

## **Summary and Discussion of Key Studies and Issues Relevant to Establishing an Occupational Exposure Limit for Airborne Beryllium**

1. Based on the large number of personal lapel samples and the completeness of the data set over the respective study periods, the studies by Cummings, Madl and Schuler and Johnson, briefly described below, provide the most complete and thorough studies upon which to base an 8-hour time weighted average (TWA) occupational exposure limit (OEL) for beryllium. Based on a critical analysis of the data and findings in these studies and with no consideration of technical or economic feasibility we believe the preponderance of the evidence supports the adoption of an OEL of no lower than  $0.6 \mu\text{g}/\text{m}^3$  in inhalable fraction 8-hour Time Weighted Average. Since 2000, as part of its beryllium control model, BeST has used an exposure level of  $0.6 \mu\text{g}/\text{m}^3$  as an action level, which has been successful in preventing chronic beryllium disease (CBD) and reducing sensitization to background levels. As a result of these research findings, BeST has adopted an 8-hour TWA Recommended Exposure Guideline (REG) for airborne beryllium of  $0.6 \mu\text{g}/\text{m}^3$  and is communicating this REG to its downstream customers and interested stakeholders.
  - A. The study by Cummings et al. provides an analysis of the effectiveness of the industry's beryllium exposure control model including the use of an exposure action limit of  $0.2 \mu\text{g}/\text{m}^3$  (in thoracic fraction, CFC sampling method used in the US, corresponding to 0.6 in inhalable fraction used for metal in EU, according to the Fraunhofer ITEM study (Kock et al.2015)). 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 as the background rate found in the non-occupationally exposed population.
  - B. The study by Madl et al. with over 3800 personal samples was published in 2007. The Madl study uses four different methods to reconstruct historical exposures of each worker. These analyses provide a more complete picture of exposure response. This comprehensive analysis concludes that beryllium sensitization (BeS), subclinical chronic beryllium disease (sCBD) and clinical chronic beryllium disease (cCBD) occur as a result of exposures greater than  $0.4 \mu\text{g}/\text{m}^3$  and that maintaining exposures below  $0.2 \mu\text{g}/\text{m}^3$  95% of the time may prevent BeS, sCBD and cCBD in the workplace (in thoracic fraction, CFC sampling method, corresponding to 0.6 in inhalable fraction).
  - C. Schuler et al. with over 650 personal samples demonstrates that exposure levels of  $0.2 \mu\text{g}/\text{m}^3$  and below (in thoracic fraction, CFC sampling method, corresponding to 0.6 in inhalable fraction) are not associated with subclinical/surveillance chronic beryllium disease (sCBD).
  - D. The Johnson et al. study with over 217,000 personal samples demonstrated that the Cardiff beryllium control model achieved compliance with the United Kingdom 2

$\mu\text{g}/\text{m}^3$  8-hour Maximum Exposure Limit (MEL) over 98 percent of the time and prevented clinical chronic beryllium disease (cCBD).

The Madl study's larger, more complete and thorough sampling data and analysis supersedes the data and analysis performed of the same facility by Kelleher et al. There are significant gaps in Kelleher's paper that prevent it from adding to our understanding of exposure levels that may lead to sCBD and cCBD. For example, Kelleher's exposure analysis relied on a total of 100 personal samples and in some cases, as few as four samples for a particular job. Madl's data set included over 3,800 personal samples and over 600 general area samples. Kelleher assumed that exposures had not changed over time, whereas Madl analyzed historical data and clearly demonstrated that exposures did change over time.

2. Because CBD has been identified in persons exposed less than one year and CBD results from an immune response, beryllium is not a conventional dose/response toxin. Since CBD only occurs in a small subset of the exposed population, development of an OEL for beryllium should not rely on the mean and median exposure data or life-time weighted average data from either the 2001 study by Kelleher et al. or the 2007 study by Madl. The analysis provided by Madl identified for clinical and subclinical CBD workers the 95<sup>th</sup> percentile exposures during the highest exposed year worked as the data most relevant to identifying an appropriate 8 hour OEL. We believe the highest year of exposure is the best metric because use of multiple years of data dilutes the actual worker high and low exposures. This approach to data analysis and interpretation aligns with the recommendations found in the AIHA text *A Strategy for Assessing and Managing Occupational Exposures*. The use of median data tends to mask important aspects of workplace exposures relevant to exposure health risks by simply not considering the health significance of the upper half of the measured exposure values. Even the Kelleher study cautions against the use of its central tendency data when considering an OEL for beryllium where it stated:

*“Comparisons of our data with occupational exposure limits, however, must be made with caution because occupational exposure limits are based on the upper tail of the exposure distribution rather than on measures of central tendency.”*

3. For beryllium related disease, chronic beryllium disease is the adverse health effect (material impairment of health) upon which to adopt an OEL. The American Conference of Governmental Industrial Hygienists (ACGIH) Biological Exposure Indices (BEI<sup>®</sup>) Committee determined that the appropriate adverse health effect is chronic beryllium disease (CBD) and not beryllium sensitization (BeS). Prior to the 1980s, the term “beryllium sensitization” referred to the inflammatory response in the lungs (a health effect) associated with the early physical symptoms of clinical CBD. Today, beryllium sensitization does not refer to an inflammatory response, but refers to a laboratory test result which may indicate that a person's immune system can recognize and respond to the presence of beryllium. Although different tests are used to detect immune system beryllium sensitization, the test most frequently used today is the beryllium blood lymphocyte proliferation test (BeBLPT).

The BeBLPT is a laboratory test used to indicate whether a person is sensitive to beryllium by measuring if a response occurs when a water-soluble beryllium compound is added to immune cells isolated from a blood sample. A lymphocyte proliferation response does not represent a “material impairment of health”; it does not shorten life expectancy, compromise organ or tissue function or otherwise adversely affect health. Sensitization to beryllium as measured by the BeBLPT is not an illness or disability and, as such, is not considered a health effect. The BeBLPT, in and of itself, does not detect subclinical or clinical CBD. Diagnosing subclinical CBD requires a biopsy to obtain samples of lung tissue using a medically invasive procedure called a bronchoscopy, which has associated health risks, such as a collapsed lung, bleeding or infection and a possibility of death.

Key studies relevant to the issue of identifying the appropriate health effect upon which to base an OEL are as follows.

The Madl study is the only study to identify the differences in worker health outcomes by denoting those workers who tested as beryllium sensitized (BeS), and those diagnosed with subclinical CBD (sCBD) or clinical CBD (cCBD). Of these outcomes, only cCBD is a material impairment of health.

The studies by Donovan and Cher described below demonstrate that the Beryllium Blood Lymphocyte Proliferation Test (BeBLPT) is not a reliable indicator of beryllium sensitization (BeS) due to the inconsistent performance of the test, the absence of a standardized method of testing, inconsistent test interpretation, the variability of test outcomes and the reversion of positive results to normal after retesting over time. Donovan provides evidence that BeS, as defined as two positive BeBLPT results in an individual, occurs in persons not occupationally exposed to beryllium and that worker BeBLPT results often oscillate between positive and negative results. Since BeS is only defined today as an in-vitro test result (BeBLPT), BeS should not be used as a health end-point by ACGIH as a basis for its beryllium NIC. In addition, sensitization is not a material impairment of health and does not meet ACGIH’s position statements regarding the “TLV® Basis”.

- The study by Donovan et al. found that: approximately 1% of new employees with no known occupational exposure or possible take-home exposures to beryllium confirmed as BeS from the time of hire. Confirmation was based on two positive BeBLPT results. The authors also concluded that workers BeBLPT results oscillated between positive and negative, and that at least one negative or borderline/negative result was observed in 100% of new workers who underwent follow-up testing after they had been confirmed BeBLPT positive. The authors also noted the variation in intra- and inter-laboratory testing methods and concluded:

*“The detection of confirmed positive results in non-occupationally exposed persons, the apparent reversions of previously confirmed positive results, the identification of a positive BeBLPT peak prevalence period and variation in intra- and inter-laboratory test methods and interpretation should be considered when interpreting results from studies utilising the BeBLPT, especially when considering worker-specific interventions”*

- The study by Cher et al. 2006 demonstrated that persons can be misclassified as BeS due solely to the variation in the testing performance of the laboratories that

conduct the BeBLPT. The study is based on the analysis of over 8,800 BeBLPT results using Statistical Process Control methods. The authors stated:

*“During the period of this study, all laboratories displayed variation in test results that were beyond what would be expected due to chance alone. Patterns of test results suggested that variations were systematic.”*

- A 2006 study by Borak et al.<sup>13</sup> using World Health Organization (WHO) criteria reviewed the reliability and appropriateness of using the BeBLPT as a screening tool and found that the accuracy and reliability of the BeBLPT is uncertain and concluded that *“There is currently insufficient scientific evidence to support the use of BeLPT for routine screening of asymptomatic individuals.”*
4. The sensitization produced by beryllium (lymphocyte proliferation) is not the same as normally considered for a compound considered to be a chemical sensitizer. The concept of chemical sensitizer is well documented and widely understood. A sensitizer is most often defined as *“a chemical that causes a substantial proportion of exposed people or animals to develop an allergic reaction in normal tissue after repeated exposure to the chemical.”* A chemical allergy is generally considered to be an adverse reaction to a chemical resulting from previous sensitization to that chemical or to one that is structurally similar. After an initial allergic reaction to a chemical, very small subsequent exposures can evoke a severe response. The range of chemical sensitization response is broad and generally manifests itself in forms such as a skin rash, eye irritation, allergic asthma, or even anaphylactic shock.

Occupational exposure to insoluble forms of beryllium is not at all associated within the above generally accepted concepts of a chemical sensitizer. Chemical sensitization has not been demonstrated in persons exposed to insoluble forms of beryllium either in massive or particulate forms. No dermal sensitization reaction such as skin rash, hives, irritation of the nose, throat, skin or eye, is associated with dermal exposures to insoluble forms of beryllium. There is no short-term immunological mediated respiratory reaction such as allergy or asthma involving shortness of breath, chest tightness, wheeze, cough, and irritation associated with airborne exposures to insoluble forms of beryllium. Insoluble forms of beryllium include beryllium metal, beryllium aluminum composites (AlBeMet<sup>®</sup>), beryllium oxide and alloys containing beryllium such as copper beryllium. These insoluble forms comprise nearly the entire commercial market for beryllium.

Skin reactions and lung reactions have occurred with exposures to beryllium salts such as beryllium sulfate and beryllium fluoride during the chemical extraction of beryllium by the primary producers. These soluble beryllium salts should be considered as chemical sensitizers.

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