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Critique of ACGIH (2009) documentation for Threshold Limit Value for Beryllium and Compounds

ToxStrategies, Inc. has prepared a critique of the American Conference of Governmental Hygienists (ACGIH) documentation for the threshold limit value (TLV) for beryllium and compounds (ACGIH 2009). This critique focuses on ACGIH's approach to setting the TLV and the epidemiological studies of beryllium-exposed workers that provide the underlying basis for the TLV value. Because the TLV is based on the occurrence of beryllium sensitization (BeS) and chronic beryllium disease (CBD), the critique addresses only these endpoints.

Background

In 2009, ACGIH adopted a TLV as an 8-hour time-weighted average (TLV-TWA) of 0.00005 milligrams per cubic meter (mg/m^3) [0.05 micrograms per cubic meter (μg/m^3)] for beryllium and compounds, as beryllium, applied to inhalable particulate matter. The critical effects were BeS and CBD among beryllium-exposed workers of various industries. ACGIH specifically cited Kelleher et al. (2001) and Madl et al. (2007a)[1] as the basis of the 0.05 μg/m^3 value. The Stanton et al. (2006), Schuler et al. (2005), and Rosenman et al. (2005, corrected in 2006) studies were also cited. However, the 0.05 μg/m^3 TLV was specifically derived from the findings of Madl et al. (2007a). Even though this study investigated several exposure metrics, the ACGIH selected lifetime weighted (LTW) mean exposure as the basis for the TLV. The LTW is the cumulative mean exposure level divided by the duration of exposure and represents the average exposure level for the duration of employment.

Executive Summary

Our primary comments on the documentation for ACGIH TLV for beryllium and beryllium compounds are summarized in the Executive Summary.

1) ACGIH Did Not Use a Traditional Risk Assessment Approach to Set the TLV

1 Kelleher et al. (2001) and Madl et al. (2007) both studied workers of the same beryllium machining facility. Kelleher et al. (2001) was a case control study, and Madl et al. (2007) expanded the exposure characterization for workers who had been sensitized or were diagnosed with CBD in the Kelleher et al. (2001) study (the cases), as well as for seven additional workers who had been sensitized or diagnosed with CBD since the Kelleher et al. (2001) study. Madl et al. (2007) did not provide further evaluation of the controls in Kelleher et al. (2001).

ACGIH developed the TLV from a study that investigated the exposures of workers who had been sensitized and/or developed subclinical or clinical CBD (Madl et al. 2007a). Although the exposure characterization process of this study was rigorous, it did not evaluate the exposures of those who did not develop BeS or CBD, and thus the frequency of effect (BeS and/or CBD) cannot be assessed relative to exposure. In fact, Kelleher et al. (2001), an earlier case-control study of the beryllium-exposed workers studied by Madl et al. (2007a) and which was cited as one of the primary sources for the TLV, could not establish an exposure-response relationship for BeS and CBD with any exposure metric studied, including LTW median exposure. Thus, it appears that ACGIH reached the position that there were inadequate data to use traditional risk assessment approaches to characterize the exposure-response relationship, and instead relied on information regarding the exposures of cases (Madl et al., 2007a) without information regarding exposures of the controls.

This is a limitation because without a denominator (controls or total exposed population), it is not possible to quantify the exposure-response relationship and thus, one cannot predict risk by exposure levels, assess whether a threshold has been established, or know whether the exposure metric chosen (LTW average exposure in this case) is in fact causally related to and/or predictive of BeS and CBD. For these reasons, the NRC (2008) concluded that the data in Madl et al. (2007a) could not be used for risk assessment. The TLV should be reconsidered today using traditional risk assessment methodology applied to the data from Schuler et al. (2012), which includes the most complete and rigorous exposure reconstruction conducted to-date and observable exposure-response relationships that may be used for risk assessment. Notably however, Schuler et al. (2012) did not quantify the occurrence of CBD or BeS with the exposure metric of LTW average exposure, and as discussed in the next point, studies of BeS and CBD among Be exposed workers have not shown that LTW average exposure is predictive of an increased risk of BeS and CBD.

2) The LTW Exposure-Metric Should Not Be Used as the Basis of the TLV-TWA

Madl et al. (2007a) reconstructed beryllium exposures for 27 cases of BeS, subclinical CBD or clinical CBD using five different approaches, providing a median, mean and 95th percentile estimate for each approach. Without any discussion, ACGIH chose to base the TLV-TWA on the mean LTW exposure—one of five exposure metrics studied—even though Madl et al. (2007a) cautioned that LTW exposure may not be the best metric for predicting BeS and CBD, because BeS can occur within a relatively short duration of exposure in association with higher concentrations than mean LTW exposures. Mean LTW values are based on annualized average data and do not characterize peak exposure. Madl et al. (2007a) state, "…work in higher potential exposure jobs such as in the machining of beryllium metal and beryllium oxide shows greater prevalence of BeS and CBD than lower exposure jobs." Further, the authors note, "The results of this study show that cumulative exposure estimates (i.e., LTW) do not reflect the upper bound measurements that potentially led to BeS and CBD." Although we recognize that the study design of Madl et al. (2007a) does not allow for differentiation of the most appropriate exposure metric, the findings of the original authors should not be disregarded without comment.

LTWs are generally derived using annualized or multi-year averages of datasets, which often involve combining averaged data that are averaged more than one time. The averaging of averaged data over a year or multi-year timeframe mask the variations in the daily samples from which the averages were derived, and thus, the LTW is not comparable to an 8-hour exposure limit value. Furthermore, LTW exposure does not account for the duration of exposure (as a simple measure of cumulative exposure would) or peak exposure concentrations, which is arguably a better exposure metric because a higher-level exposure, as opposed to long-term average exposure, is generally considered necessary for triggering an immune response. In light of this evidence, it would have been more appropriate to use the conclusions of the original authors (Madl et al., 2007a) and set the TLV at 0.2 μg/m^3, which is the 95th percentile TWA exposure for highest year worked using all the original and supplemental data[2].

3) The 0.05 μg/m^3 TLV Is an Arbitrarily Selected Value and Not Supported by the Results of Madl et al. (2007a)

ACGIH arbitrarily created LTW exposure ranges of 0.05 to 0.1, 0.1 to 0.2 μg/m^3, and >2μg/m^3 from the Madl et al. (2007a) study data, stating that no cases had mean LTW exposure estimates below 0.05 μg/m^3, and three cases had mean LTW exposure estimates between 0.05 to 0.1 μg/m^3 (the remaining cases had mean LTW exposures greater than 0.1 μg/m^3). However, this is not a range that was reported by Madl et al. (2007a); in fact, upon inspection of Table III of Madl et al. (2007a), the actual mean LTW exposure estimates for these three cases occurred at 0.09, 0.1 and 0.1 μg/m^3. Thus, even if mean LTW exposure was the appropriate exposure metric for purposes of establishing a TLV, the ACGIH arbitrarily chose a value of 0.05 μg/m^3, which is nearly a factor of two lower than the lowest mean LTW exposure estimate reported in the Madl et al. (2007a) study (0.09 μg/m^3).

4) The Stanton et al. (2006), Schuler et al. (2005) and Rosenman et al. (2005, as corrected in 2006) Studies Do Not Offer Support For the TLV-TWA of 0.05 μg/m^3

ACGIH states that studies conducted by Stanton et al. (2006), Schuler et al. (2005), and Rosenman et al. (2005) also support a TLV-TWA of 0.05 μg/m^3; however, upon inspection, none of these studies appear to support the ACGIH TLV recommendation.

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[2] This is described as Approach 2 in Madl et al. (2007a).

Stanton et al. (2006) evaluated workers at three copper-beryllium alloy distribution centers and characterized exposures for the 1996 to 2004 time period. Only one employee was identified with BeS and subsequently diagnosed with CBD. ACGIH acknowledges that the one worker with BeS and CBD was employed in the shipping/receiving department for 22 years and likely had significant exposure to beryllium oxide powder. Further, this worker was employed from 1978 to 2000; thus, 18 of his 22 years of exposure occurred prior to any of the air measurements. As the authors cautioned, the exposure characterization conducted from 1996 to 2004 in this study should not be used to offer conclusions regarding this individual's exposure over his entire exposure period. In short, the exposure characterization cannot be used to evaluate the beryllium exposures that sensitized and/or caused CBD in the only affected individual, and it is tenuous to argue that this study could be used to support any value as a TLV.

Stanton et al. (2006) reported that the median of full-shift personnel lapel samples for sample collected from 1996 to 2004 was 0.03 μg/m^3, the mean was 0.05 μg/m^3, and 97% of the samples were less than 0.2 μg/m^3. Although it may seem that these data support the TLV-TWA of 0.05 μg/m^3, the data would also support limited risk at exposures <0.2 μg/m^3 because essentially no CBD or BeS was observed when 97% of exposure measurements were less than 0.2 μg/m^3. Interestingly, the highest exposures (95th percentile) at the service center handling bulk product was 0.26 μg/m^3 with no detected BeS and CBD.

Schuler et al. (2005) evaluated workers at a copper-beryllium alloy facility. Ten of 144 employees were identified with BeS, of which six were diagnosed with CBD. Schuler et al. (2005) reported that the prevalence of CBD for those ever working in three subcategories under wire and rod production was significantly greater than the prevalence of CBD in those workers that had never worked in these areas.[3] Median beryllium concentrations estimated for these three job/process subcategories were 0.03, 0.12, and 0.06 μg/m^3. Again, these data may appear to support the TLV-TWA of 0.05 μg/m^3. However, as noted by ACGIH, the median beryllium concentrations for job categories with no statistically significant risk of CBD ranged from 0.02 to 0.11μg/m^3 (vs. 0.03 to 0.12 μg/m^3 for those job categories with a statistically significant risk). ACGIH points out, but then ignores, that the real difference between these groups of job categories is not the range of median concentrations, but the percentage of measurements exceeding 0.2 μg/m^3 (25% vs. 7% or less), leading the study authors to suggest that their results

[3] ACGIH refers to this latter group as "non-exposed controls" but that is a mischaracterization of the comparison group and in fact there is no "non-exposed" or control group in this study.

provide an opportunity to identify better exposure metrics than historical total mass airborne Be measurements. Thus, Schuler et al. (2005) is supportive of the conclusions of Madl et al. (2007a) that keeping occupational exposures below 0.2 μg/m^3 may prevent BeS and CBD.

Moreover, this study provides a further example of why traditional risk assessment approaches with the most informative exposure-metric, which does not appear to be LTW, are needed to quantify the exposure-response relationship. Based on Schuler et al. (2005), and as explained by Madl et al. (2007a), median concentration is not an appropriate exposure metric. Rather, the Schuler et al. (2005) study seems to more strongly support the exposure limit suggested by Madl et al. (2007a) of 0.2 μg/m^3 because, regardless of median exposures, when a larger percentage (25%) of exposures exceed 0.2 μg/m^3, the risk of BeS and CBD was significantly increased.

Rosenman et al. (2005, as corrected in 2006) conducted medical screening of 577 former workers from a beryllium processing facility, identifying 40 workers with BeS and 44 cases of CBD. The study authors attempted to correlate BeS and CBD prevalence to various measures of beryllium exposure, but could not identify an exposure-response for any of the exposure metrics evaluated. ACGIH reports that Rosenman et al. (2005) conclude that the prevalence of BeS and CBD in their study is higher than that reported in other studies, but ACGIH also notes that the reported mean and peak beryllium concentrations are also higher, with mean concentrations generally greater than 1 μg/m^3. It is therefore unclear why ACGIH believes that this study supports the TLV-TWA of 0.05 μg/m^3. If anything, this study supports a TLV of 0.2 μg/m^3 because, as ACGIH notes, there were no workers identified with BeS or diagnosed with definite or probable CBD with Daily Weighted Average (DWA) exposure concentrations of <0.2 μg/m^3.

5) The Additional Studies Cited by ACGIH as Supportive of the TLV Do Not Provide Adequate Data to Quantify Exposure-Response or Develop a TLV-TWA

In addition to the aforementioned studies, ACGIH cited Johnson et al. (2001), Kreiss et al. (1996, 1997), Cummings et al. (2007), Day et al. (2006, 2007), Cullen et al. (1987), and Maier et al. (2008) as epidemiology studies with exposure and health data pertinent to the development of the TLV-TWA for beryllium. However, the criteria used by ACGIH to reach these determinations are not clear. These studies are quite limited due to poor exposure characterization, exposure misclassification and/or inadequate statistical power, as stated by the original study authors. These studies generally lack exposure-response data with few individuals that actually have BeS and CBD, and thus, are not useful to support the development of a TLV-TWA. Furthermore, citing these studies as supportive of the TLV gives a false sense of consensus regarding the appropriateness of the TLV in the published literature.

Instead, Madl et al (2007a), Stanton et al. (2006), Schuler et al. (2005) and Rosenman et al. (2005, as corrected in 2006) are the better studies, and as discussed previously, data from these studies support a TLV-TWA of 0.2 μg/m^3.

6) The TLV Should be Based on the Upper Bound Exposure Measure such as Peak Exposure, Highest Job Worked, or 95th Percentile Concentrations

LTW—cumulative mean (or in some cases median) exposure divided by exposure duration—is not an ideal exposure metric for either BeS and CBD as evidenced by the numerous studies cited by ACGIH wherein an exposure-response relationship between LTW and BeS or CBD could not be observed. The LTW exposure measure captures neither the upper-bound nor the potential for cumulative burden of beryllium in the lung from long-term exposure as an indicator of increased disease. As such, LTW exposure is not a reasonable exposure metric for the assessment of CBD or BeS risk.

BeS and CBD are mediated through triggering an immune response, and for chemicals that induce hypersensitivity, it appears that peak exposure is more important than time-weighted average exposure (NRC, 1992). It is noteworthy that the time between initial exposure to beryllium and the development of BeS can be short as 3 months with higher prevalence of BeS among workers with one year or less of employment tenure observed in several studies (Schuler et al. 2005, Donovan et al. (2007), Henneberger et al. 2001). Hence, early peak exposure is more likely to be predictive of BeS than a long-term average exposure. As noted above, ACGIH chose to base the TLV on the findings of Madl et al. (2007a); however, the study authors clearly do not support LTW as the most appropriate exposure metric. Moreover, several of the studies cited by ACGIH in support of the TLV also find that the prevalence of BeS and CBD is highest among workers in jobs that result in higher peak exposures (Schuler et al. 2005; Rosenman et al. 2006; Kreiss et al. 1996) again supporting an upper-bound exposure measure as more appropriate given the available data. Finally, it is important to consider the practical application of a TLV, which is treated as an average daily limit of exposure, and thus more consistent with an upper-bound exposure measure.

7) ACGIH Sets the TLV for Beryllium as an Inhalable Fraction with No Basis

The ACGIH TLV documentation provides no meaningful basis for applying the TLV-TWA for beryllium and compounds to the inhalable fraction as opposed to the total airborne fraction. In fact, all of the data upon which ACGIH relies for the TLV value were derived from sampling of total mass measurements. Specifically, the LTW from Madl et al. (2007) was estimated based on total mass rather than inhalable fraction. Hence, using the results of Madl et al. (2007a) as the basis for the TLV, and then applying a different exposure metric (inhalable fraction) is not scientifically reasonable or sound.

Although somewhat counterintuitive, it is understood that the inhalable method generally gathers greater mass than the total method (Volwein et al. 2011; Weiner et al. 1996; Dufresne et al. 2009). Thus, by setting the TLV for inhalable fraction, the TLV is essentially more conservative (lower) than would be supportable by the studies cited as the basis for the value. Further, Dufresne et al. (2009) found that beryllium concentrations varied considerably in side-by-side samplers collecting total and inhalable fractions. Therefore, not only is the TLV, as an inhalable fraction, more conservative than warranted, it is also more uncertain than had the TLV been set for total mass.

8) ACGIH Should Set Separate TLVs for Insoluble Beryllium, such as Beryllium Oxide and Metal, and Soluble Beryllium Salts

It is well known that the toxicity of soluble metal compounds is often different from that of insoluble and metal forms (NAS 2008; Virji et al. 2011). For example, a relatively low prevalence of BeS (0.47%; 95% CI 0.21 to 0.88%) was reported among aluminum smelter workers exposed to soluble forms of beryllium (Taiwo et al. 2010). By comparison, workers exposed to beryllium oxide and metal, or metal alloys, which are of low solubility, have much higher rates of sensitization, as high as 14.6% (Rosenman et al. 2005). Although the exposure concentrations of beryllium among aluminum smelter workers are comparable to those in other industries, aluminum smelting workers are exposed predominantly to soluble forms of beryllium, which are rapidly cleared from the body (Stefaniak et al. 2008). Stefaniak et al. (2003, 2008) hypothesized that exposure aerosol physical properties, chemical properties, and physicochemical properties affect beryllium lung burdens, and that the ongoing presence of a lung reservoir of beryllium (a significant retained dose) may be necessary for the development of CBD. Hence, because different forms of beryllium demonstrate different biological kinetic properties, specific TLVs are warrented for soluble and insoluble forms of beryllium. The TLV developed by ACGIH using the Madl et al. (2007a) study should be considered specific to insoluble forms.

9) Targeted Engineering Control Programs that Prevent Exposures in Excess of 0.2 μg/m^3 *are Effective in Reducing the Risk of BeS*

Several studies have demonstrated that new engineering and health and safety controls implemented in 2000 at beryllium manufacturing and production facilities, which maintain airborne beryllium exposures below 0.2 μg/m^3, have successfully limited the occurrence of BeS. Specifically, Cummings et al. (2007), Bailey et al. (2010), and Thomas et al. (2009) found that implementing the comprehensive preventive program reduced the prevalence of sensitization ranging from 9% to 12%, prior to the new program, to only 1% to 4% thereafter. Considering that the background rate of BeS in new workers is approximately 1% (Donovan et al. 2007), these studies demonstrate that maintaining exposures below 0.2 μg/m^3, i.e., using 0.2 μg/m^3 as a limit, is an effective means to reduce BeS, and thus the risk of CBD. Finally, these observations support the conclusions of Madl et al. (2007a) that maintaining exposures below 0.2 μg/m^3 95% of the time may prevent BeS.

Summary and Conclusions

We find that the available published literature on BeS and CBD, including the data cited as the basis of the TLV, do not in fact support a TLV value of 0.05 μg/m^3, but rather provide stronger support for a TLV of 0.2 μg/m^3 as summarized below:

Study	Observations
Madl et al. (2007a)	TWA for the highest year exposed represented the most robust dataset, and 95th percentile TWA was approximately 0.2 μg/m^3 or greater for all of the cases
Stanton et al. (2006)	No CBD or BeS was observed when 97% of exposure measurements were less than 0.2 μg/m^3
Schuler et al. (2005)	Regardless of median exposures, when a large percentage (25%) of exposure measurements exceeded 0.2 μg/m^3, the risk of BeS and CBD was significantly increased. Among non-cases exposures exceeded 0.2 μg/m^3 in only 7% of samples
Rosenman et al. (2005; as corrected in 2006)	There were no workers identified with BeS or diagnosed with definite or probably CBD with DWA exposure concentrations of <0.2 μg/m^3
Cummings et al. (2007)	A reduction in sensitization was found for workers hired after establishment of enhanced preventive program designed to maintain exposures <0.2 μg/m^3
Bailey et al. (2010)	The preventive program designed to maintain exposures <0.2 μg/m^3 reduced the prevalence of BeS
Thomas et al. (2009)	Fewer workers became sensitized after implementation of the program designed to maintain exposures <0.2 μg/m^3

Other important considerations for the ACGIH TLV include:

- ACGIH selected the LTW exposure metric from Madl et al. (2007a) even though the authors cautioned against doing so.
- ACGIH arbitrarily selected the lower bound of a range of exposures from Madl et al. (2007a), but that lower bound (0.05μg/m^3) was not reported as

such by the original authors, and is nearly two-fold lower than the lowest LTW exposure associated with CBD or BeS.

- ACGIH provided no support for use of the LTW as an exposure metric that is predictive of BeS or CBD risk.
- ACGIH provides no real justification for applying the TLV-TWA to the inhalable fraction, especially given that the data upon which the TLV-TWA is based are total mass measurements.
- The TLV should be specific to insoluble form of beryllium, not all forms.

Although the data available in 2009 to conduct a traditional risk assessment may have been insufficient to assess exposure-response, basing the TLV on information regarding exposure among cases, without information on the frequency of BeS and CBD with measures of exposure, leads to uncertain results. The new study by Schuler et al. (2012) reported an exposure-response for BeS and CBD with multiple exposure metrics and provides a superior data set to conduct risk assessment and establish a TLV.

Detailed Analysis of ACGIH (2009) Documentation

The ACGIH TLV-TWA for beryllium and compounds is reportedly based on two studies, Kelleher et al. (2001) and Madl et al. (2007a), and supported by three additional studies, Stanton et al. (2006), Schuler et al. (2005), and Rosenman et al. (2005; as corrected in 2006). In addition, the TLV documentation includes several additional studies that ACGIH considered to have exposure and health data relevant to the development of the TLV. The following discussion presents a detailed critique of ACGIH's documentation of the basis for their TLV recommendation for beryllium and beryllium compounds.

Studies used as Primary Basis for the TLV

Kelleher et al. (2001) conducted a nested case-control study of 235 workers in a beryllium precision machining plant, including 20 cases (20 individuals with BeS and 13 with CBD) and 206 controls (9 of the original 215 controls were excluded because of incomplete work histories). Beryllium exposure was estimated for cases and controls in terms of cumulative beryllium exposure and LTW (sum of median 8-hr TWA exposure estimates divided by exposure duration) based on 100 breathing zone samples collected using a personal cascade impactor and a job exposure matrix (JEM) developed from interviews of 43 long-term employees. Cumulative and LTW median exposure estimates were calculated based airborne measures of beryllium in total particles, particles < 6 microns (μm), and particles <1 μm.

Although exposure estimates for cases were generally higher than for controls using the investigated exposure metrics, the differences were not statistically significant. The authors note that the limited power of their study and uncertainty in their historical exposure estimates may have affected their ability to detect a difference. Regarding median total beryllium LTW exposures, Kelleher et al. (2001) present the distribution of cases and controls with <0.02 μg/m^3, 0.02-0.10 μg/m^3, 0.10-0.20 μg/m^3, 0.20-0.50 μg/m^3, and 0.50-1.00 μg/m^3. No cases of BeS or CBD were observed for median total beryllium LTW exposures <0.02 μg/m^3. Importantly, Kelleher et al. (2001) caution against comparing their estimates of median LTW to occupational exposure limits (OELs) because OELs are based on the upper tail of the exposure distribution and not on the central tendency.

As discussed in more detail to follow, Madl et al. (2007a) further analyzed the exposures of the cases identified in Kelleher et al. (2001) using additional exposure data and alterative exposure metrics. Madl et al. (2007a) concluded that Kelleher et al. underestimated historical exposures of beryllium-sensitized and CBD workers because contemporaneous data were not used to estimate historical exposures and a limited number of samples were collected for each job category.

Madl et al. (2007a) conducted a surveillance-industrial hygiene (IH) study at the same beryllium precision machining plant evaluated by Kelleher et al. (2001). At the time of the study, the number of cases had increased from 20 to 27. Beryllium exposure was recalculated for the original 20 cases and 7 additional cases based on 3,831 personal lapel samples and 616 general area samples collected between 1980 and 2005. The IH data were subdivided into three eras based on engineering controls: 1) 1980-1995, when some engineering controls were in place, 2) 1996-1999, when additional controls were implemented, and 3) 2000-2005, which represent the current day environment at the plant. Beryllium exposure was calculated according to the following five approaches: 1) TWA for highest year exposed based on available IH data, 2) TWA for highest year exposed based on supplemented IH data (in cases when highest year exposed had less than 6 measurements), 3) TWA for highest job title exposed based on available IH data, 4) TWA for all years and jobs worked pooled by era of engineering controls, and 5) LTW exposure based on TWA exposures (supplemented with IH data by era) for all years worked for each job title weighted by work history.

The exposure estimates based on smaller units of time (e.g., years) or more historical time periods were higher than for those based larger units of time (e.g., pooled over years) or more recent time periods. The LTW estimate (Approach 5) was generally the lowest exposure calculated for a particular case of all of the methods used. For the 20 original cases, median total beryllium LTW exposure estimates by Madl et al. (2007a) were sometimes higher and other times lower than those estimated by Kelleher et al. (2001), but the difference was no more than a factor of 10 and generally within a factor of 3.

Importantly, Madl et al. (2007a) conclude that LTW exposures may not be the best metric for evaluating an exposure-response relationship for BeS or CBD or developing a TLV for beryllium and compounds because BeS and CBD can occur with relatively short-term exposures in weeks to months and LTW exposures do not necessarily reflect higher exposures that may have occurred for a short-period of time. For example, past short-term high exposure jobs can be diluted with long-term low exposure jobs. Instead, the authors suggest that an upper bound concentration estimate or exposures within the first few months of the first year of employment may better reflect exposures that contribute most to identification of BeS or CBD. Madl et al. (2007a) further conclude that Approach 2 (i.e., TWA for highest year exposed based on supplemented IH data) represented the most robust dataset that still captured upper bound exposures. Based on this approach, the 95th

percentile TWA was approximately 0.2 μg/m^3 or greater for all of the cases. The authors conclude, "Thus, maintaining exposures below 0.2 μg/m^3 95% of the time may prevent BeS and CBD in the workplace."

Wambach (2007) questioned whether the 95th percentile is a better exposure metric than the mean because both are similarly affected by excursions in the upper tail of the exposure distribution. Madl et al. (2007b) replied that the mean and 95th percentile would be interchangeable as risk indicators only when the exposure distribution for each job title, operation and time period are similar, and illustrated that substantial error could be introduced when there are up to 5-fold differences in the ratio of the mean and 95th percentile, as was the case for the data from this facility. Madl et al. (2007b) further conclude that, for purposes of compliance, an employer should interpret TWA OELs as an upper percentile of a workers exposure profile rather than a long-term average concentration. If not, then airborne exposures would have to be maintained at a substantially lower concentration to ensure that exposures for a given worker on a given day do not exceed the long-term average value.

It is noteworthy that ACGIH cites the Wambach (2007) letter to the editor, but not Madl et al.'s published response.

ACGIH Reliance on Madl et al. (2007a) as Primary Basis of TLV-TWA

Although ACGIH purports that the TLV-TWA for beryllium and compounds is based on Kelleher et al. (2001) and Madl et al. (2007a), the TLV value is based solely on the data in Madl et al. (2007a). Further, without any discussion, ACGIH chose to base the TLV-TWA on the mean estimates for LTW exposure, even though Madl et al. (2007a) caution that LTW exposure may not be the best metric for BeS and CBD. Further, ACGIH arbitrarily creates LTW exposure ranges of 0.05 to 0.1 μg/m^3, 0.1 to 0.2 μg/m^3, and >2μg/m^3, stating that no cases had mean LTW exposure estimates below 0.05 μg/m^3, and three cases had LTW exposure estimates between 0.05 to 0.1 μg/m^3 (the remaining cases had mean LTW exposures greater than 0.1 μg/m^3). Upon inspection of Table III of the Madl et al. (2007a) study; however, the actual mean LTW exposure estimates for these three cases were 0.09, 0.1 and 0.1 μg/m^3. Thus, even if mean LTW exposure was the appropriate exposure metric for purposes of establishing a TLV, the ACGIH arbitrarily choose a value of 0.05 μg/m^3, which is nearly a factor of two lower than the lowest estimated mean LTW exposure estimate from the Madl et al. (2007a) study.

As discussed further below, sensitization and immune-mediated effects are typically considered to be induced by peak, rather than average, exposure.

Kelleher et al. (2001) investigated both cases and controls, but did not report an exposure-response relationship with median LTW exposure estimates. This information would suggest that LTW is not predictive of BeS or CBD risk. Unfortunately, Kelleher et al. (2001) did not provide sufficient information to allow for the evaluation of alternative exposure metrics that might be more predictive of BeS and CBD.

Neither Kelleher et al. (2001) or Madl et al. (2007a) offer data that can be used for traditional risk assessment and are thus are not optimal studies to serve as the basis of the TLV. Although the recent study by Schuler et al. (2012) was completed subsequent to the ACGIH's adoption of the TLV, this study reports an exposure-response for BeS and CBD with several exposure-metrics, demonstrating that if the exposure characterization is rigorous, the identification of an exposure-response relationship is possible. Schuler et al. (2012) offers superior data for risk assessment and the derivation of a TLV.

Stanton et al. (2006), Schuler et al. (2005), and Rosenman et al. (2005; as corrected in 2006) in Support of the TLV

Stanton et al. (2006) conducted a surveillance-Industrial Hygiene (IH) study of workers at three copper-beryllium distribution centers. One of the distribution centers was established in 1963 and stocked bulk product materials. The other two distribution centers, one established in 1968 and the other in 1972, handled largely strip products. Eighty-eight of 100 employees participated in the study. One employee was identified with BeS and was subsequently diagnosed with CBD. The authors also evaluated 393 full-shift personal lapel samples for airborne beryllium collected between 1996 and 2004. The overall median beryllium concentration was 0.03 μg/m^3, the arithmetic mean was 0.05 μg/m^3, and the 95th percentile upper tolerance limit (UTL) ranged from 0.07 to 1.18 μg/m^3. All samples were below 2.0 μg/m^3, and 97 percent were below 0.2 μg/m^3. The highest concentrations were measured in bulk products and strip production, with lower concentrations measured in production support and administration.

The single case of CBD identified in this study spent his entire 22-year career (1978-2000) as a shipper/receiver at one of the strip centers, which had lower measured concentrations than other distribution centers and in a work category/job with among the lowest measured beryllium concentrations. Stanton et al. (2006) noted, however, that his exposures were likely unique to shipping and receiving, in that it included weighing and repackaging dusty copper-beryllium alloy ingots, and unloading trailer vans potentially contaminated with beryllium oxide. Importantly, the authors also note that "…because data in his job category were limited in number (35) and <u>no</u>

samples were taken on this job in the 18-year period before 1996, we cannot draw firm conclusions about exposure conditions he may have experienced over the entire time he was employed." (emphasis added). Thus, it is reasonable to surmise that the exposures of this individual cannot be characterized based on the airborne sampling conducted from 1996-2004, and therefore, the study generally consists of 87 individuals who were not sensitized and for which 97% of exposure measurements were below 0.2 $\mu g/m^3$. Although the authors concluded that their results indicate that workers are still at risk for BeS and CBD at very low airborne exposure levels when all routes of exposure are not well understood or managed, it seems that their data would generally support limited risk at exposures <0.2 $\mu g/m^3$, which is consistent with the conclusions of Madl et al. (2007a).

Schuler et al. (2005) conducted a cross-sectional survey of workers at a copper-beryllium alloy and strip finishing facility. A total of 185 employees were invited to participate in the study. Of these, 152 employees who were not known to have BeS or CBD at the time of the survey, and one individual known to have CBD participated in the study. A total of 144 employees were evaluated statistically. Ten employees were identified with BeS, of which 6 were diagnosed with CBD. Schuler et al. (2005) evaluated the prevalence of BeS and CBD based on four general work categories (production of rod and wire materials, production of strip metal, production support, and administration), and then by several job or process subcategories within each work category. Schuler et al. (2005) also evaluated total mass beryllium airborne sampling data collected between 1969 and 2000, including 650 personal, 4,524 general area, and 815 short-duration high-volume samples collected in these work categories or associated with the job/process subcategories. The authors calculated median and 95th percentile UTL concentrations, and the 95 percent upper confidence limit (UCL) for the fraction of samples that exceed 2.0$\mu g/m^3$ or 0.2 $\mu g/m^3$.

The prevalence of CBD was significantly higher in only one of the four work categories, i.e., for those having ever worked in rod and wire production, compared to those who had never worked in this area. Within this work category, the prevalence of CBD was significantly higher for those who ever worked in the point and chamfer, wire annealing and pickling, and wire drawing processes as compared to those who had never worked in these areas; BeS was also significantly elevated for these processes. The prevalence of BeS and CBD was not significantly elevated for those having ever worked in strip metal production, production support, or administration. Based on personal samples, the median concentrations were 0.03, 0.12, and 0.06 $\mu g/m^3$ in the point and chamfer, wire annealing and pickling, and wire drawing areas, respectively. Median concentrations in the other process areas range from 0.02 to 0.11 $\mu g/m^3$. The only area with exceedences of 2.0µg/m^3 was wire annealing and pickling (6%), with exceedences of 0.2 µg/m^3 of 6%, 54%, and 13% in the point and chamfer, wire annealing and pickling, and wire drawing areas, respectively. These latter samples represent approximately 25% of the samples across these three areas. Exceedences of 0.2 µg/m^3 in the other process areas were 7% or less. Schuler et al. (2005) note that although median concentrations were generally very low across all process areas, the number of samples in the upper tail of the exposure distribution was highest in the rod and wire production area, and no statistically significant risk of BeS or CDB was identified for any individual process or job where less the 5% of the samples exceeded 0.2 µg/m^3. The authors also note, "The process-related risks we identified provide an opportunity to further investigate exposure metrics that may better predict health hazards than historical total mass airborne beryllium measurements." These observations support the conclusions of Madl et al. (2007a) that LTW is not an appropriate exposure-metric and that maintaining exposures below 0.2 µg/m^3 95 percent of the time may prevent BeS and CBD.

Rosenman et al. (2005; as corrected in 2006) conducted a medical screening of 577 former workers from a beryllium processing facility. Forty workers were identified with BeS and 44 other workers were diagnosed with CBD. The authors constructed a task exposure matrix (TEM) and JEM based on DWA exposures estimated from task-specific monitoring data weighted by the duration of that task in the shift. Task-related exposure measurements were available for two time periods, 1957-1962 and 1971-1976. Exposures for years without data were estimated by interpolating between previous and subsequent values; data from 1976 were used to estimate exposure for later years. In addition, no data were available for 39 of 130 job titles; therefore, exposures for these tasks were estimated based on recollections from long-term workers. Cumulative, mean, and peak exposure concentrations were estimated for soluble, insoluble and mixed beryllium particles and for dust, fume and mixed beryllium particle size fractions. Other exposure measures evaluated included duration, first decade worked, and last decade worked.

The prevalence of BeS (7.0%) and CBD (7.6%) was higher than reported in other studies,[4] but generally consistent with that reported for the higher exposed subgroups within these studies. Rosenman et al. (2005; as corrected in 2006) report that they found either no exposure-response relationship or,

[4] Unlike other studies, Rosenman et al. (2005) do not include workers diagnosed with CBD in the count of workers identified with BeS (i.e., a worker cannot have CBD without also being sensitized to beryllium). Because BeS is required for CBD, it is nonsensical that the incidence of CBD is reported to be higher than BeS. Had the authors done so, the prevalence of BeS, including those with CBD, is 14.6%.

if found, the exposure-responses were inversely related. The authors speculate that a possible explanation is that they did not consider the role of genetic predisposition to both sensitization and disease. However, the authors also note that the exposure metrics developed for study participants were based on relatively sparse data, with major gaps in the mid-1960s and from 1977 to 1981.

ACGIH Reliance on Stanton et al. (2006), Schuler et al. (2005) and Rosenman et al. (2005; as corrected in 2006) as Supporting Basis of TLV-TWA

Despite ACGIH's suggestion to the contrary, none of these studies support a TLV-TWA of 0.05 μg/m^3. The airborne beryllium data from Stanton et al. (2006) is limited to a fairly recent time period, with neither the authors nor ACGIH explaining why these data would be applicable to earlier time periods. Thus, the exposures measured are not necessarily representative of those for the workers in this study. Furthermore, the single case of CBD was employed for the most part (18 of 22 years) prior to when airborne beryllium data were collected. In addition, the data in Stanton et al. (2006) also support limited risk at exposures <0.2 μg/m^3 because essentially no CBD or BeS was observed when 97% of exposure measurements were less than 0.2 μg/m^3. With regard to Schuler et al. (2005), if anything, this study supports the conclusions of Madl et al. (2007a) that an upper bound exposure metric is more appropriate than a LTW average and maintaining exposures below 0.2 μg/m^3 may prevent BeS and CBD in the workplace. Finally, it should be recognized that the exposure estimates in Rosenman et al. (2005) are highly uncertain because of large gaps in the data and associated assumptions that had to be made. Nevertheless, similar to Schuler et al. (2005), this study would support a TLV of 0.2 μg/m^3 rather than the ACGIH TLV-TWA of 0.05 μg/m^3.

Inadequate data in the additional studies cited by ACGIH to evaluate exposure-response relationship and develop a TLV-TWA

Johnson et al. (2001) evaluated area measurements and personal lapel measurements of airborne beryllium concentrations for workers in the Cardiff Atomic Weapons Establishment Plant. Although data were collected over the entire 36-year period of operation, only those data collected during the period 1981 to 1997 were evaluated because these data were available electronically, including area sampling records at 101 locations and personal lapel sampling records collected from 153 employees. Particle size distribution was not assessed in Johnson et al. (2001). A notable feature of the Cardiff protection 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. Those who worked in foundry areas had the highest concentration, and area sample concentrations were found to be lower than personal sample concentrations. The annual personal sampling concentrations for all workers ranged from 0.11 to 0.72 μg/m^3 with 95th percentiles ranging from 0.22 to 1.89 μg/m^3. The mean annual area sample concentrations for all locations ranged from 0.02 to 0.32 μg/m^3, and the area sample 95th percentile concentrations for all years were below 0.5 μg/m^3.

The Cardiff plant had a workforce of more than 400 workers, and the authors expected to observe 4 to 20 cases of clinical CBD based on reported prevalence rates. Only one CBD case was detected at the plant. This individual had a systemic beryllium reaction from a minor cut to a finger on a beryllium oxide-contaminated grinding wheel, and the treating physician concluded that the resulting ulceration was progressive. The systemic reaction progressed eventually into the lung, and the individual was treated with corticosteroids. Although the potential for inhalation exposure could not be ruled out for development of CBD in this one individual, his inhalation exposure to beryllium was not quantified, and the primary route of exposure was suggested to be dermal. Further, subclinical CBD and BeS could not be determined because the beryllium lymphocyte proliferation test (BeLPT) was only used experimentally at the plant and its use was discontinued over concerns regarding the reliability of the test. Therefore, as such, the detection of subclinical CBD may be underestimated. Overall, the study is not useful to describe BeS prevalence. Because only one CBD case with uncharacterized exposure was identified, the study data are not useful for evaluating an exposure-response relationship for BeS. However, Johnson et al. (2001) concluded that the Cardiff experience "…appears to have successfully prevented the incidence of clinical CBD with the exception of one unique case." Thus, the study is not useful to support the TLV of 0.05 μg/m^3.

Kreiss et al. (1996) evaluated 136 workers in beryllium ceramics plants from 1980 to 1992. DWA exposures for a workday were estimated quarterly using a formula incorporating average general area, full-shift area and breathing zone measurements based on time studies for most jobs. Cumulative beryllium exposure was estimated for study participants by summing the quarterly DWAs for their job titles, weighted by days of employment in the job title during the quarter, accounting for the reported time away from work. Thus, in essence a DWA is equivalent to a LTW. Average beryllium exposure was calculated by dividing the cumulative exposure, expressed in μg/m^3-days, by the total number of days worked. Machining processes had higher DWA estimates compared to other work processes with a median DWA of 0.9 μg/m^3. Particle size distribution was not considered in this study.

Eight workers were found to have BeS, of which 6 were diagnosed with CBD. Notably, the study was not able to demonstrate that individuals with BeS had higher estimated exposures than those without BeS, indicating the potential for misclassification of exposure or that the exposure-metric selected was not predictive of BeS and CBD. The authors noted that exposure data for the early years were not available and cumulative exposure may have been underestimated. Hence, the study is not useful to describe exposure-response relationships.

Kreiss et al. (1997) was a cross-sectional survey of workers in a beryllium ceramics plant and production facility where 646 active employees were interviewed and examined with BeLPTs and clinical evaluations. All industrial hygiene measurements of beryllium mass concentrations collected from 1980 to 1993 were evaluated. As in Kreiss et al. (1996), DWA exposure for a working day was estimated in this study using quarterly average general area, continuous area, and breathing zone measurements based on time studies for most jobs. Quarterly DWA estimates were constructed for individual jobs and job categories. Cumulative and average beryllium exposures were calculated in the same manner as described in Kreiss et al. (1996). Particle size distribution was not considered in this study.

In Kreiss et al. (1997), the risk of CBD was indicated to be process-related, with employees who worked with ceramics having the highest prevalence of disease. However, no association between CBD and cumulative or average exposure to beryllium was found. In addition, there were no significant differences in both average and cumulative exposures between individuals who had BeS compared to those who were not sensitized. In their discussion of the study results, the authors indicated that misclassification of biologically pertinent exposure was possible due to the reliance on historical measurements and that DWAs seemed to be a poor estimate of personal exposure. Particle size or other characteristics were thought to likely be more important contributors of risk than DWA exposure concentrations, and it is likely that the methods of beryllium exposure assessment did not adequately describe exposures from accidents. As a result, the findings of Kreiss et al. (1997) cannot be considered to be supportive of the 0.05 $\mu g/m^3$ TLV.

Cummings et al. (2007) assessed the effectiveness of exposure-control program to prevent sensitization at a beryllium oxide ceramics manufacturing facility; this plant was the same one evaluated in Kreiss et al. (1996). One hundred twenty-six workers hired from 2000 to 2004 were compared to 69 workers hired from 1993 to 1998 for BeS. Mean age and tenure were reported to be similar between the two groups. The incidence of

BeS among those hired in 2000-2004 was 0.7 cases per 1,000 person-months, whereas 5.6 cases per 1,000 person-months were observed for workers hired from 1993 to 1998. The sensitization prevalence for the 2000 to 2004 workers was 1% (1/97) and that for the 1993 to 1998 workers was 8.7% (6/69). Although a reduction in sensitization was found for the workers hired after establishment of enhanced preventive program, Cummings et al. (2007) noted that there was little change in airborne beryllium levels in the production areas, and no exposure-response assessment for individuals with BeS was presented. Hence, the study does not support the 0.05 μg/m^3 TLV.

Day et al. (2006) is a review of published literature that assessed the state of knowledge concerning skin exposure to beryllium. In Day et al. (2006), it was noted that physiochemical properties (e.g., particle size, morphology, surface, area, and chemistry) as well as bioavailability vary between the different Be-containing materials, but no data were presented on beryllium concentrations in air and on individuals with BeS and CBD. Overall, the study is not useful to evaluate exposure-response relationships.

Day et al. (2007) measured beryllium in workplace air, on work surfaces, on cotton gloves worn by employees over nitrile gloves, and on the necks and faces of employees after implementation of a control program at a beryllium alloy strip and wire finishing facility. The control program was in response to medical surveillance findings of Schuler et al. (2005). At the time of this study, approximately 125 workers were employed. A strong correlation was observed between the concentrations of beryllium in air and the levels of beryllium on necks and faces, but the concentrations were low suggesting that air-to-skin exposure may be of less importance in this facility than in more dusty environments. Importantly, no individuals with BeS or CBD cases were evaluated in Day et al. (2007) and as such, the study is not useful for evaluating an exposure-response relationship.

Cullen et al. (1987) evaluated 5 workers with CBD at a precious metal refinery and conducted a health survey of 45 workers at the same facility. TWA personal air sampling data were measured during a 2-week period in July and in November 1983, and the highest exposure was reported for ball-mill and crusher job titles. Of the 5 CBD cases, 4 were from the furnace area where the mean concentration was 0.52 μg/m^3. It should be noted, however, that air samples collected for this 2-week period may not be reflective of current or past exposure conditions from which the 5 workers developed CBD (from 1972 to 1985). In addition, the small number of CBD cases and limited characterization of exposure for those who did not develop CBD limit this study's usefulness for supporting the TLV, and it certainly does not provide support for the 0.05 μg/m^3 value selected by ACGIH.

Maier et al. (2008) evaluated 16 cases of CBD that occurred between 1948 and 1969 in community neighborhoods surrounding beryllium facilities. This study was a case-series report, and medical records were reviewed. Of the 16 cases, 8 were identified to be community-acquired (5 definite and 3 probable). All cases lived within 1.05 miles of the plant on average and significant changes in the plant emissions did not occur until the late 1960s. The cases' year of residence near the beryllium facility began for the most part around 1950, and the cases did not have occupational or paraoccupational exposure to beryllium (e.g., living with an individual who is occupationally exposed, also referred to as take-home exposure).

It was reported that based on the 1958 ambient air sampling, potential exposures to these individuals, may have ranged, on average, from 0.0155 to 0.028 $\mu g/m^3$, with some exposures potentially over 0.35 $\mu g/m^3$. However, these exposure estimates were uncertain, and the authors acknowledged that some unknown paraoccupational exposure could have accounted for the development of CBD in the patients. In addition, although these cases were identified as being community-acquired, the National Research Council (NRC) considered their exposures to occur before controls were instituted in the 1970s to reduce beryllium emissions into the air of surrounding communities (NRC, 2008). NRC also noted that cases of CBD occurred in people thought to have trivial, unrecognized, or brief exposure to beryllium, and in some of these cases, it was not possible to rule out occupational exposures to beryllium and that CBD can be developed from beryllium exposures that would generally be considered incidental (NRC, 2008). As such, this study does not provide data that could be used to support the TLV.

Use of LTW as the Exposure-Metric for an Immune-Mediated Response

Although there has been much progress in the current understanding of the immunologic basis of CBD and immunopathic mechanisms that may contribute to the development of CBD, the exact mechanism of action from exposure to disease development remains unclear (NRC, 2008). CBD is a systemic granulomatous disorder found in the lungs predominantly, and it is thought that an immune response to beryllium may trigger CBD pathogenesis. CD4+ T lymphocytes recognize beryllium as an antigen that initiates cell proliferation and release of cytokines and inflammatory mediators. The release of inflammatory mediators results in an accumulation of mononuclear-cell infiltrates and fibrosis and leads to the development of non-caseating granuloma (a lesion typical of CBD) (NRC, 2008). BeS refers to the CD4+ T-cell immune response, which is measured with *in vitro* assays (i.e., BeLPT).

In many instances of chemicals that induce hypersensitivity, it appears that peak exposure is more important than time-weighted exposure (NRC, 1992). Hence, additional data are needed to determine the nature of exposures most likely leading to the induction of BeS and/or the development of CBD, and LTW is not likely to be the most appropriate exposure metric, as evidence by the lack of established exposure-response relationship with this exposure metric.

LTW is not equivalent to a peak dose and likely mischaracterizes the true beryllium exposure associated with BeS among workers. For example, an employee who works for one month with an average exposure of 1 μg/m^3 has exactly the same LTW measure (1 μg/m^3) as an employee who works 20 years with exposure that might vary from 0 to 10 μg/m^3, but with an average of 1 μg/m^3. In addition, LTWs are generally derived using annualized or multi-year averages of data sets, which often involve combining averaged data that are averaged more than one time. The averaging of averaged data over a year or multi-year timeframe may mask the variations in the daily samples from which the averages were derived, and thus, the final calculation will likely not be comparable to an 8-hour exposure value with daily up and down variation that will not likely be captured with LTWs. Thus, the LTW exposure measure captures neither the upper-bound nor the potential for cumulative burden of beryllium in the lung from long-term exposure as an indicator of increased disease. As such, LTW exposure does not seem reasonable for the assessment of risk for either CBD or BeS. Further, the LTW may include periods of zero exposure as was done in the Van Dyke et al. (2011) exposure reconstruction.

The preferable exposure metric is one that is predictive of the exposure-response relationship. In 2009, the available studies reviewed by ACGIH do not support an exposure-response relationship for LTW average exposure. However, the latest study of beryllium-exposed workers (Schuler et al. 2012), which included a very rigorous exposure evaluation, has reported an exposure-response for several exposure-metrics with both BeS and CBD. Risk assessment of the Schuler et al. (2012) data may be used to establish an OEL, without the significant limitations and uncertainties of the current ACGIH TLV.

Inhalable Fraction

The only basis provided in the ACGIH documentation for constraining the TLV-TWA to the inhalation fraction is the following statement: “Due to the potential for beryllium particles to interact with immune compromised 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 particular matter." ACGIH provides no further discussion or evidence to support this statement. Further, the data presented in the Madl et al. (2007a) study, upon with the TLV-TWA is primarily based, are total mass measurements, not the inhalable fraction. Although Kelleher et al. (2001) collected air samples using a cascade impactor, and reported their data based on total mass, particles <6 μm and particles <1 μm, no measures of inhalable fraction were provided. Further, inspection of Table 6 of Kelleher et al. indicates that any possible exposure-response relationship is limited to particles <1 μm; therefore, the particle size data in the paper cited as a primary basis for the TLV does not support ACGIH's decision to set the TLV for the inhalable fraction. Moreover, other studies that have evaluted particle size, e.g., Schuler et al. (2012), do not suggest any obvious difference in exposure-response based on particle size.

The upper range of the marple cascade impactor is 50 μm aerodynamic diameter whereas the upper range for inhalable is 100 μm aerodynamic diameter (Volwein et al. 2011). Although somewhat counterintuitive, it is understood that the inhalable method generally gathers greater mass than the total method (Volwein et al. 2011; Weiner et al. 1996; Dufresne et al. 2009). Thus, by setting the TLV for inhalable fraction, the TLV is essentially more conservative (lower) than would be supportable by the studies cited as the basis for the value. In addition, Dufresne et al. (2009) found that beryllium concentrations varied considerably in side-by-side samplers that collected total and inhalable fractions in a magnesium foundry and 3 aluminum smelters using 4 different sampling methodologies. Therefore, not only is the TLV, as an inhalable fraction, more conservative than warranted, it is also more uncertain than had the TLV been set for total mass.

Beryllium Metal and the Different Forms of Beryllium Have Different Toxicological Properties, and the TLV should be for Beryllium Metal and Insoluble forms of Beryllium

Pulmonary deposition and disposition of inhaled beryllium compounds vary with solubility (NRC, 2008), and it is well known that the toxicity of soluble metal compounds differs from that of insoluble and metal forms (NAS 2008; Virji et al. 2011). The soluble form of beryllium is thought to be less toxic because particles dissolve and are cleared more rapidly than the insoluble forms, and thus less are available to the immune system (Stefaniak et al. 2008). The solubility of beryllium metal in artificial lung fluid is low, while solubility in artificial lysosomal fluid is moderate when compared to beryllium salts. Stefaniak et al. (2003, 2008) hypothesized that exposure aerosol physical properties, chemical properties, and physicochemical properties affect beryllium lung burdens, and that the ongoing presence of a lung reservoir of beryllium may be necessary for the development of CBD.

Taiwo et al. (2010) evaluated BeS prevalence among 3,185 workers from 9 aluminum smelters owned by 4 different aluminum-producing companies. The workers were primarily exposed to soluble forms of beryllium. Personal monitoring beryllium samples obtained from the smelters showed a range of exposures from <0.01 to 13.00 μg/m^3 as a TWA. Nine workers were sensitized, resulting in a prevalence rate of only 0.47% (95% CI 0.21 to 0.88%), and 2 were diagnosed with probable CBD (Taiwo et al. 2010). Although the participation rate was 60% among the at-risk smelter workers in this study and could potentially be under estimated, the authors concluded that the prevalence was likely to be even lower than 0.47% because the study was conducted only in aluminum smelters determined to have significant beryllium exposure.

The lower prevalence of BeS is observed among aluminum smelter workers in Taiwo et al. (2010), as compared to workers in other industries where exposures are to beryllium metal, alloys and ceramics, suggests that solubility is an important chemical characteristic affecting sensitization. Among workers of other industries that are exposed to insoluble forms of beryllium (beryllium metal, oxide, and metal alloys), the BeS prevalence is reported as high as 14.6% (Rosenman et al. 2005, corrected in 2006). Because different forms of beryllium have different toxicological properties, specifics TLVs are needed for soluble and insoluble forms of beryllium. Stefaniak et al. (2008) suggests that this observation may be due to the accumulation of the less soluble forms in the lung, as soluble forms are cleared more rapidly. Setting TLVs for different forms of beryllium is consistent with the approach applied by ACGIH for hexavalent chromium (ACGIH, 2004). The TLV set by ACGIH is based on Madl et al. (2007a) and therefore should be considered representative of a value for insoluble beryllium.

Targeted Engineering Program

Since 2000, several studies have demonstrated that new engineering and health and safety controls at beryllium manufacturing and production facilities, which maintain airborne beryllium exposures below 0.2 μg/m^3, have successfully limited the occurrence of BeS. The targeted engineering controls reported in Cummings et al. (2007), Bailey et al. (2010), Thomas et al. (2009) indicate that the comprehensive preventive program is effective in reducing sensitization. Specifically, Cummings et al. (2007), Bailey et al. (2010), and Thomas et al. (2009) found that implementing the comprehensive preventive program reduced the prevalence of sensitization ranging from 9 to 12%, prior to the new program, to only 1 to 4% thereafter. Considering that the background rate of BeS in new workers is approximately 1% (Donovan et al. 2007), these studies demonstrate that maintaining exposures below 0.2 μg/m^3, i.e., using 0.2 μg/m^3 as a limit, is an effective means to reduce the risk of BeS and CBD. Although some of this work was published after the ACGIH TLV was established, these studies demonstrate that the 0.2 μg/m^3, when used as a limit for exposure, reduces the risk of sensitization, and therefore CBD. It is noteworthy that these studies support the Madl et al. (2007a)'s conclusions and a TLV of 0.2 μg/m^3.

Bailey et al. (2010) evaluated the effectiveness of an enhanced preventive program at a production plant that opened in 1953, conducting copper-beryllium alloy production, followed by beryllium metal operation in 1957 and beryllium oxide production in 1958. In February 2000, an enhanced preventive program known as the Beryllium Worker Model was implemented to reduce potential occupational exposures to beryllium. The program included a combination of increased orderliness and cleanliness in the workplace, dermal and respiratory protection, personal cleanliness, particle migration control using work practices and engineering controls, and worker training and involvement.

Using existing BeLPT surveillance data, this study evaluated longitudinal incidence data from workers hired after the preventive program began and cross-sectional prevalence data for the works hired before the program's implementation to estimate prevalence and incidence rates of BeS. Referred to as the Pre-Program Group, workers who began work on-site between January 15, 1993 and August 9, 1999 and who participated in the 1999 cross-sectional survey were evaluated. The Program Group was comprised of workers hired from 2000 to 2006. BeLPTs for the Program Group were sent primarily to a single commercial laboratory; to make the findings comparable between the two groups, the study analyzed BeLPT results for both groups, at least initially, at the same laboratory. A worker was sensitized if he had two abnormal BeLPTs at any laboratory that was triggered from a non-normal test (abnormal, borderline negative, or uninterpretable BeLPT) at the first laboratory.

The Pre-Program Group consisted of 258 workers, and the Program Group consisted of 290 workers. For the Program Group, only 6 workers were sensitized during employment; for the Pre-Program group, 23 were sensitized. The sensitization prevalence for the Pre-Program and Program groups were 8.9% and 2.1%, respectively. The Pre-Program Group had an estimated incidence rate of 3.7/1,000 person-months. In the Program Group, the incidence rate was estimated to be 1.7/1,000 person-months. These findings indicated that the preventive program reduced the prevalence of BeS and support a TLV no lower than 0.2 μg/m^3.

Cummings et al. (2007) was the first study to assess the effectiveness of this exposure-control program to prevent sensitization at a beryllium oxide ceramics manufacturing facility; this plant was the same one evaluated in Kreiss et al. (1996). As discussed above, the study found that the enhanced preventive program was effective in reducing BeS.

Thomas et al. (2009) examined the efficacy of a preventive program among workers at a copper-beryllium alloy processing facility. The preventive program was implemented in June 2000. De-identified medical surveillance data were analyzed with the inclusion of 82 workers hired from June 2000 to November 2006. These program workers were followed through June 2007, and underwent a BeLPT at hire and again at 3, 6, 12, 24, and 48 months post-hire. In addition, the program workers were further subdivided into pre- and post-enclosure program groups; the pre-enclosure program group was comprised of workers hired from June 2000 through December 2001, and the post-enclosure program group was comprised of workers hired from January 2002 through November 2006.

Three among the 82 program workers were sensitized during employment compared to 5 workers sensitized among 43 workers hired between 1993 and March 2000 (referred to as the legacy workers). Hence, the sensitization prevalence were 12% (5/43) and 4% (3/82) for the legacy and program workers, respectively. Sensitization incidence rates were calculated using the sum of the months of sensitization-free employment as the denominator. For the program workers, the sensitization-free period was designated as time until the first non-normal test result. Baseline BeLPT status for the legacy workers was unknown and thus, a true incidence rate could not be calculated for these individuals. As an estimate of incidence, the number of sensitized workers per person-months was calculated for the legacy workers, with the sensitization-free time defined as the time of hire until the 2000 survey BeLPT to estimate person-months. In the legacy group, five workers developed BeS during a total of 1,323 months of employment for a rate of 3.8/1000 person-months. Three of the program workers developed sensitization during a total of 1,579 person-months for an incidence rate of 1.9/1000 person-months. The incidence rate ratio comparing the legacy group with the program group was 2.0 (95% CI 0.5 to 10.1). In the pre-enclosure program group, two workers were sensitized during a total of 846 months of employment yielding an incidence rate of 2.4/1000 person-months. In the post-enclosure program group, one worker was sensitized during a total of 733 months of employment, for a sensitization incidence rate of 1.4/ 1000person-months. These results indicate that fewer workers became sensitized after implementation of the program.

Although these data provide a relatively new perspective on the assessment of BeS risk, it is important to consider that these data provide practical support for a TLV of 0.2 μg/m^3, used as an upper limit of daily TWA exposure, which is how TLVs are practically applied, not as LTW exposures.

Summary and Conclusions

The available published literature on BeS and CBD, including the data cited as the basis of the TLV, do not in fact support a TLV value of 0.05 μg/m^3, but rather provide stronger support for a TLV of 0.2 μg/m^3.

Specific concerns with the ACGIH TLV analysis include:

- ACGIH selected the LTW exposure metric from Madl et al. (2007a) even though the authors cautioned against doing so.
- ACGIH arbitrarily selected a lower bound of a range of exposures from Madl et al. (2007a), but the authors did not bind the data as such, and the lower bound (0.05μg/m^3) is nearly two-fold lower than the lowest LTW exposure associated with CBD or BeS.
- ACGIH provided no support for use of the LTW as an exposure metric that is predictive of BeS or CBD risk.
- ACGIH provides no real justification for applying the TLV-TWA to the inhalable fraction, especially given that the data upon which the TLV-TWA is based are total mass measurements.
- The TLV should be specific to insoluble form of beryllium, not all forms.
- Recent data demonstrates that maintaining exposures below 0.2 μg/m^3 , in a comprehensive worker protection model program, reduces the risk of sensitization and CBD.

Although the data available in 2009 to conduct a traditional risk assessment may have been insufficient to assess exposure-response, basing the TLV on information regarding exposure among cases, without information on the frequency of BeS and CBD with exposure, leads to uncertain results. The new study by Schuler et al. (2012) reported an exposure-response for BeS and CBD with multiple exposure metrics and provides a superior data set to conduct risk assessment and establish a TLV.

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