BeST
Beryllium Science & Technology Association

Scientific Perspectives on

Establishing an Occupation Exposure Limit Value (OEL)

Beryllium Metal

January 2013

Summary

The Beryllium Science and Technology Association wishes to provide the most recent scientific information for establishing an occupational exposure limit value (OEL) for beryllium metal.

The members of the Beryllium Science and Technology Association are the leading international suppliers of high-performance engineered materials containing beryllium. We have concentrated our operations and skills on advancing the unique performance capabilities and applications of beryllium-based materials. As the world leaders in beryllium production and technology, we strive to be the experts in medical knowledge of beryllium and in the environmental, occupational health and safety aspects of the material.

We suggest that any change to the existing OEL should reflect current scientific studies that clearly support the establishment of an OEL of no lower than 0.2 $\mu g/m^3$ (total dust sampling method).

In addition to scientific studies that we used to develop our protection model, our practical experience in implementing our control procedures for over 10 years has demonstrated that an exposure limit of 0.2 $\mu g/m^3$ provides a high margin of safety for workers exposed to beryllium.

We desire to share our expertise and submit convincing evidence in the form of scientific studies that must be considered as the prime studies for establishing an OEL of 0.2 $\mu g/m.^3$ In addition, we offer our relevant REACH work and the supporting documentation that we intend on submitting to have the current harmonized classification for beryllium changed to reflect the OECD compliant test results required for classification pursuant to REACH.

We welcome this opportunity to provide input to this transparent and open process and respectfully request that our submission be given the utmost consideration because beryllium is a critical and strategic material to the European Economic Area (EEA).

We believe an OEL of 0.2 $\mu g/m^3$ is clearly supported by the preponderance of the scientific evidence in safeguarding the health of those exposed to beryllium, is achievable, and would not be disruptive to employment, the economy, and the security of EEA.

Natural Sources of Beryllium in the General Environment

Beryllium is a natural occurring element, and is present at levels of 0.5 to 2 ppm or higher in soils and rocks throughout the world. The average ambient concentrations of beryllium in the soil in the United States range from 2.8 to 5 mg/kg (ppm).

It is commonly found in coal, oil, wood, vegetables, foodstuffs and gemstones such as aquamarine and emerald. Beryllium is commonly present in many industrial, construction and household products; e.g., ceiling tiles, fertilizers, detergents, charcoal, cat litter, concrete block, concrete floors, metals and roofing materials, oil absorbing materials, steel, copper, sandpaper, abrasive blasting agents and grinding wheels.

Beryllium is found at ppb levels in most plants and vegetables and has been measured (fresh weight) in rice at 72 μg/kg, lettuce at 16 μg/kg, kidney beans at 2200 μg/kg, peas at 109 μg/kg and potatoes at 0.59 μg/kg. Naturally occurring beryllium is present in tobacco; therefore tobacco smoke is a potential source of exposure to beryllium in the general population.

In air, beryllium compounds are present mostly as fine dust particles. The dust eventually settles over the land and water. Rain and snow aid in the removal of beryllium from air. The average ambient concentration in air in the United States is 0.00003 $\mu g/m^3$, while the median concentration in cities is 0.0002 $\mu g/m^3$.

Beryllium enters waterways from the erosion of rocks and soil, but most of the beryllium in water settles in material on the bottom. Beryllium in soil does not dissolve in water but remains bound to the soil. Once in the soil the beryllium is unlikely to move deeper into the ground and enter groundwater. It is generally believed that beryllium is captured by clay minerals by the process of sorption on the surfaces of mineral grains. Beryllium is so promptly adsorbed from neutral water by mineral and glass surfaces that it can exist in solution only as complexes. In an extensive study of water samples from the Western United States, beryllium was detected in only three highly acid mine waters. Beryllium was not found in 95% of 1,577 drinking water samples obtained throughout the United States (Trace Elements in the Environment U.S. Department of Commerce PB-274-428).

According to the WHO Beryllium in Drinking Water Background document development of WHO *Guidelines for Drinking Water Quality 2009*:

"*The general population may be exposed to trace amounts of beryllium by inhalation of air, consumption of drinking-water and food, and inadvertent ingestion of dust. The estimated total daily beryllium intake in the USA was 423 ng, with the largest contributions from food (120 ng/day, based on daily consumption of 1200 g of food containing a beryllium concentration of 0.1 ng/g fresh weight) and drinking-water (300 ng/day, based on daily intake of 1500 g of water containing beryllium at 0.2 ng/g), with smaller contributions from air (1.6 ng/day, based on daily inhalation of 20 m3 of air containing a beryllium concentration of 0.08 ng/m3) and dust (1.2 ng/day, based on daily intake of 0.02 g/day of dust containing beryllium at 60 ng/g). Beryllium intake through air and dust can be increased 2–3 orders of magnitude in the vicinity of a point source, such as a coal-fired power plant.*

The WHO document also states that:

"Beryllium is rarely, if ever, found in drinking-water at concentrations of concern. Therefore, it is not considered necessary to set a formal guideline value. A health-based value for beryllium in drinking-water would be 12 µg/l."

Beryllium is naturally occurring in ground water and surface water. Beryllium has been measured in ground water in the United States at an average concentration of 13.6 µg/l and in surface water at an average concentration of 23.8 µg/l. Concentrations of beryllium in drinking water range from 0.010 to 1.22 µg/l with an average of 0.19 µg/l. An Australian survey found 0.08 µg/l beryllium in rainwater.

The U.S. Agency for Toxic Substances and Disease Registry (ATSDR) has estimated that within the United States, about 45% of airborne beryllium is due to anthropogenic releases of beryllium. Natural sources, such as windblown dust and volcanic activity, account for 55% of beryllium released to the atmosphere. Electric utilities comprise about 80% of the anthropogenic emissions, while industry and metal mining accounts for about 20% of the anthropogenic emissions. However, disposal of coal ash, incinerator ash and waste may increase the concentration of beryllium in soil. In air, beryllium compounds are present mostly as fine dust particles. Fish do not accumulate beryllium from water into their bodies to any great extent

Beryllium metal is currently restricted by Annex XVII which prohibits use of beryllium by the general public.

Prevention of Chronic Beryllium Disease and Beryllium Sensitisation

The primary potential health risk associated with the processing of beryllium metal and beryllium-containing materials is chronic beryllium disease (CBD). Throughout the history of beryllium usage in Europe, prevention of CBD has dictated the level of risk management measures employed to protect workers and the public. Inhalation of beryllium particulate is the primary toxicologically relevant route of exposure for CBD. Controlling worker occupational exposures to beryllium can include process ventilation, defined work practices and personal protective equipment.

The vast majority of beryllium used today is in solid forms of metals containing beryllium, such as pure beryllium metal, copper-beryllium alloys (CuBe), aluminium-beryllium alloys (AlBe) and nickel-beryllium alloys (NiBe) and in solid form, and as contained in finished products, present no special health risks. Manufacturing operations are capable of safely processing beryllium-containing alloys. However, like many industrial materials, beryllium does present a health risk, if handled improperly. The inhalation of beryllium dust, mist or fume can cause a serious lung condition in some individuals. The degree of risk varies depending on the form of the product, and how the material is processed and handled. All metal removal operations performed on beryllium metal and beryllium containing alloys must be performed with appropriate work practices and engineering controls designed to control the release or generation of airborne beryllium-containing dust, mist or fume. The highest potential for exposure exists in foundries that customarily also melt and cast a wide variety of other alloys, very few of which contain beryllium. The more common alloys used in foundries that occasionally cast beryllium containing alloys are bronzes like CuCrZr, CuNiSi, CuP, CuAl, CuAlNi. Master alloys containing 1 – 10% beryllium are added to molten copper and other alloying elements, to introduce beryllium into the alloy before it is cast into moulds. Further processing may occur to meet customer specifications. This processing is usually performed at other locations having the capabilities for further processing.

Potential for exposure to beryllium-containing particulate should be determined by conducting a workplace exposure characterization which includes air sampling in the worker's breathing zone and beryllium work areas. Facilities handling beryllium-containing materials in ways which generate particulate are encouraged to use engineering and work practice controls, including personal protective equipment, to control potential worker exposure.

A safe workplace model was developed by the beryllium producing industry that focuses on keeping beryllium work areas clean and keeping particles and solutions containing beryllium out of the lungs, off the skin, off of clothing, in the work process, in the work area and on the plant site. Worker and management education and motivation are important components. A combination of engineering, work practice and personal protection approaches are used, as needed, to attain the reduction in potential occupational exposure. This model, which incorporates an OEL of 0.2 µg/m^3, prevents sensitization to beryllium (BeS), subclinical chronic beryllium disease (CBD) and clinical CBD. The model is based on the knowledge, experience and understanding gained from the most recent studies which includes the potential exposure risks posed by the various chemical forms of beryllium and disease prevention methods tailored to specific material processing operations, engineering, work practice control, and personal protective measures that have been demonstrated to be effective in preventing sensitization and CBD.

As compared to studies conducted a decade ago and the vastly different exposure profiles that existed in decades past, the current toxicology assessments of beryllium, lead to a much different conclusion on the risks related to beryllium.

It is now clear that workplace exposures to beryllium metal that exist today do not present a cancer risk as borne out by more recent research results that have been published in peer reviewed journals by scientific experts. It has also been shown that the worker protection program, with an OEL of 0.2 µg/m^3, developed by the beryllium industry in conjunction with many years of cooperative research with the National Institute of Occupational Safety and Health in beryllium production facilities in the United States, is effective in preventing CBD and beryllium sensitization.

The independent peer reviewed studies by Cummings, Madl, Schuler and Johnson, briefly described herein, provide the most complete and thorough studies for establishing an Occupational Exposure Limit Value (OEL) for beryllium. A critical analysis of the data and findings in these studies from a risk assessment perspective supports the adoption of an OEL of no lower than 0.2 µg/m^3. Considering the fact that beryllium is a critical material, establishment of a lower limit poses the potential for irreparable harms to the industry and to the economies of manufacturing countries.

The study by Cummings et al. 2007 provides an analysis of the effectiveness of beryllium exposure control efforts including the use of an exposure action limit of 0.2 µg/m^3. This study demonstrates that this exposure control model, in use since 2000, has been effective in reducing the detection of beryllium sensitization from over 8% to 1%, which is same level as the background rate found in the non-occupationally exposed population.

The Schuler 2005 study performed a cross-sectional survey to examine prevalence of beryllium sensitization (BeS) and CBD, and relationships between BeS and CBD and work areas/processes at a copper beryllium alloy strip and wire finishing facility. Schuler 2005 represents a study where the American Industrial Hygiene Association (AIHA) exposure assessment guide recommended number of air samples to assess worker exposure is met with both an ample number of workers (N=153) and excellent exposure data (N>15/job classification. The study concluded:

> "*Sensitization and CBD were associated with an area in which beryllium air levels exceeded 0.2 µg/m^3, and not with areas where this level was rarely exceeded.*
>
> *Employees at this copper beryllium alloy facility had similar prevalences of sensitization and CBD as workers at facilities with higher beryllium air levels*."

A major challenge for evaluating the exposure-response relationship for BeS and CBD is that most studies have used inconsistent sampling and exposure assessment methodologies and definitions for BeS and CBD. These differences have often prevented direct comparisons between studies, as well as the identification of a clear exposure-response relationship for BeS and CBD.

In the study by Madl, et al. 2007, a large data set of 3,831 personal lapel and 616 general area samples provided an opportunity to use several methods to reconstruct each worker's exposure prior to the ascertainment of BeS or the diagnosis of subclinical or clinical CBD, followed by an exposure-response analysis to determine whether a threshold for BeS and CBD could be identified. Four different methods were used to reconstruct historical exposures of each worker as industrial hygiene data were pooled by year, job title, era of engineering controls, and by complete work history (life-time weighted average) prior to diagnosis. The Madl study concluded:

> "*Results showed that exposure metrics based on shorter averaging times (i.e., year versus complete work history) better identified the upper bound worker exposures which could have contributed to the development of BeS or CBD. It was observed that all beryllium sensitized and CBD workers were likely exposed to beryllium concentrations greater than 0.2 µg/m^3 (95th percentile) and 90% were exposed to concentrations greater than 0.4 µg/m^3 (95th percentile) within a given year of their work history. Based on this analysis, it would appear that BeS and CBD generally occurred as a result of exposures greater than 0.4 µg/m^3 and that maintaining exposures below 0.2 µg/m^3 95% of the time may prevent BeS and CBD in the workplace."*

The authors noted that, in important respects, their study was the first of its kind stating that:

> *"An effective OEL is one that reduces or eliminates the risk of an adverse health effect or outcome in the majority of the working population. Unlike many other chemicals, identifying the exposure metric upon which to derive the OEL is particularly difficult for beryllium due to its immunologic pathogenesis. Historically, epidemiologic studies have studied BeS and CBD prevalence in relation to the mean or median beryllium concentration for the longest or most recent job title held. In general, these studies have found that certain job titles or operations may pose an increased or lesser risk of BeS and CBD, but none have shown an exposure-response pattern for these endpoints. The majority of these studies reconstructed worker exposures based on broad job classifications and have not evaluated the beryllium exposures which may have contributed to the identification of BeS or diagnosis of CBD in each worker. Our analysis is not only the first to reconstruct worker exposures to beryllium based on individual work history, but also is the first to evaluate a variety of exposure reconstruction methods and their influence on the exposure-response patterns for BeS and CBD. The results of our analyses show that the magnitude of the upper bound exposures, which may have led*

to the development of BeS and CBD, is typically not reflected in historical exposure estimates that are averaged over several years (e.g., LTW). Given the immunologic basis of BeS and CBD and that these endpoints have been documented, in some cases, as a result of relatively short-term exposures (e.g., < 1 year), it is important to not only understand central tendency estimates of exposure but also upper bound exposures.

In addition to understanding the plausible range of exposures which may contribute to the identification of BeS and diagnosis of CBD, for purposes of deriving an OEL, it is important to characterize the level of exposure below which the risk of disease is not substantially increased. The majority of studies conducted to date have involved cross-sectional studies which have not included adequate control comparison groups or an evaluation of worker-specific exposures. The analysis described in this study was the first to derive exposure estimates specific to each beryllium sensitized worker and CBD case. Because individual work exposures were derived based on specific job history and exposure data, this analysis provides a better understanding of the range of exposures to airborne beryllium that is associated with BeS or CBD. Based on this analysis of beryllium sensitized and CBD workers, it would appear that BeS and CBD generally occurred as a result of exposures greater than 0.4 µg/m^3 and that maintaining exposures below 0.2 µg/m^3 95% of the time may prevent BeS and CBD in the workplace."

The 2001 Department of Energy (DOE) study by Johnson reviewed and analyzed the results of the beryllium monitoring program at the Atomic Weapons Establishment beryllium facility in Cardiff Wales. The Cardiff study analyzes the single most extensive historical database of personal exposure monitoring data within the beryllium industry. A notable feature of the program was that it included personal exposure monitoring on every worker for every day worked over 36 years of operation. More than 200,000 personal samples were collected between 1981 and 1997 representing the last 16 years the facility was in operation. Based on these extensive sampling data, the Cardiff facility achieved compliance with the 2 µg/m^3 8-hour OEL 98 percent of the time. Since its inception, the Cardiff facility maintained a state-of-the-art exposure management program which included strict and consistent use of engineering controls, work practices, housekeeping, process containment, migration controls and the use of personal protective equipment. The Cardiff program resulted in one case of clinical CBD over 36 years of operation. Johnson concluded that the Cardiff experience "…appears to have successfully prevented the incidence of clinical CBD with the exception of one unique case."

The 2011 study by Schuler , an epidemiological surveillance study by the National Institute for Occupational Safety and Health at a beryllium production facility in the United States, was conducted to detect sub-clinical (asymptomatic) chronic beryllium disease (CBD) among a population of 264 workers at the world's largest primary beryllium production facility over a six year period. The strengths of this study lie in its design and in the detailed data that were available, both from workers (*e.g.,* specific work histories) and from existing historical sampling data where 4022 full-shift personal cassette samples representing 269 different jobs was available for analysis (averaging over 14 samples per job title). The personal exposure data was adjusted for changes in worker exposure over time by estimating the overall annualized changes in exposure using 76,349 area samples collected over the study period. The exposure estimates for each job were applied to each worker's work history to generate worker-specific historical exposure profiles, which were then summarized for use in epidemiologic analyses. This analysis, creating job exposure matrices for all categories of production, production support and administrative personnel, is unsurpassed by any previous study. The study observed that 6 of the 264 workers exposed above 0.38 µg-yrs/m^3 were determined to have asymptomatic sub-clinical CBD. The study also showed that persons having cumulative exposures below 0.38 µg-yrs/m^3 did not have subclinical or clinical chronic beryllium disease.

The 2013 study by Schuler (Long-term Efficacy of a Program to Prevent Beryllium Disease – Draft only) concluded: "The combination of increased respiratory and dermal protection, enclosure and improved ventilation of high-risk processes, dust migration control, improved housekeeping, and worker and management education showed utility in reducing sensitization in the program's first nine years. The low rate (0.6%, 1/175) among Late Program workers suggests that continuing refinements have provided additional protection against sensitization compared to the program's early years."

Classification Issues – Confusion between tests of Beryllium Metal versus Soluble Beryllium Compounds

The recent research conducted pursuant to REACH clearly demonstrates that differentiation between beryllium and the compounds of beryllium is a critically important issue because of the different physico-chemical and toxicological properties of the different beryllium compounds, especially when compared to those of beryllium metal and metallic alloys of beryllium. The current EU classification applies to "beryllium and its compounds" as a group. According to REACH, classification for the individual substance beryllium metal is required, and thus the classification of beryllium metal together with beryllium compounds is not compliant with the legislative requirements.

Recently performed OECD-compliant animal testing demonstrates that beryllium metal is not toxic after single oral bolus application, it is not a skin irritant and it is not an eye irritant. According to the guinea pig maximization test, beryllium metal is not a skin sensitiser. These results are contrary to the current harmonised classification of beryllium. Since all known human respiratory sensitisers elicit positive responses in predictive tests for contact sensitisation potential, beryllium metal is not a respiratory sensitiser in the classic sense.

Furthermore, occupational health surveillance of beryllium metal production workers has indicated that exposure to beryllium metal is not associated with the development of respiratory allergic reactions such as asthma and rhinitis. It should also be noted that the testing results, compiled for the REACH Beryllium Dossier under OECD testing protocols, clearly indicated that Be metal should not be classified as a skin irritant, an eye irritant, an acute inhalation toxin, a skin sensitizer, or orally toxic as it is today. Attached to this report is a dossier that supports a change in the harmonized classification of beryllium (Annex XV dossier).

Genotoxicity

One thousand five hundred thirty-one (1,531) publications were identified dealing directly with toxicity of beryllium and its compounds, of which 38 addressed carcinogenicity and 21 genotoxicity. The results were screened for beryllium metal as the substance of interest. None of the genotoxicity studies were conducted with beryllium metal, and no carcinogenicity study with oral or dermal exposure to beryllium metal was identified. However, one study with beryllium metal was identified, but not considered to add relevant information for risk characterisation under human exposure conditions due to the unphysiologic routes of exposure in this study (intramuscular or intrapleural injection). The genotoxicity tests conducted pursuant to

REACH (Strupp 2010) in vitro using beryllium metal powder, covering gene mutation, chromosome aberration, DNA repair and its inhibition, did not reveal any genotoxic potential for beryllium metal when extracted under simulated lung conditions. No signs of DNA repair as a measure of direct DNA damage, no gene mutation or clastogenicity were observed. Based on these test results, beryllium metal is not a mutagen, clastogen or DNA damager. Beryllium metal extracts did reduce DNA repair of rat hepatocytes that were severely damaged by external stimulus, while no effects were observed in slight or moderately damaged cells. This finding is in agreement with a publication on a soluble beryllium compound. Due to absence of effects at slight or moderate DNA damage (up to doses leading to 50% of the treated cells initiating DNA repair), relevance to human toxicity is considered rather low because the general, as well as the occupationally exposed, population does not have a high degree of background DNA damage. It is recognized that the in vitro systems used in testing have limitations with respect to quantitative assessment. These test results suggest that even if beryllium is considered to be a carcinogen - based upon the weak associations of the past - it clearly exhibits no non-threshold effects.

Animal Carcinogenicity

Most of the animal studies examined soluble beryllium compounds, which are rarely used in industrial settings and are not utilized in any consumer applications The above mentioned literature analysis revealed proof of carcinogenicity in the rat, while the database on other rodent species was found to be weak and not clearly indicating carcinogenicity. No carcinogenicity data on beryllium metal in non-rodent species was identified. The analysis of the animal studies indicated that none of the studies were conducted under GLP and only three studies were designed and reported in a way that they could be evaluated as "reliable with restrictions (2)" according to the system proposed by Klimisch. The other publications were "not assignable (4)" under the Klimisch system, as methods and results were only reported in abstract form without description of any experimental details or tabulation of data. Despite the overall low quality of reporting, application of a weight-of-evidence approach leads to the conclusion that the rat shows a carcinogenic response to inhaled beryllium metal. However the conclusion is very questionable considering the recent scientific reviews suggesting lung overload to be the cause for the observations. (Sivulka 2006, ILSI Risk Science Institute Workshop 2000). One potential reason for this difference may be the different mechanisms in clearing particles from the lung, especially after exposure to high doses. It should also be noted, that over the years, experimental attempts were made to reproduce this effect in other species, but the test animals failed to elicit carcinogenic responses.

Hollins 2009 reported similar findings and stated: "It is important to note that the majority of beryllium inhalation studies were conducted 40 yr ago, long before rigorous standardized bioassay criteria were established. With the exception of the ITRI studies, none of the studies would meet current expectations regarding design, statistical power, histopathology, or quality control. Relative differences in cancer defense mechanisms, however, may make rats a poor model for human cancer concerns. Humans have evolved many types of defenses that collectively ensure that they are orders of magnitude more resistant to spontaneous tumors than rats (Ames and Gold 1990). In addition, rats appear to be susceptible to tumors when fibrosis develops; this progression from fibrosis to tumor formation is often associated with doses that overwhelm clearance mechanisms and are unrealistic compared to human exposure conditions. Studies conducted more recently (early 1990s) by ITRI suggest carcinogenicity in rats and in lung tumor-sensitive mice (but not in other mice); however, rat lung tumors were produced in animals exposed to very high (up to 1,200 mg/m3) beryllium concentrations, resulting in high (up to 450 µg/g lung) initial beryllium lung burdens.

Thus, taken as a whole, these 33 studies offer little to resolve the issue of whether carcinogenic responses to beryllium in experimental animals support the designation of beryllium as carcinogenic to humans."

Epidemiology

It is important to emphasise that there is there is no epidemiological investigation on carcinogenicity of beryllium metal as an individual substance. The past beryllium studies were conducted on beryllium production workers in the United States and deal with basically the same cohorts who were exposed to very high levels of beryllium and – very importantly - to multiple compounds and forms of beryllium as well as other known carcinogens (asbestos, silica, coal tar etc.). Many shortcomings of the early studies (for example absence of a correction for smoking habits, comparison to inadequate controls etc.) have been intensively discussed in the scientific literature. Data from European disease registries and leading medical practitioners does not identify a link between beryllium exposure and lung cancer. The U.K. Industrial Injuries Advisory Council Position Paper 27, December 2009 Beryllium and Lung Cancer "states: "The main epidemiological evidence on occupational risks of lung cancer in beryllium-exposed workers derives from large US studies of beryllium process workers and of a US national register of beryllium workers. Although there have been several research reports, the evidence base is restricted to only a few cohorts with relevant data. The Council found no UK-relevant studies to inform its inquiries."

Data from European disease registries and leading medical practitioners do not identify a link between beryllium exposure and lung cancer. The Schweizerische Unfallversicherungsanstalt, in discussions with industry, reported that no lung cancer cases were observed in an occupationally beryllium-exposed population that was followed for over 20 years. A manuscript prepared by the European Commission on beryllium in relation to occupational diseases (Information Notices on Occupational Diseases: A Guide to Diagnosis, 2009) states that: *"The causal relationship between prolonged or repeated exposure to beryllium and the occurrence of bronchial cancer has not been firmly established, and due to the multi-causality of the occurrence of this type of cancer, the recognition of the occupational origin must lie on a thorough assessment based on rigorous scientific criteria taking into account all possible etiologies. Each case must therefore be considered separately."*

Epidemiology studies of human occupational exposure and effects (primarily lung cancer) do not provide consistent results. There is no epidemiological investigation on carcinogenicity of beryllium metal as an individual substance, but most of the exposed workers had a history of exposure towards beryllium compounds as well. Five original studies have been conducted, and have been re-analysed and commented several times. The early epidemiological work had shortcomings in exposure reporting and confounding factors were not adequately addressed (Mancuso et al. 1969/1970/1979/1980; Wagoner et al. 1980; Infante et al., 1980; Steenland et al., 1991). They were recently reviewed in detail (Hollins et al., 2009).

A small mortality study on 30 cases of beryllium-exposed workers who died from chronic beryllium disease is available (Williams, 1996). No case of lung cancer was identified among those deaths.

In a study *(Eurogip. Work-related Cancers: What Recognition in Europe 2010)* of multi-year cancer statistics from the data in occupational disease registries for Germany, Austria, Belgium, Denmark, Spain, Finland, France, Italy, Luxembourg, Netherlands, Portugal, the Czech Republic, Switzerland and Sweden covering 32 million workers: Only (1) case of cancer related to beryllium was reported. This compares to approximately 2.4 million new cancer cases diagnosed each year in Europe.

The US National Institute for Occupational Safety and Health (NIOSH) funded and performed a series of overlapping cohort mortality studies of lung cancer in beryllium workers, which culminated in the most comprehensive cohort mortality study to date, a cohort mortality study of 9332 workers at eight facilities, published in 1992 (Ward et al., 1992). The study recommended the performance of a nested control study of the relationship of estimated beryllium exposure to lung cancer, which was subsequently carried out and published in 2001 (Sanderson et al., 2001).

In the cohort mortality study (Ward et al., 1992), the overall standardized mortality ratio (SMR) was statistically significantly elevated in the beryllium-exposed cohort, but the statistical significance was lost after correction for smoking. When analysing the 8 study cohort individually, two had significantly elevated lung cancer SMRs (1.69 and 1.24, respectively). One of these was reduced to 1.49 after correction for smoking, the others corrected to 1.09, 0.96 or 1.02, depending on the smoking-correction method and reference used (Ward et al., 1992; Levy et al., 2002). Despite the paucity of statistically significant elevated SMRs after correction for smoking, the study presented a series of analyses and *ad hoc* observations on the smoking-uncorrected SMRs. No analyses or *ad hoc* comparisons were performed on smoking corrected SMRs. The selective analysis led to the conclusion that “Occupational exposure to beryllium is the most plausible explanation for the increased risk of lung cancer observed in this study”. A published study (Levy et al 2009) reanalysed the data of the cohort mortality study (Ward et al., 1992) using proportional hazards analysis and re-examined patterns without conditioning on statistical significance. This study concluded “The patterns observed provide little support for an association of lung cancer with beryllium work factors. This result is likely due to the absence in the original study of a significant overall excess of lung cancer after smoking adjustment.”

The nested control study (reference earlier Sanderson et al., 2001) performed as follow-up to (Ward et al., 1992) used the largest single plant cohort in the cohort mortality study. Cases did not have significantly higher values for any of the exposure metrics until exposure was lagged with latency assumptions of 10 and 20 years, resulting in significant case control differences being observed. The study was criticised with the argument that cases and controls had different mean ages of hire and that the lagging results were severely attenuated when these differences were narrowed by closer case-control matching on age at hire (Levy et al., 2007). Also, in simulations in which cohort members were selected at random to serve as “cases”, large differences between these randomly selected subjects and their controls were observed when exposure was lagged (Deubner et al., 2007).

In response to these criticisms the study data was reanalyzed (Schubauer-Berigan et al., 2008) using date of birth or age at hire as covariates, with the result that the relationship of lagged exposure to lung cancer was attenuated. Most importantly in this reanalysis, neither time worked with beryllium nor cumulative beryllium exposure were significantly associated with lung cancer whether lagged or unlagged, agreeing with Levy 2007. This analysis showed that while average and maximum exposure were not significantly associated with lung cancer unlagged or lagged 20 years, an association persisted at lag 10 years.

There has been extensive commentary (Langholz 2009, Heim 2009, Wacholder 2009, Deubner 2009) on these three studies. This commentary has suggested that the results in Levy 2007 may be affected by negative bias due to the method of control selection and that residual date-of-birth confounding may be present in the results in Schubauer-Berigan 2008. Thus, it was believed that there was uncertainty as to whether the rates of lung cancer are significantly increased in beryllium workers after smoking correction and whether the degree of beryllium exposure in beryllium workers (exposure to different species of beryllium) is related to the development of lung cancer. This uncertainty was articulated in a review (Hollins 2009) and also in the EU Commission manuscript "Information Notices on occupational Diseases: A guide to Diagnosis" (European Commission, 2009). A similar conclusion was reached by the Beryllium SIEF as a result of the studies conducted pursuant the REACH regulation.

In 2011, Rothman et al demonstrated that simulations and reanalysis showed that much of the reported association with lagged exposure was attributable to confounding by year of birth and year of hire and that lagging changes the exposure variable and can thus lead to changes in the amount of confounding. (Confounding after Risk-Set Sampling in the Beryllium Study of Sanderson et al.). Dr. Rothman's analysis of the original data in the first study identified serious confounding, which questions the validity of the studies. Confounding is a term used when comparisons between two groups of subjects are distorted, or incorrect, because the groups differ in some important characteristic not considered by the study. In this study failure to consider differences in date of date of birth and date of hire led to the incorrect conclusion that exposure to beryllium resulted in an increase risk of lung cancer among beryllium production workers in the United States.

Similarly, Dr. Rothman, found that the paper by Schubauer-Berigan was seriously flawed and that the paper's strongest observation, that lung cancer was related to time from first employment, was inaccurate due to "sparse data bias". Sparse data bias can occur when too little data is divided up between too many adjustment categories with the result that many of the categories have rates of zero, due to lack of cases in the categories. This expert finding is not understood by those who do not have the depth of knowledge needed to understand the significance of this finding.

The issue of carcinogenicity has been transformed from the perspective that beryllium metal is carcinogenic to a perspective that exposure to beryllium does not cause cancer. Dr. Paola Boffetta and Dr. Jack Mandel, renowned experts in epidemiology and carcinogenicity, performed the most recent comprehensive review of all the scientific evidence. Their study "Occupational exposure to beryllium and cancer risk: A review of the epidemiologic evidence" concluded: "The studies of beryllium disease patients do not provide independent evidence and the results from other studies do not support the hypothesis of an increased risk of lung cancer or any other cancer. Overall, the available evidence does not support a conclusion that a causal association has been established between occupational exposure to beryllium and the risk of cancer."

Beryllium a Critical Substance

Beryllium Designated as a Critical Material with a Lack of Suitable Alternatives

According to the European Commission "*The most significant threats originate from perceived risks associated with the use of beryllium in electronic products. EU regulatory fears and NGO propagated "banning" of the use of materials containing beryllium lead to unwarranted attempts to find substitutes that do not offer the same qualities with respect to performance, sustainability and environmental protection. The data that authorities rely on is not current and does not reflect the most recent scientific studies. In general, authorities are reluctant to break from the past and are not open to new scientific studies even if they are* *conducted in accord with OECD guidelines or originate from proven workplace strategies. Because the cost of beryllium is high compared with that of other materials, it is used in applications in which its properties are crucial. In some applications, certain metal matrix or organic composites, high-strength grades of aluminium, pyrolytic graphite, silicon carbide, steel, or titanium may be substituted for beryllium metal or beryllium composites. Copper alloys containing nickel and silicon, tin, titanium, or other alloying elements or phosphor bronze alloys (copper-tin-phosphorus) may be substituted for beryllium-copper alloys, but these substitutions can result in substantially reduced performance."* (European Commission Critical Raw Materials for the EU - Report of the Ad-hoc Working Group on defining critical raw materials, 2010).

The inability to replace beryllium is also reflected in the United States Geological report on Beryllium (2010). The report states: *"Due to its high costs beryllium is only used in applications where its properties are crucial. Therefore, it is hard to substitute. Nevertheless, certain metal matrix or organic composites, high-strength grades of aluminum, pyrolytic graphite, silicon carbide, steel, or titanium may be substituted for beryllium metal or beryllium composites. There are some possible substitutes in specific alloys, but often combined with a loss in performance."*

The Öko-Institut e.v., in its "Study on Hazardous Substances in Electrical and Electronic Equipment, Not Regulated by the RoHS Directive" did not propose beryllium or beryllium oxide as candidates or phase out substances because *"after evaluation of all available data and information these substances do not clearly fulfil the defined selection criteria as described in Section 2.2 and/or they are not present in the final product in their original chemical form due to reaction with the matrix and/or there is a low risk of exposure to human and environment and/or there is not yet sufficient information on possible exposure and effects available to give a justified recommendation on an inclusion in the RoHS Directive."* The report further stated: *"In the middle-term it is unlikely that Beryllium will be subject to authorisation under REACH (cf. 6.2.1) Beryllium is further needed because of its functionality. Inclusion in RoHS not recommended."*

Exposure Profiles and Risk Management

The industry has initiated risk management measures to prevent chronic beryllium disease among workers which have reduced the levels of worker exposure to beryllium in modern industry by a thousand-fold lower than the exposure levels in the 1940s.

In general, most operations utilize beryllium-containing materials in a finished or semi-finished form where no special controls are needed. Only those operations involving the generation of airborne particulate require the use of specialized controls.

To give a general overview on the use and processes applied in a condensed form, the terminology developed under REACH is used in the following table:

Sectors of Use (SU)	
SU3	Industrial uses: Uses of substances as such or in preparations at industrial sites
SU2b	Offshore industries
SU14	Manufacture of basic metals, including alloys
SU15	Manufacture of fabricated metal products, except machinery and equipment
SU16	Manufacture of computer, electronic and optical products, electrical equipment
SU17	General manufacturing, e.g. machinery, equipment, vehicles, other transport equipment

SU23	Electricity, steam, gas water supply and sewage treatment
SU24	Scientific research and development
SU0	Other: Manufacture of medical and defence equipment
Process Category (PROC)	
PROC1	Use in closed process, no likelihood of exposure
PROC2	Use in closed, continuous process with occasional controlled exposure
PROC4	Use in batch and other process(synthesis) where opportunity for exposure arises
PROC5	Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact)
PROC8b	Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities
PROC14	Production of preparations or articles by tabletting, compression, extrusion, pelletisation)
PROC15	Use as a laboratory reagent
PROC21	Low energy manipulation of substances bound in materials and/or articles
PROC22	Potentially closed processing operations with minerals/metals at elevated temperature. Industrial setting.
PROC23	Open processing and transfer operations with minerals/metals at elevated temperature
PROC24	High (mechanical) energy work-up of substances bound in materials and/or articles
PROC25	Other hot work operations with metals
PROC26	Handling of solid inorganic substances at ambient temperature
Chemical Product Category (PC)	
PC7	Base metals and alloys
PC20	Products such as pH regulators, flocculants, precipitants, neutralization agents and other unspecific
Environmental Release Category (ERC)	
ERC3	Formulation in materials
ERC6b	Industrial use of reactive processing aids
ERC12a	Industrial processing of articles with abrasive techniques (low release)
Article Category (AC)	
AC1	Vehicles
AC2	Machinery, mechanical appliances, electrical / electronic articles
AC7	Metal articles
Other	Offshore industries, manufacture of electric/electronic (connectors/shieldings) products, medical and optical products, general manufacturing (machinery, tools, equipment, marine, aeronautic and space transport equipment, nuclear power plants, defence applications)

Recycling

Recycling, mostly from scrap generated during the manufacturing of beryllium products, may account for as much as 10% of apparent consumption [USGS 2009]. Also, copper beryllium or nickel beryllium alloy scrap is directly recycled back to produce new alloy since it is attractive from both an economic and energy conservation point of view. The pure beryllium metal components used in technological applications have extremely long lifetimes, and, therefore, return to the recycle stream very slowly. Some, because of applications in space or because of their sensitive military nature, do not return at all. When these components finally return, they can be easily recycled. However, recovery of beryllium metal from copper beryllium alloys that are included in components of post consumer scrap (like electronics) is difficult because of the small size of the components, difficulty of separation, overall low beryllium content per device and the low beryllium content in the copper beryllium alloy (average 1.25 % beryllium). The alloy makes up approximately 0.15% of the copper used in electrical equipment which, during pre-processing of end-of-life equipment, is collected together with other copper in the scrap and diluted to ~ 2 ppm in the copper recycling stream. In responsible copper recycling processes, the extremely small quantities of beryllium are immobilized in slags. Therefore, most of the scrap is recycled for its copper value, since beryllium recovery is not economically feasible. As a result, for old scrap the recycling flow value is quite high (~75%), but the recycled content and particularly the End-of Life Recycling Rate (EOL RR) material specific rate are very low.

Old scrap in recycling flow	Recycled content	EOL RR/Material specific	EOL RR/Material unspecific
= 14% in USA [USGS 2004] 75% globally [Materion Brush 2009]	= 10% in USA [USGS 2004] 22-25 % globally [Materion Brush 2009]	7% in USA [USGS 2004] 0% globally [Materion Brush 2009]	Same rate as copper scrap [Brush 2009]* Note that this Be goes to slag during final metal recovery!

In an effort to quantify the potential for worker exposure to airborne beryllium, a case study was conducted at four precision stamping facilities processing copper beryllium.

These facilities performed a variety of mechanical and thermal activities during the manufacture of beryllium-containing components for the electronic industry. The study found that one hundred percent (100%) of the 145 samples obtained from mechanical, thermal and support operations were below 0.2 μg/m³. The following is a summary of the results:

PRECISION STAMPING CASE STUDY SUMMARY OF AIRBORNE BERYLLIUM EXPOSURES			
Process Category	Number of Sample Observations	Number of Samples greater than 2.0 μg/m³	Number of Samples greater than 0.2 μg/m³
Mechanical			
• Stamping Press Operators	49	0	0
• Die Repair	27	0	0
• Assembly	14	0	0
• Dry Tumble Deburr	4	0	0
Thermal			
• Heat Treating (inert atmosphere)	9	0	0
• Resistance Welding	8	0	0
Support			
• Inspection	17	0	0
• Shipping/Packing	17	0	0

Additionally, a study was conducted in 2010 at a leading post-consumer electronic recycling facility in the EU. This facility processes waste electronic products and separates the materials into several value streams including, plastics, steel, copper, aluminium and precious metals. The study involved collecting personal breathing zone samples on workers for beryllium. All results were below the limit of detection or the limit of quantification and well below any regulatory limit.

Electronic Recycling Case Study Summary of Airborne Beryllium Exposures in a Recycling Facility within the EU			
Process Category	Number of Sample Observations	Number of Samples greater than 2.0 μg/m^3	Number of Samples greater than 0.2 μg/m^3
Pre-Sort	9	0	0
Sorting	31	0	0
Shredding	16	0	0
Separation of Value Streams	12	0	0

It is clearly evident that electronic recycling processes within the EEA do not present an exposure hazard to workers.

Additionally, the UNEP Mobile Phone Partnership Initiative (MPPI) Project 3.1 (March 2009) report stated

> *"Beryllium is not an absolute barrier to environmentally sound material recovery and recycling, but it is a consideration in selection of appropriate recovery processes and facilities."*

The well managed copper recycling processes that currently exist in the EEA, coupled with the small amounts of beryllium metal that are present in electronic wastes, support the need to continue to advance the use of beryllium-containing materials in electronic products where miniaturisation, decreased raw material utilisation and improved energy efficiency are drivers in product designs and consumer expectations.

Beryllium Worker Protection Model

As mentioned previously, the members of BeST have worked cooperatively with the governmental authorities and particularly the National Institute of Occupational Safety & Health (NIOSH) to develop a protective model that prevents chronic beryllium disease and minimizes beryllium sensitisation to background levels. The thirteen years of research resulted in an enhanced Beryllium Worker Protection Model that was based on reducing worker exposure via all routes of entry. The main goal of the Beryllium Worker Protection Model was to prevent CBD and BeS sensitization by preventing beryllium from entering the lungs and included the use of engineering controls to reduce employee exposures to below the self imposed exposure limit of 0.2 μg/m^3 that was demonstrated to be scientifically supportable and effective at preventing CBD and beryllium sensitization.

The model focused on keeping work areas visibly clean, reducing skin exposure; maintaining company supplied work clothing visibly clean; controlling particulate migration at the process, within the work area, and at plant boundaries; keeping the workplace organized and improving housekeeping to meet a standard of visibly clean surfaces; and preparing beryllium workers to effectively use the new beryllium safety model.

As a result of the leading studies indicating this model of beryllium safety is effective, an e-learning, computer-based tool called the "Interactive Guide to Working Safely with Beryllium and Beryllium-Containing Materials" was developed.

This award winning training tool is available at http://berylliumsafety.com.

Summary

Beryllium metal, copper-beryllium alloys (CuBe), aluminium-beryllium alloys (AlBe) and nickel-beryllium alloys (NiBe), in solid form and as contained in finished products, present no special health risks. Most manufacturing operations conducted properly on well-maintained equipment are capable of processing beryllium-containing alloys with a high margin of safety by keeping exposures to within our limit of 0.2 $\mu g/m^3$.

Facilities handling beryllium-containing materials in ways which generate particulate should be encouraged to use engineering and work practice controls to control potential worker exposures. Our knowledge, experience and understanding gained from the most current and the most relevant studies has resulted in preventing sensitization and CBD.

Research findings suggest that consistently keeping airborne exposure in beryllium production operations to beryllium below of 2.0 $\mu g/m^3$ can prevent clinical CBD. Recent research findings have also indicated that individuals at operations with exposures that rarely exceed 0.2 $\mu g/m^3$ did not experience sensitization or subclinical CBD.

We welcome the opportunity to partner with regulatory authorities and downstream users to share our expertise to ensure workers are protected with a high margin of safety.

We are very concerned that setting a limit in the EU that is not achievable will undermine worker protection and lead to a state of non-compliance or more likely result in migration of the manufacturing base to alternative regions of the world.

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