individuals with BeS or CBD had been employed at the plant less than three months. Workers with BeS or CBD were more likely to have worked as a machinist (odds ratio, 4.4; 95% confidence interval [CI], 1.1–17.6).

To determine the relationship between beryllium exposure and the incidence of BeS/CBD, the workers were divided into two groups: workers with confirmed BeS/CBD (termed "cases") and workers without disease (termed "controls"). Only the 20 individuals identified with BeS/CBD in the first two rounds of surveillance (1995 and 1997) were included as cases; 206 of the remaining 215 individuals without detected sensitization or disease were included in the "control" group. Based on interviews with the workers, job categories for each individual were assigned. Eighteen of the 20 workers in the case group reported having experience as a machinist in the plant.

Personal cascade impactor samples were collected in areas where beryllium machining occurred (n = 59) and in areas not associated with beryllium machining (n = 41). Samples were taken from the workers' breathing zone. Exposure estimates were calculated from the samples for each job title for total beryllium exposure, exposure to particles < 6 µm, and exposure to particles of size < 1 µm aerodynamic diameter. Comparisons of beryllium air concentrations made in 1995 to 1997 as part of this study with historical values from 1981–1984 showed no statistical differences.

Cumulative occupational beryllium exposure for each worker in the case and control groups was calculated as:

$$\Sigma(\text{each job-specific exposure type}) \times (\text{years of exposure in the specific job title}) = \mu g/m^3\text{-years}.$$

Individual LTW average beryllium exposure was computed by dividing the cumulative exposure for each job title held, expressed in µg/m^3-years by the total number of years employed at the plant (µg Be/m^3).

For the 100 personal impactor beryllium samples collected, the median total beryllium exposure was 0.13 µg/m^3 (range of 0.006 to 22.62), with 50 samples indicating concentrations below 0.2 µg/m^3 and nine samples indicating concentrations > 2 µg/m^3. There were no statistical differences between the cumulative exposure (µg/m^3-years) of the cases compared to the controls. LTW averages (µg/m^3) for the cases were similar to those of the controls. An exposure mean or median concentration of total beryllium particles for both cases and controls was 0.25 µg/m^3. Exposure concentrations of particles < 6 µm among cases and controls were 0.20, and 0.14 µg/m^3, respectively. Exposure concentrations of particles < 1 µm were 0.13 and 0.11 for the cases and controls, respectively.

Twelve of the 20 cases had LTW exposure > 0.2 µg Be/m^3. Sixteen cases had LTW exposures > 0.1 µg Be/m^3 total particulate mass. Four of the cases had exposures between 0.02 and 0.1 µg Be/m^3. No BeS or CBD was found at LTW exposure below 0.02 µg Be/m^3 total particulate mass. Of note is that four workers with less than three months of employment and no stated previous beryllium exposure (Newman et al., 2001) were diagnosed with BeS or biopsy-confirmed CBD (n = 2).

Madl et al. (2007) made a more comprehensive exposure assessment of the same beryllium machining plant examined by Kelleher et al. (2001). Greater numbers of personal (N = 3831) and area (N = 616) samples were used for the time periods 1980 to 1995 and for 1995 to 1999 to recalculate the LTW

average exposures for the 20 cases of BeS and subclinical CBD reported by Kelleher. Further, exposure assessment data for the period 2000 to 2005 were reported and used to calculate LTW exposures for an additional seven workers newly identified as beryllium sensitized or having subclinical CBD.

During the period between 1995 and 1999, a number of improvements were made to reduce worker exposures to beryllium, including removing pressurized air hoses that were used for cleaning, discouraging dry sweeping, fabrication of enclosures for deburring processes, installation of local exhaust in several departments, mandatory use of uniforms, modifying access to production areas using air showers, installation of vacuum units and implementation of a work shoe policy.

The exposure reconstruction for the three time periods was achieved using five different approaches and included calculation of median, mean and 95th percentile estimates and exceedance fractions for 0.02, 0.2 and 2 μg/m^3.

Of the 27 individuals in the plant with BeS or subclinical CBD, using data for all years worked for each job title with supplemented data, one individual had a median LTW between 0.02 and 0.05 μg/m^3 total beryllium particle mass, six had LTW between 0.05 and 0.1 μg/m^3, eight had LTW between 0.1 and 0.2 μg/m^3, five had LTW between 0.2 and 0.4 μg/m^3, and the remaining seven had LTW > 0.4 μg/m^3.

When the LTW was calculated on the basis of mean exposure concentrations rather than median values, the data were skewed slightly due to the higher values. The following was found: no individuals had LTWs below 0.05 μg/m^3, three had LTWs between 0.05 and 0.1 μg/m^3, seven had LTWs between 0.1 and 0.2 μg/m^3, three had LTWs between 0.1 and 0.2 μg/m^3, eight had LTWs between 0.4 and 0.8 μg/m^3, two had LTWs between 0.8 and 1.6 μg/m^3, and the remaining four had LTWs > 1.6 μg/m^3.

For the 95th percentiles, only 1 of 27 cases had an LTW between 0.1 and 0.2 μg/m^3. The rest were above 0.2 μg/m^3. This observation led the authors to conclude that BeS and CBD may be preventable if exposures are maintained below 0.2 μg/m^3 95% of the time.

Wambach (2007) commented on the exposure-response analysis of Madl et al. (2007), particularly the use of median, mean and 95th percentile LTW levels values. Wambach concluded that the overall exposure estimates were in agreement with Kelleher et al. (2001), and that there was no greater value in using the 95th percentile than a mean or median.

Johnson et al. (2001) have reported on the experience of the Cardiff Atomic Weapons Establishment plant in Cardiff Wales, U.K. This facility employed more than 400 employees between 1961 and 1997. Metallic beryllium was primarily used. In addition to extensive air monitoring, the industrial hygiene program in the plant also utilized surface contamination controls, engineering, worker, and material controls to reduce beryllium exposure. The electronic database included 367,757 area-sampling records at 101 locations and 217,681 personal lapel-sampling records from 194 employees over the period of 1981 to 1997. Mean annual personal sampling concentrations for all workers ranged from 0.11 to 0.72 μg/m^3. Foundry workers had the highest concentrations with a mean of 0.87 μg/m^3. Mean annual area sample concentrations for all locations ranged from 0.02 to 0.32 μg/m^3. No data are available on particle size distribution. During its period of operation, the plant experienced only one clinical case of CBD, which the authors speculated may have been induced by a wound exposure rather than inhalation exposure.

However, the authors state in the discussion section, "…it is important to emphasize that although the Cardiff site has the most extensive workplace measurements data base of all beryllium facilities in existence, these measurements do not necessarily reflect actual worker exposures. For example, respiratory protection was commonly used by Cardiff workers while personnel sampling was conducted, and we have not adjusted the air sampling results to account for this factor." Specific individual, job-specific, or respiratory protection use data were not available.

Kreiss et al. (1997) evaluated the risk factors of beryllium disease and sensitization related to work processes in a beryllium manufacturing plant producing pure metal, oxide, alloys, and ceramics. The plant surveyed was opened in 1953 and employed an estimated 2274 people between its opening and the conduct of the survey (1993–1995). Ceramic production was moved to another facility in 1984.

Among employees who began work after 1984, an 8% prevalence (4/50) of BeS and CBD was found in beryllium metal production (specifically in the pebble plant and vacuum melting operations) compared with a 0.7% prevalence (1/140) among employees in all other operations. Further, for people employed after 1983, employees with abnormal blood tests only were more likely to have worked in the pebble plant than in other parts of the plant (46.2% versus 20.5% among other locations). Median beryllium concentrations measured in the pebble plant were 0.4, 1.1, and 0.9 μg Be/m^3 for general area measurements, breathing zone measurements, and lapel samples, the latter being collected in 1990 to 1992 only. Percentages of samples exceeding a 2 μg/m^3 TWA or a 5 μg/m^3 STEL were 6.4, 11, and 27.5 for the general area, breathing zone, and lapel samples, respectively.

Kreiss et al. (1996) examined the prevalence of BeS and CBD among workers in a beryllia ceramics plant in operation since 1980. The cohort consisted of 136 employees. Daily weighted average (DWA) exposures for a workday were estimated quarterly

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using a formula incorporating average general area, full-shift area, and breathing zone measurements based on time studies for most jobs. The DWA formulas were modified over the years as jobs within the plant changed. DWA values were available for three job titles from 1/81 to 12/82, six job titles from 1/83 to 9/85, 14 titles from 10/85 to 3/88, and 19 titles from 4/88 to 9/91. Some extrapolation was done for work periods without data.

Eight beryllium-sensitized employees were identified (5.9% incidence). Six of these eight (overall incidence 4.4%) were diagnosed with CBD. Machinists had a sensitization rate of 14.3% compared to an overall rate of 1.2% among other employees. General area and breathing zone measurements for major processes during the 10/85 to 3/88 period were below 0.8 µg Be/m^3.

The results of this study suggest that machining exposures resulting in a 14.3 odds ratio for BeS were for the most part below 2 µg/m^3.

Cummings et al. (2007) provided an update on the prevalence of BeS at this beryllium oxide ceramics manufacturing facility where significant improvements in exposure controls were implemented between 2000 and 2004. They compared the sensitization rates for workers hired from 2000 to 2004 to workers hired between 1993 and 1998. Airborne beryllium levels were similar during these two periods with median, geometric mean and 95th percentile upper tolerance limit values of 0.2, 0.21 and 1.25 µg Be/m^3 in production areas in 1994 to 1999 and 0.18, 0.18 and 1.66 Be/m^3 in 2000 to 2003, respectively. The sensitization prevalence estimate was 8.7% for 1993 to 1998 and only 1% for 2000 to 2004, suggesting that work practices and other controls beyond reducing airborne levels were important for controlling BeS. Preventing dermal exposure was considered particularly important.

Day et al. (2006) also emphasized the importance of dermal exposure, in addition to genetic susceptibility, as a potential important route for BeS. They hypothesized that inhalation and deposition of airborne particles is still required for the progression of CBD. Day et al. (2007) assessed potential dermal exposure pathways in a beryllium alloy strip and wire finishing facility and measured beryllium levels of 0.95 µg Be/100 cm^2 in production areas, 0.59 µg Be/100 cm^2 in production support areas and 0.05 µg Be/100 cm^2 in administrative office areas. They also detected beryllium contamination on cotton gloves (GM = 0.07–196.5 µg Be/100 cm^2), the neck (GM = 0.003–0.14 µg Be/100 cm^2), and face (GM = 0.003–0.13 µg Be/100 cm^2).

Rosenman et al. (2005, corrected in 2006) evaluated 577 former workers from a beryllium processing facility and attempted to relate the development of BeS and CBD to exposures to beryllium compounds of different forms (e.g., soluble versus insoluble) and particle size (fume versus dust) as well as mixed exposures. The prevalence of definite or probable CBD of 7.6% (44/577) and BeS of 7.0% (40/557) was higher than reported in other studies although mean and peak exposures were also higher. Mean and peak exposures for non-soluble Be particles ranged from 1.6–1.7 µg Be/m^3 and 5.1–6.1 µg Be/m^3, respectively. The corresponding ranges for soluble particles were 0.8–0.9 and 1.1–3.3 µg Be/m^3, respectively. The mean and peak exposures for dusts ranged from 1.5–1.6 and 5.1–6.6 µg Be/m^3, while the range for fumes was 0.5–0.9 and 0.8–3.3 µg Be/m^3, respectively. There was no difference in exposures in individuals with or without evidence of BeS or CBD. Disease outcomes were also compared to DWA exposure concentrations calculated using task-based sampling and the amount of time spent during the shift in each task. There were no cases of definite or probable CBD with DWAs of 0.02 to < 0.2 µg Be/m^3, 33 cases for the range 0.2 to < 2 µg Be/m^3 and 7 cases for DWAs ≥ 2 µg Be/m^3. There were no cases of BeS for DWAs of 0.02 to < 0.2 µg Be/m^3, 24 cases for DWAs from 0.2 to < 2 µg Be/m^3, and 13 cases for DWAs > 2 µg Be/m^3.

Stanton et al. (2006) performed a cross-sectional survey of 100 employees at three copper-beryllium alloy distribution centers. Only one worker was found to be sensitized so the prevalence was 1%. The median full-shift personal lapel sample concentration was 0.03 µg Be/m^3 with an arithmetic mean of 0.05 µg Be/m^3 and 97% of samples below 0.2 µg Be/m^3. The worker with BeS/CBD worked in a production support job as a shipper/receiver for 22 years and handled drums of BeO powder with external contamination and beryllium scrap while transferring in and out of trailer vans. He also had dermal contact while weighing and repackaging dusty ingots.

The relationship between airborne concentration of beryllium in the working environment and BeS was also examined in a four-year survey (1992–1995) conducted at beryllium-copper alloy manufacturing facilities in Japan (Yoshida et al., 1997). The work environment in the alloy plant was divided into four areas for these analyses, a Be-Cu alloy process area (A1), a Be-Cu metal mold manufacturing process (A2), a Be-Cu cold rolling, drawing and heat-treatment process (B1), and a Be-Cu slitting pretreatment process (B2). The average beryllium concentrations in the four areas over the four-year period were 0.16 to 0.26, 0.01 to 0.02, 0.03 to 0.19, and < 0.01 µg/m^3 for Areas A1, A2, B1, and B2, respectively. For Area A1, maximum concentrations in years 1992, 1993, 1994, and 1995 were 0.59, 0.74, 1.85, and 1.04 µg/m^3, respectively, while for Area A2, the maximum concentrations achieved were 0.04, 0.06, 0.05, and 0.03 µg/m^3. A beryllium lymphocyte proliferation stimulation index of 2 (200% above baseline) was taken as positive. The overall percentages of individuals with positive BeLPTs over the four-year period were 11, 8, 1, and

0 for areas A1, A2, B1, and B2, respectively. A beryllium industry response to this paper cited several potential flaws, the most significant of which was the fact that many of the workers tested had beryllium exposure 5 to 10 years prior to the study and exposure history for these periods was not available (Beryllium Industry Science Advisory Committee, 1998).

Cullen et al. (1987) identified five cases of CBD among an estimated population of 140 workers in a company engaged in the refining and reclamation of precious metals from industrial scrap materials, many of which contained beryllium or beryllium alloys that may have had varying compositions over time. The workers presenting with CBD were exposed during the mid 1960s to early 1980s. Four worked in the furnace area, and one worked primarily in the metal crusher/separation area. In 1983, personal sampling for workers in six job categories was conducted to estimate the beryllium exposure of the workers presenting with CBD. The validity of the exposure assessment conducted many years after the workers contracted CBD was supported by claims by company personnel that operations in the plant had not changed in that time period, and in fact, the type of scrap in use during the air sampling likely contained higher concentrations of beryllium than used previously. Beryllium concentration was 0.50 ± 0.44 μg/m^3 (n = 29 in the samples from the furnace tenders and 2.7 ± 7.2 μg/m^3 (n = 36) from the crushers. The authors indicated that airborne metal in the furnace area represented primarily fume (oxides produced by heating) and in the crusher area was metal alloy dust (from mechanical operations).

Additional insights into the relationship between Be exposure and BeS and CBD come from studies of residents living near beryllium facilities. Maier et al. (2008) reported on the evaluation of 16 cases of potential community-acquired CBD. They were able to confirm eight cases of CBD in residents that had no occupational or ancillary exposure to beryllium. Three of the eight cases were from the same family, emphasizing the importance of genetic factors in CBD. On average, the cases lived 0.37 miles (range 0.1 to 1.05 miles) from the facility. Based on monitoring data from 1958, ambient beryllium concentrations ranged from 0.0155 to 0.028 μg Be/m^3. Some exposures may have exceeded 0.35 μg Be/m^3.

Cancer

A number of epidemiology studies have examined the potential for beryllium to cause respiratory tract tumors in workers exposed to airborne beryllium. The majority of these studies have been retrospective cohort studies of workers exposed in beryllium processing facilities. The plants (n = 7) are located in Ohio and Pennsylvania and have been analyzed and reanalyzed a number of times. While the early studies were not well-controlled in regards to confounding factors (Mancuso, 1970, 1979, 1980; Mancuso and el-Attar, 1969; Bayliss et al., 1971; Wagoner et al., 1980), more recent studies have utilized improved techniques to suitably address confounding factors such as smoking and appropriate control populations (Ward et al., 1992; Steenland and Ward, 1991; Sanderson et al., 2001). The conclusions of some of these studies have also been questioned based on study design, and concern for inadequate consideration of confounding factors such as smoking (MacMahon, 1994; Eisenbud et al., 1997; Levy et al., 2002). Eisenbud et al. (1997) also raised the issue of the potential contribution of high levels of sulfuric acid mist in the Lorain plant to the higher SMR for lung cancers observed among workers at that plant location.

Ward et al. (1992) performed an analysis of 9225 male workers at seven beryllium-processing plants in Pennsylvania and Ohio and observed a significant increase in cancers of the trachea, bronchi, and lung (standard mortality ratio [SMR], 1.26; 95% confidence interval [CI], 1.12–1.42) for all seven plants combined. These results included 9225 male workers. Analysis of the plant-by-plant cohorts demonstrated that the greatest effects were observed in the Lorain (SMR of 1.69) and Reading (SMR of 1.24) plants. In the total plant analysis, the time since the beginning of employment, but not the duration of employment, was significantly associated with lung cancer deaths. Those workers whose latency period to tumors (i.e., time since initiation of employment) was greater than 30 years had a significant elevation in SMR (1.46). Importantly, the decade in which the workers were hired was significantly associated with an increased lung cancer risk. Exposure levels were significantly higher in the 1930s and 1940s (a decrease in exposure levels began following the establishment of strict exposure limits in 1949), and no increase in the SMR for lung cancer was observed for the 1950 and 1960 decades.

SMRs in the Lorain, Reading and other plants were reduced to 1.49 (1.13–1.03), and 1.08 (0.91–1.31), respectively, when some adjustments were made for smoking. Only the SMR for the Lorain, Ohio workers remained significantly increased.

IARC (1993) concluded, based on evaluation of the beryllium cohort studies and results of studies of beryllium carcinogenesis in laboratory animals, that there is sufficient evidence in both humans and experimental animals that beryllium is carcinogenic. Several aspects of the beryllium cohort studies supported IARC's conclusion that the work environment consisting of refining, machining, and producing beryllium metal and alloys was causally associated with an increased risk of lung cancer in workers. These included: 1) the large number of

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lung cancer cases, providing a stable estimate of the mortality ratio; 2) the consistency of the lung cancer excesses in most of the beryllium plants; 3) the greater excess in workers hired before 1950, after which workplace exposures became lower and more controlled; 4) the higher risk of lung cancer in the plant with the greatest proportion of cases of acute beryllium pneumonitis, including cases recorded in the Beryllium Case Registry; and 5) the highest risk for lung cancer occurring in the plants where the risk for pneumoconiosis and other respiratory diseases was the highest. Potential confounding by smoking was addressed in several ways and did not appear to explain the increased risk for lung cancer in beryllium workers.

Further information on the role of beryllium dose in the development of lung cancer is provided by Sanderson et al. (2001) in a case-control study of beryllium workers restricted to the Reading, Pennsylvania plant. The study examined five matched control cases for each of 142 lung cancer cases. One goal of the study was to evaluate lung cancer in regard to cumulative, average, and maximum beryllium exposure concentrations. The overall lung cancer mortality rate was increased in the Reading plant (SMR = 1.22; 95% CI, 1.03–1.43). Importantly, the majority of the cases and controls began employment during the uncontrolled exposure levels during the 1940s. While uncorrected cumulative, average, and maximum exposure levels for the cases and controls were not significantly different, introduction of a lag period of 10 or 20 years into the analysis demonstrated that the beryllium exposure levels for the cases were approximately double that of the controls and significantly different.

Levy et al. (2002) published an alternate approach to the statistical analysis of the cancer incidence among the cohort examined by Ward et al. (1992). Several alternatives to the approach taken by Ward et al. were cited including population providing background incidence of lung cancers for SMR calculations, corrections for smoking history, and pooling of cases among plants to calculate an overall SMR. In the alternate approach taken by these authors, comparisons of lung cancer rates among beryllium workers were made to the corresponding incidence in the city where the beryllium plant was located. Cancer rates for U.S. veterans were used to correct for the contribution of smoking to the lung cancer incidence among beryllium workers. Finally, a meta-analysis was used to analyze smoking adjusted data from the different plants. Using this approach, the authors found lower, and generally not statistically significant, SMRs for cancer among beryllium workers and concluded that the results do not show a causal association between beryllium exposure and lung cancer.

Levy et al. (2007) reanalyzed the nested case-control study of Sanderson et al. (2001). When using non-transformed exposure metrics, they did not find elevated odds ratios for Be associated lung cancer and attributed the positive findings of Sanderson et al. to an imbalance in case and control matching in terms of year of birth and date of hire.

The NIOSH investigators (Schubauer-Berigan et al., 2008) responded with their own reanalysis using conditional logistic regression, with adjustments made for age of hire and birth year and use of alternative log-transformation adjustments. Elevated lung cancer risk was no longer associated with cumulative exposure but it was significantly associated with average and maximum exposure when a 10-year lag was used.

Brown et al. (2004) conducted a nested case-control study examining the association between lung cancer mortality and cumulative internal dose among workers at the Rocky Flats plant in Colorado, between 1951 and 1989. Also examined were the incidences of cancer related to cumulative exposure to asbestos, beryllium, hexavalent chromium, and nickel. The authors reported no increased risk for any of the chemical exposures, including beryllium. No exposure assessment data were provided for any of the chemicals.

TLV® Chronology

Beryllium

1957: *proposed*: TLV–TWA, 0.002 mg/m^3, as Be
1959–1985: TLV–TWA, 0.002 mg/m^3, as Be
1973: *proposed*: A2, Suspected Human Carcinogen
1975–1985: A2, Suspected Human Carcinogen
1976–1978: TLV–STEL, 0.025 mg/m^3
1979: TLV–STEL withdrawn

Beryllium and compounds

1986–1996: TLV–TWA, 0.002 mg/m^3, as Be; A2, Suspected Human Carcinogen
1996: *proposed*: TLV–STEL, 0.01 mg/m^3, as Be; A1, Confirmed Human Carcinogen
1997: TLV–TWA, 0.002 mg/m^3, as Be; TLV–STEL, 0.01 mg/m^3, as Be; A1, Confirmed Human Carcinogen
1999: *proposed*: TLV–TWA, 0.0002 mg/m^3, as Be, Inhalable particulate mass; Sensitizer (SEN); A1, Confirmed Human Carcinogen
2005: *proposed*: TLV–TWA, 0.00005 mg/m^3, as Be, Inhalable particulate mass; Skin; SEN; A1, Confirmed Human Carcinogen
2006: *proposed*: TLV–TWA, 0.00005 mg/m^3; TLV–STEL, 0.0002 mg/m^3, as Be, Inhalable particulate mass; Skin; SEN; A1, Confirmed Human Carcinogen
2009: Adopted: TLV–TWA, 0.00005 mg/m^3, as Be, Inhalable particulate matter; Skin; SEN; A1, Confirmed Human Carcinogen
Literature search current through mid 2008
2013: *proposed*: TLV–TWA, 0.00005 mg/m^3, as Be, Inhalable particulate matter; Skin; RSEN; DSEN; A1, Confirmed Human Carcinogen
2014: Adopted: TLV-TWA, 0.00005 mg/m^3, as Be, Inhalable particulate matter; Skin (soluble compounds); RSEN (soluble and insoluble compounds); DSEN (soluble compounds); A1, Confirmed Human Carcinogen

References

Agency for Toxic Substances and Disease Registry (ATSDR): Toxicological profile for beryllium. Update. ATSDR, US Public Health Service, Atlanta, GA (2002).

Anderson O: Effects of coal combustion products and metal compounds on sister-chromatid exchange (SCE) in a macrophagelike cell line. Environ Health Perspect 47:239–253 (1983).

Ashby J; Ishidate M Jr; Stoner GD; et al.: Studies on the genotoxicity of beryllium sulphate in vitro and in vivo. Mutat Res 240:217–225 (1990).

Bayliss DL; Lainhart WS; Crally LJ; et al.: Mortality patterns in a group of former beryllium workers. In: Proceedings of the American Conference of Governmental Industrial Hygienists 33rd Annual Meeting, Toronto, Canada, pp 94–107. American Conference of Governmental Industrial Hygienists (ACGIH®), Cincinnati, OH (1971).

Beryllium Industry Science Advisory Committee: Letter to the Editor. Ind Health 36:389–391 (1998).

Borak J: The beryllium occupational exposure limit: Historical origin and current adequacy. J Occup Environ Med 48(2):109–116 (2006).

Borak J; Woolf SH; Fields CA: Use of beryllium lymphocyte proliferation testing for screening of asymptomatic individual: An evidence-based assessment. JOEM 48:937–947 (2006).

Brooks AL; Griffith WC; Johnson NF; et al.: The induction of chromosome damage in CHO cells by beryllium and radiation given alone and in combination. Radiat Res 120:494–507 (1989).

Brown SC; Schonbeck MF; McClure D; et al.: Lung cancer and internal lung doses among plutonium workers at the Rocky Flats Plant, a case-control study. Am J Epidemiol 160:163–172 (2004).

Casto BC; Meyers J; DiPaolo JA: Enhancement of viral transformation for evaluation of the carcinogenic or mutagenic potential of inorganic metal salts. Cancer Res 39:193–198 (1979).

Cher DJ; Deubner DC; Kelsh MA; et al.: Assessment of the beryllium lymphocyte proliferation test using statistical process control. Inhalation Toxicol 18:901–910 (2006).

Christiani DC; Mehta AJ; Yu C-L: Genetic susceptibility to occupational exposures. Occup Environ Med 65:430–436 (2008).

Clary JJ; Bland LS; Stokinger HE: The effect of reproduction and lactation on the onset of latent chronic beryllium disease. Toxicol Appl Pharmacol 33:214–221 (1975).

Cullen MR; Kominsky JR; Rossman MD; et al.: Chronic beryllium disease in a precious metal refinery. Clinical epidemiologic and immunologic evidence for continuing risk from exposure to low level beryllium fume. Am Rev Resp Dis 135:201–208 (1987).

Cullen MR: Screening for chronic beryllium disease: one hurdle down, two to go. Am J Respir Crit Care Med 171:3–4 (2005).

Cummings KJ; Deubner DC; Day GA; et al.: Enhanced preventative programme at a beryllium oxide ceramic facility reduces beryllium sensitisation among new workers. Occup Environ Med 64:134–140 (2007).

Curtis GH: Cutaneous hypersensitivity due to beryllium. Arch Dermatol Syphilol 64:470–482 (1951).

Day GA; Stefaniak AB; Weston A; et al.: Beryllium exposure: dermal and immunological considerations. Int Arch Occup Environ Health 79:161–164 (2006).

Day GA; Dufresne A; Stefaniak A; et al.: Exposure pathway assessment at a copper-beryllium alloy facility. Ann Occup Hyg 51(1):67–80 (2007).

Deubner DC; Lowney YW; Paustenbach DJ; et al.: Contribution of incidental exposure pathways to total beryllium exposures (Review). Appl Occup Environ Hyg 16:568–578 (2001).

Deubner D; Kent M: Keeping beryllium workers safe: An enhanced preventative model. J Occup Environ Hyg 4:D23–D30 (2007).

DiPaolo JA; Casto BC: Quantitative studies of in vitro morphological transformation of Syrian hamster cells by inorganic salts. Cancer Res 39:1008–1013 (1979).

Donovan E; Kolanz M; Galbraith D; et al.: Performance of the beryllium blood lymphocyte proliferation test based on a long-term occupational surveillance program. Int Arch Occup Environ Health 81(2):165–178 (2007).

Dunkel VC; Zeiger E; Brusick D; et al.: Reproducibility of microbial mutagenicity assays. I. Tests with Salmonella typhimurium and Escherichia coli using a standardized protocol. Environ Mutat 6:1–254 (1984).

Eisenbud M; Kotin P; Miller F; et al.: Is beryllium carcinogenic in humans? J Occup Environ Med 39:205–208 (1997).

Finch GL; Hoover MD; Hahn FF; et al.: Animal models of beryllium-induced lung disease. Environ Health Perspect 104(Suppl 5):973–979 (1996).

Freiman DG; Hardy HL: Beryllium disease. The relation of pulmonary pathology to clinical course and prognosis based on a study of 130 cases from the US Beryllium Case Registry. Hum Pathol 1(1):25–44 (1970).

Friedman PS; Moss C; Shuster S; et al.: Quantitative relationships between sensitizing dose of DNCB and reactivity in normal subjects. Clin Exp Immunol 53: 709–715 (1983).

Gaede KI; Amicosante M; Schurmann M; et al.: Function associated transforming growth factor-beta gene polymorphism in chronic beryllium disease. J Mol Med 83(5):397–405 (2005).

Haley PJ; Bice DE; Finch GL; et al.: Animal models of human disease: chronic beryllium lung disease. Comp Path Bull 25:3–4 (1993).

Health and Safety Executive (HSE): Toxicity Review 27, Part 2: Beryllium and Beryllium Compounds. HSE, London (1992).

Henneberger P; Goe S; Miller W; et al.: Industries in the United States with airborne beryllium exposure and estimates of the number of current workers potentially exposed. J Occup Environ Med 1:648–659 (2004).

Hsie AW; Johnson NP; Couch DB; et al.: In: Quantitative Mammalian Cell Mutagenesis and a Preliminary Study of the Mutagenic Potential of Metallic Compounds. Oak Ridge National Laboratory, Oak Ridge, TN (1978).

Hsie AW; O'Neill JP; San Sebastian JR; et al.: Quantitative mammalian cell genetic toxicology: study of the cytotoxicity and mutagenicity of seventy individual environmental agents related to energy technologies and three subfractions of crude synthetic oil in the CHO/HGPRT system. Environ Sci Res 15:291–315 (1979).

International Agency for Research on Cancer (IARC): IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol 58, Beryllium, Cadmium, Mercury

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and Exposures in the Glass Manufacturing Industry, pp 41–117. IARC, Lyon, France (1993).
Johnson JS; Foote K; McClean M; et al.: Beryllium exposure control program at the cardiff atomic weapons establishment in the United Kingdom. Appl Occup Environ Hyg 16(5):619–630 (2001).
Kada T; Hirano K; Shirasu Y: Screening of environmental chemical mutagens by the rec-assay system with Bacillus subtilis. In: Chemical Mutagens. Principles and Methods for Their Detection, Vol 6, pp 149–173. F J de Serres, A Hollaender (Eds). Plenum, New York (1980).
Kanematsu N; Hara M; Kada T: Rec assay and mutagenicity studies on metal compounds. Mutat Res 77:109–116 (1980).
Kelleher PC; Martyny JW; Mroz MM; et al.: Beryllium particulate exposure and disease relations in a beryllium machining plant. J Occup Environ Med 43:238–249 (2001).
Keshava N; Zhou G; Spruill M; et al.: Carcinogenic potential and genomic instability of beryllium sulphate in BALB/c-3T3 cells. Mol Cell Biochem 222:69–76 (2001).
Kligman AM; Basketer DA: A critical commentary and updating of the guinea pig maximization test. Cont Dermat 32:129–134 (1995).
Kolanz M; Madl A; Kelsh M; et al.: A comparison and critique of historical and current exposure assessment methods for beryllium: Implications for evaluating risk of chronic beryllium disease. Appl Occup Environ Hyg 16(5):593–614 (2001).
Kreiss K; Wasserman S; Mroz MM; et al.: Beryllium disease screening in the ceramics industry. J Occup Med 35:267–274 (1993a).
Kreiss LS; Mroz MM; Zhen B; et al.: Epidemiology of beryllium sensitization and disease in nuclear workers. Am Rev Respir Dis 148:985–991 (1993b).
Kreiss K; Mroz MM; Newman LS; et al.: Machining risk of beryllium disease and sensitization with median exposures below 2 µg/m^3. Am J Ind Med 30:16–25 (1996).
Kreiss K; Mroz MM; Zhen B; et al.: Risks of beryllium disease related to work process at a metal, alloy, and oxide production plant. Occup Environ Med 54:605–612 (1997).
Kreiss K; Day GA; Schuler CR: Beryllium: A modern industrial hazard. Annu Rev Public Health 28:259–277 (2007).
Kuroda K; Endo G; Okamoto A; et al.: Genotoxicity of beryllium, gallium and antimony in short-term assays. Mutat Res 264:163–170 (1991).
Larramendy ML; Popescu NC; DiPaolo JA: Induction by inorganic metal salts of sister chromatid exchanges and chromosome aberrations in human and Syrian hamster cell strains. Environ Mutagen 3:597–606 (1981).
Levy PS; Roth HD; Hwang PM; et al.: Beryllium and lung cancer: a reanalysis of a NIOSH cohort mortality study. Inhal Toxicol 14(10):1003–1015 (2002).
Levy PS; Roth HD; Deubner DC: Exposure to beryllium and occurrence of lung cancer: A reexamination of findings from a nested case-control study. J Occup Environ Med 49:96–101 (2007).
MacMahon B: The epidemiological evidence on the carcinogenicity of beryllium in humans. J Occup Med 36:15–24 (1994).
Madl AK; Unice K; Brown J; et al.: Beryllium sensitization and chronic beryllium disease in a beryllium metal machining plant: analysis of beryllium exposure and implications for an occupational exposure limit. J Occup Environ Hyg 4(6):448–466 (2007).
Maier LA: Beryllium health effects in the era of the beryllium lymphocyte proliferation test. Appl Occup Environ Hyg 16:514–520 (2001).
Maier LA: Genetic and exposure risks for chronic beryllium disease. Clin Chest Med 23:827–839 (2002).
Maier LA; Martyny JW; Liang J; et al.: Recent chronic beryllium disease in residents surrounding a beryllium facility. Am J Resp Crit Care Med 177:1012–1017 (2008).
Mancuso TF; el-Attar AA: Epidemiological study of the beryllium industry. Cohort methodology and mortality studies. J Occup Med 11:422–434 (1969).
Mancuso TF: Relation of duration of employment and prior respiratory illness to respiratory cancer among beryllium workers. Environ Res 3:251–275 (1970).
Mancuso TF: Occupational lung cancer among beryllium workers. In: Dust and Disease, pp 463. Pathotox Publishers, Park Forest, IL (1979).
Mancuso TF: Mortality study of beryllium industry workers' occupational lung cancer. Environ Res 21:48–55 (1980).
McCanlies EC; Ensey JS; Schuler CR; et al.: The association between HLA-DPB1Glu69 and chronic beryllium disease and beryllium sensitization. Am J Ind Med 46: 95–103 (2004).
Miyaki M; Akamatsu N; Ono T; et al.: Mutagenicity of metal cations in cultured cells from Chinese hamster. Mutat Res 68:259–263 (1979).
Morgareidge K; Cox GE; Bailey DE; et al.: Chronic oral toxicity of beryllium in the rat. Toxicol Appl Pharmacol 41:204–205 (1977).
Newman LS: Significance of the blood beryllium lymphocyte proliferation test. Environ Health Perspect 104(Suppl 5):953–956 (1996).
Newman LS; Lloyd J; Daniloff E: The natural history of beryllium sensitization and chronic beryllium disease. Environ Health Perspect 104(Suppl 5):937–943 (1996).
Newman LS; Mroz MM; Maier LA; et al.: Efficacy of serial medical surveillance for chronic beryllium disease in a beryllium machining plant. J Occup Environ Med 43(3):231–237 (2001).
Newman LS; Maier LA; Martyny JW; et al.: Letter to the Editor. J Occup Environ Health D48–D50 (2005a).
Newman LS; Mroz MM; Balkissoon R; et al.: Beryllium sensitization progresses to chronic beryllium disease: a longitudinal study of disease risk. Am J Respir Crit Care Med 171(1):54–60 (2005b).
Nickell-Brady C; Hahn FF; Finch GL; et al.: Analysis of K-ras, p53 and c-raf-1 mutations in beryllium-induced rat lung tumors. Carcinogenesis 15:257–262 (1994).
Nikula KJ; Belinsky SA; Hoover MD; et al.: Comparative pulmonary carcinogenicity of inhaled beryllium in A/J and C3H/HeJ mice. In: Inhalation Toxicology Research Institute Annual Report 1993–1994, pp 81–83. ITRI-144. SA Belinsky et al. (Eds). National Technical Information Service, Springfield, VA (1994).
Nikula KJ; Belinsky SA; Hoover MD; et al.: Comparative pulmonary carcinogenicity of beryllium in A/J and C3H/HeJ mice. Toxicologist 15:47 (abstract) (1995).
Nikula KJ; Swafford DS; Hoover MD; et al.: Chronic granulomatous pneumonia and lymphocytic responses induced by inhaled beryllium metal in A/J and C3H/HeJ mice. Toxicol Pathol 25(1):2–12 (1997).

Nishioka H: Mutagenic activities of metal compounds in bacteria. Mutat Res 31:185–189 (1975).

Ogawa HI; Tsuruta S; Niyitani Y; et al.: Mutagenicity of metal salts in combination with 9-amino-acridine in Salmonella typhimurium. Jpn J Genet 62:159–162 (1987).

Reeves AL; Deitch D; Vorwald AJ: Beryllium carcinogenesis. I. Inhalation exposure of rats to beryllium sulfate aerosol. Cancer Res 27(3):439–445 (1967).

Richeldi L; Sorrentino R; Saltini C: HLA-DPB1 glutamate 69: a genetic marker of beryllium disease. Science 262(5131):242–244 (1993).

Rosenman K; Hertzberg V; Rice R; et al.: Chronic beryllium disease and sensitization at a beryllium processing facility. Environ Health Perspect 113:1366–1372 (2005).

Rossman TG; Molina M: The genetic toxicology of metal compounds. II. Enhancement of ultraviolet light-induced mutagenesis in Escherichia coli WP2. Environ Mutat 8:263–271 (1986).

Sackett HM; Maier LA; Silveira LJ; et al.: Beryllium medical surveillance at a former nuclear weapons facility during cleanup operations. J Occup Environ Med 46(9):953–961 (2004).

Sanderson WT; Ward EM; Steenland K; et al.: Lung cancer case-control study of beryllium workers. Am J Ind Med 39:133–144 (2001).

Schepers GWH; Durkan TM; Delahunt AB; et al.: The biological action of inhaled beryllium sulfate: a preliminary chronic toxicity study on rats. Arch Ind Health 15:32–58 (1957).

Schubauer-Berigan MK; Deddens JA; Steenland K; et al.: Adjustment for temporal confounders in a reanalysis of a case-control study of beryllium and lung cancer. Occup Environ Med 65:379–383 (2008).

Schuler CR; Kent MS; Deubner DC; et al.: Process-related risk of beryllium sensitization and disease in a copper-beryllium alloy facility. Am J Ind Med 47:195–205 (2005).

Selivanova LN; Savinova TB: Effects of beryllium chloride and oxide on sexual function of female rats and development of their progeny. Gig Sanit 8:44–46 (in Russian) (cited in ATSDR, 2002) (1986).

Sharma P; Shah Z; Shukla S: Protective effect of Tiron (4,5-dihydroxybenzene-1,3-disulfonic acid disodium salt) against beryllium-induced maternal and fetal toxicity in rats. Arch Toxicol 76:442–448 (2002).

Simmon VF: In vitro assays for recombinogenic activity of chemical carcinogens and related compounds with Saccharomyces cerevisiae D3. J Natl Cancer Inst 62:901–909 (1979).

Stange AW; Hilmas DE; Furman FJ; et al.: Beryllium sensitization and chronic beryllium disease at a former nuclear weapons facility. Appl Occup Environ Hyg 16:405–471 (2001).

Stange AW; Furman FJ; Hilmas DE: The beryllium lymphocyte proliferation test: Relevant tissues in beryllium health surveillance. Am J Industrial Med 46: 453–462 (2004).

Stanton ML; Henneberger PK; Deubner DC; et al.: Sensitization and chronic beryllium disease among workers in copper-beryllium distribution centers. J Occup Environ Med 48:204–211 (2006).

Steenland K; Ward E: Lung cancer incidence among patients with beryllium disease: A cohort mortality study. J Natl Cancer Inst 83:1380–1385 (1991).

Stefaniak AB; Day GA; Hoover MD; et al.: Differences in dissolution behavior in a phagolysosomal simulant fluid for single-constituent and multi-constituent materials associated with beryllium sensitization and chronic beryllium disease. Toxicol In Vitro 20:82–95 (2006).

Tinkle SS; Antonini JM; Rich BA; et al.: Skin as a route of exposure and sensitization in chronic beryllium disease. Environ Health Perspect 111:1202–1208 (2003).

US Environmental Protection Agency (US EPA): Toxicological Review of Beryllium Compounds. EPA Report No 635/R-98/008. US EPA, Washington, DC (1998).

US Environmental Protection Agency (US EPA): Toxicological Review of Beryllium Compounds. EPA Report No NCEA-S-2696. Update of inhalation cancer assessment and other selected text. US EPA, Washington, DC (Draft – May, 2008). Online at: http://cfpub.epa.gov/ncea/cfm/recorddisplay.cfm?deid=189634 (2008).

US Geological Survey (US GS): Beryllium. In: Minerals Yearbook, Vol I, Metals and Minerals. Online at: http://minerals.usgs.gov/minerals/pubs/commodity/myb/ Accessed 9/2008 (2006).

Vorwald AJ; Reeves AL: Pathologic changes induced by beryllium compounds. Arch Ind Health 19:190–199 (1959).

Vorwald AJ; Reeves AL; Urban ECJ: Experimental beryllium toxicology. In: Beryllium: Its Industrial Hygiene Aspects, pp 201–234. HE Stokinger (Ed). Academic Press, New York (1966).

Wagner WD; Groth DH; Holtz JL; et al.: Comparative chronic inhalation toxicity of beryllium ores, bertrandite and beryl, with production of pulmonary tumors by beryl. Toxicol Appl Pharmacol 15:10–29 (1969).

Wagoner JK; Infante PF; Bayliss DL: Beryllium: An etiologic agent in the induction of lung cancer, non neoplastic respiratory disease, and heart disease among industrially exposed workers. Environ Res 21:15–34 (1980).

Wambach PF: Comments on the choice of exposure metrics as risk indicators. J Occup Environ Hyg 4:D103–D108 (2007).

Wang Z; Farris GM; Newman LS; et al.: Beryllium sensitivity is linked to HLA-DP genotype. Toxicology 165(1):27–38 (2001).

Ward E; Okun A; Ruder A; et al.: A mortality study of workers at seven beryllium processing plants. Am J Ind Med 22:885–904 (1992).

Welch L; Ringen K; Bingham E; et al.: Screening for beryllium disease among construction trade workers at Department of Energy nuclear sites. Am J Ind Med 46(3):207–218 (2004).

Yoshida T; Shima S; Nagaoka K; et al.: A study on the beryllium lymphocyte transformation test and the beryllium levels in working environment. Ind Health 35:374–379 (1997).

Zakour RA; Glickman BW: Metal-induced mutagenesis in the lacI gene of Escherichia coli. Mutat Res 126:9–18 (1984).

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