DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR BERYLLIUM

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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Peer reviewers for the third pre-public draft of the Toxicological Profile for Beryllium were:

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NOTE: Peer reviewer comments are written next to "COMMENTS:" in unformatted text. Any italicized text following the comment is added for clarification purposes. Any page and line numbers that were added by the Reviewers have been kept, but often will not align with the appropriate text.

Comments provided by Peer Reviewer #1

ATSDR Charge Questions and Responses

Chapter 1. Relevance to Public Health

QUESTION: Do you agree with those effects known to occur in humans as reported in the text? If not, please explain why and provide a copy of additional references you would cite and indicate where (in the text) these references should be included.

COMMENT: I agree, however, it is not clear whether some effects (e.g., cardiovascular) are adequately described as not being directly related to beryllium exposure.

RESPONSE: *The health effects described in section 2.5 are direct toxic effects of beryllium exposure. Ward et al. (1992) indicates that the cardiovascular changes that are observed are potentially due to impairment in the lung function caused by exposure to beryllium. While it is likely that the cardiac effects are not due to direct toxicity to the heart, they are direct effects of exposure to beryllium.*

Text was added to the beginning of section 2.5: "It is possible that these effects are secondary to the respiratory effects, rather than direct toxicity to the heart."

The text later in section 2.5 reads: "An increase in deaths due to heart disease or ischemic heart disease was found in workers at a beryllium manufacturing facility (Ward et al. 1992). The study authors state that it is possible that the cardiac effects are not due to direct toxicity to the heart, but rather are a response to impaired lung function" and was not changed.

QUESTION: Are the effects only observed in animals likely to be of concern to humans? Why or why not? If you do not agree, please explain.

COMMENT: The document needs to more clearly present the significant species differences seen between human and animals with respect to the immunological basis of ABD and CBD.

RESPONSE: *Added following text to section 1.2: "Studies in different species of animals demonstrate a similar immunological response as humans as well as other toxicity. However, there are deficiencies in these studies; they do not adequately reproduce features of human CBD. Therefore, these studies cannot reliably predict exposure-response effects of beryllium exposure (NRC 2008). Humans are exposed to lower concentrations of beryllium than levels used in most animal studies, hence it is pertinent to examine the physiological changes happening at those lower doses. It is potentially likely that prior sensitization in humans is exacerbating the toxic effects."*

QUESTION: Have exposure conditions been adequately described? If you disagree, please explain

COMMENT: They have been adequately described.

RESPONSE: *No revisions were suggested.*

Chapter 2. Health Effects

QUESTION: Do the health effect conclusions made in Chapter 2 adequately reflect the findings in the published literature? If not, please suggest appropriate changes.

COMMENT: Yes.

RESPONSE: *No revisions were suggested.*

QUESTION: Were adequately designed human studies identified in the text (i.e., good exposure data, sufficiently long period of exposure to account for observed health effects, adequate control for confounding factors)? Were the major study limitations sufficiently described in the text without going into lengthy discussions? If study limitations were not adequately addressed, please suggest appropriate changes.

COMMENT: Adequate studies were considered.

RESPONSE: *No revisions were suggested.*

QUESTION: Were adequately designed animal studies identified in the text (i.e., adequate number of animals, good animal care, accounting for competing causes of death, sufficient number of dose groups, and sufficient magnitude of dose levels)? If not, does the inadequate design negate the utility of the study? Please explain.

COMMENT: Adequate studies were considered.

RESPONSE: *No revisions were suggested.*

QUESTION: Were the animal species appropriate for the most significant toxicological endpoint of the study? If not, which animal species would be more appropriate and why?

COMMENT: As I indicated earlier animal models poorly recapitulate the immunologic response and pathology associated with either ABD or CBD.

RESPONSE: *Added the following text to section 1.2: "*Studies in different species of animals demonstrate a similar immunological response as humans as well as other toxicity. However, there are deficiencies in these studies; they do not adequately reproduce features of human CBD. Therefore, these studies cannot reliably predict exposure-response effects of beryllium exposure (NRC 2008).*"*

QUESTION: Has adequate attention been paid to dose-response relationships for both human and animal data? Please explain.

COMMENT: Adequate consideration was provided.

RESPONSE: *No revisions were suggested.*

QUESTION: Are you aware of any studies that are not included in the profile that may be important in evaluating the toxicity of the substance? Please provide a copy of each study and indicate where in the text each study should be included.

COMMENT: I am not aware of any additional studies [though Haberman et al. 1998 was included]. My comments amended at the end do suggest evaluating literature related to dental materials with beryllium causing contact dermatitis/gingivitis.

RESPONSE: *Included the following text in Section 2.11 Dermal: "Haberman et al. (1998) examined the use of beryllium dental materials which may cause allergic contact dermatitis in some patients. Signs and symptoms consistent with gingivitis, oral lichen planus, leukoplakia, aphthous ulcers, and pemphigus are often associated with exposure to beryllium in dental alloys (Haberman et al. 1998)."*

QUESTION: Are you aware of any studies that are not included in the profile that may be relevant to deriving MRLs for any of the substance isomers? Please provide a copy if this is a new reference.

COMMENT: I am not aware of any studies that could be used to derive a MRL.

RESPONSE: *No revisions were suggested.*

QUESTION: Were all appropriate NOAELs and/or LOAELs identified for each study (both in the text and the Levels of Significant Exposure (LSE) tables and figures)? If not, did the text provide adequate justification for excluding NOAELs/LOAELs including, but not limited to, citing study limitations? Please suggest appropriate changes.

COMMENT: Appropriate toxicity values were used.

RESPONSE: *No revisions were suggested.*

QUESTION: Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables? If not, please explain why and suggest appropriate changes.

COMMENT: Table 2.1 - It's unclear why enlarged heart (cardiomyopathy) is considered a less serious health effect. Likewise, It's not clear why beryllium sensitization is classified as a serious effect – it's difficult to reconcile less serious and more serious effects reported in animals and this classification for sensitization in humans. I recognize this is likely the most serious effect reported in exposed humans but on face value it's not immediately apparent that this is a serious effect. For example, inflammation of the lungs seen in monkeys exposed chronically is deemed a "less serious effect" – yet CBD which has similar pathology is classified as a "serious effect". Later, granulomas are considered a serious effect – but granulomas are largely an inflammatory response. Are they a serious effect because ATSDR considers these to be pre-neoplastic since the granulomas will not in and of themselves lead to mortality or severe morbidity? Table 2.2. Jacobson 1933 (and others) – ATSDR has classified a 58% decrease in blood phosphate levels as a less serious effect; however, this appears to be the causal link to the development of beryllium rickets thus this degree of hypophosphatemia would be a serious effect (i.e., they go "hand in hand". Table 2.3 Here and elsewhere, ABD and CBD are immune-mediated hypersensitivity reaction directed in part against the beryllium antigen. Thus, hypersensitivity is a key initiating event and could

thus be classified as a serious effect. Alternatively, the serious effect seen in occupational studies that does meet the definition of a serious effect is death – the Tables could be more consistent if increased mortality was defined as the serious effect (especially since the range of effects seen in people with beryllium sensitivity can vary dramatically).

RESPONSE: *In general, reversible effects are considered less serious. Death is a serious effect, however the human studies on mortality are not included in Table 2-1. There are no studies in the Levels of Significant Exposure Tables that report increased mortality, however mortality would be considered a serious LOAEL and classified under the death endpoint. Many hypersensitivity reactions can be reversible and therefore are classified as LOAELs; not serious effect. The rationale for each classification mentioned in the comment is provided in the following table.*

Effect	Current classification	Proposed change	Rationale
Enlarged heart	LOAEL	No change	Potentially reversible (thought to be secondary to respiratory system dysfunction)
BeS	LOAEL	Change	Sensitization does not mean loss of organ or system function so it is not a sLOAEL.
CBD	sLOAEL (human studies)	No change	CBD can be managed with medications but not reversed
Lung inflammation	LOAEL (animal studies)	No change	Potentially reversible
Granulomas	sLOAEL	No change	The granulomas caused by beryllium never resolve and cause severe morbidity in the form of breathing difficulties. The breathing difficulties will not resolve so are a serious effect. IARC, EPA, and NTP classify beryllium as carcinogenic but this is not the reason for classifying granulomas as serious.
Rickets	sLOAEL	No change	Rickets can result in bone deformity causing a loss of function.
25 % decrease in blood phosphate levels	LOAEL	No change	This is a less serious effect because of the range of normal values possible for phosphate levels.

QUESTION: Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain. If citing a new reference, please provide a copy and indicate where (in the text) it should be included.

COMMENT: This section appears complete.

RESPONSE: *No revisions were suggested.*

QUESTION: Are the conclusions appropriate given the overall database? If not, please discuss your own conclusions based on the data provided and other data provided to you but not presented in the text.

COMMENT: Conclusions are appropriate.

RESPONSE: *No revisions were suggested.*

Chapter 3. Toxicokinetics, Susceptible Populations, Biomarkers, Chemical Interactions

QUESTION: Is there adequate discussion of absorption, distribution, metabolism, and excretion of the substance? If not, suggest ways to improve the text.

COMMENT: I have provided some suggested changes to the text to improve clarity (see end of this document).

RESPONSE: *Detailed responses are provided to these specific changes at the end of this document.*

QUESTION: Have all available pharmacokinetic/pharmacodynamic models and supporting data been presented? If not, please explain.

COMMENT: To my knowledge yes.

RESPONSE: *No revisions were suggested.*

QUESTION: Is there adequate discussion of the differences in toxicokinetics between humans and animals? Is there adequate discussion of the relevance of animal toxicokinetic information for humans?

COMMENT: Adequately addressed.

RESPONSE: *No revisions were suggested.*

QUESTION: Are there any data relevant to child health and developmental effects that have not been discussed in the profile and should be? Please provide any relevant references.

COMMENT: No suggested additions.

RESPONSE: *No revisions were suggested.*

QUESTION: Is there a discussion of populations at higher risk of susceptibility? Do you agree with the choice of populations? Please explain and provide any additional relevant references.

COMMENT: I agree with the choices made.

RESPONSE: *No revisions were suggested.*

QUESTION: Are the biomarkers of exposure specific for the substance? Please explain.

COMMENT: Yes they are specific. A minor point but it is appropriate to indicate that lung biopsy to obtain tissues for beryllium measurement is highly invasive and is not a "good" biomarker.

RESPONSE: *Updated text in section 3.3.1 Biomarkers of effect now reads: "Though one can determine the beryllium concentration in the lung using lung biopsy, it as an invasive procedure and does not provide information on how recent the exposure occurred because beryllium form, solubility, and particle size influence the amount of time the different types are present in the lung."*

QUESTION: Are the biomarkers of effect specific for the substance? Please explain.

COMMENT: Some of the biomarkers (e.g., BeLPT) are specific.

RESPONSE: *No revisions were suggested.*

QUESTION: Is there adequate discussion of the interactive effects with other substances? Does the discussion concentrate on those effects that might occur at hazardous waste sites? Please explain and provide any additional references.

COMMENT: This discussion was adequate.

RESPONSE: *No revisions were suggested.*

QUESTION: If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions? Please explain and provide any additional references.

COMMENT: This discussion was adequate.

RESPONSE: *No revisions were suggested.*

Chapter 4. Chemical and Physical Information

QUESTION: Are any of the values or information provided in the chemical and physical properties tables wrong or missing? Please explain and provide any additional references.

COMMENT: Values appear correct.

RESPONSE: *No revisions were suggested.*

QUESTION: Is information provided on the various forms of the substance? Please explain.

COMMENT: This section was adequate.

RESPONSE: *No revisions were suggested.*

Chapter 5. Potential for Human Exposure

QUESTION: Is the information on production, import/export, use, and disposal of the substance complete? Please explain and provide any additional relevant references.

COMMENT: This section was adequate.

RESPONSE: *No revisions were suggested.*

QUESTION: Has the text appropriately traced the substance from its point of release to the environment until it reaches the receptor population? Does the text provide sufficient and technically sound information regarding the extent of occurrence at NPL sites? Do you know of other relevant information? Please provide references for added information.

COMMENT: This section was adequate.

RESPONSE: *No revisions were suggested.*

QUESTION: Does the text cover pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media? Do you know of other relevant information? Please provide references for added information.

COMMENT: This section was adequate.

RESPONSE: *No revisions were suggested.*

QUESTION: Does the text provide information on levels monitored or estimated in the environment, including background levels? Are proper units used for each medium? Does the information include the form of the substance measured? Is there an adequate discussion of the quality of the information? Do you know of other relevant information? Please provide references for added information.

COMMENT: This section was adequate.

RESPONSE: *No revisions were suggested.*

QUESTION: Does the text describe sources and pathways of exposure for the general population and occupations involved in the handling of the substance, as well as populations with potentially high exposures? Do you agree with the selection of these populations? If not, why? Which additional populations should be included in this section?

COMMENT: This section was adequate. In each of these cases (1-5) I am not aware of missing relevant literature.

RESPONSE: *No revisions were suggested.*

Chapter 6. Adequacy of the Database

QUESTION: Do you know of other studies that may fill a data gap? Please provide any relevant references.

COMMENT: I am not aware of missing studies.

RESPONSE: *No revisions were suggested.*

QUESTION: Do you agree with the identified data needs? Please explain.

COMMENT: They are data gaps; however, this litany of data gaps largely misses the point and misleads the reader to conclude we know little about beryllium. I would urge ATSDR to identify critical data gaps – especially in light of exposure levels for occupational versus the general public. Indeed filling many of these datagaps likely will have little impact on derivation of health protective MRLs.

RESPONSE: *The following text was revised in Section 6.2 to state: "However, an animal model that exactly mimics CBD or the key precursor pathway in humans has not been found. Identification of such a model that better reflects human disease pathogenesis would be useful to the general population and to populations residing at or near hazardous waste sites."*

Language was also added to the Epidemiology and Human Dosimetry section of 6.2 which now reads: "Studies conducted in people residing around beryllium processing facilities would be useful to further understand risk outside of the occupational setting."

QUESTION: Are the data needs presented in a neutral, non-judgmental fashion? Please note any bias in the text.

COMMENT: These were presented in a neutral way.

RESPONSE: *No revisions were suggested.*

Chapter 7. Regulations and Guidelines

QUESTION: Are you aware of any additional regulations or guidelines that should be included? Please provide citations.

COMMENT: I am not aware of missing regulations.

RESPONSE: *No revisions were suggested.*

QUESTION: Are there any that should be removed? Please explain.

COMMENT: The list provided is adequate

RESPONSE: *No revisions were suggested.*

Minimal Risk Levels (MRLs)

QUESTION: If no MRLs have been derived, do you agree that the data do not support such a derivation? Please explain.

COMMENT: I agree with the decisions to not derive MRLs in the majority of the cases. However, since the chronic inhalation value is derived from human epidemiology studies and represents an immunological response – it's possible that the chronic MRL may also be health protective for an intermediate exposure.

RESPONSE: *As a general rule, a longer duration MRL will typically be protective of a shorter duration MRL since specific health effects, or increased severity typically occur at lower levels in longer than shorter duration studies. ATSDR chose not to specify the chronic duration MRL as being protective of an intermediate exposure. The reasons are because an intermediate health effect may not yet be identified, and may likely occur at a higher dose level than those seen at the lower chronic duration MRL value.*

QUESTION: If MRLs have been derived, do you agree with the proposed MRL values? Explain. If you disagree, please specify the MRL value that you would propose.

a. Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose.

COMMENT: MRL Chronic inhalation. Given the large number of occupational studies it does not appear to be warranted to include a modifying factor of 3 for an inadequate database since the agreement among different studies regarding a NOAEL is reasonably coherent.

RESPONSE: *ATSDR agreed and removed the modifying factor from the chronic inhalation MRL calculation.*

QUESTION: Please comment on any aspect of our MRL database assessment that you feel should be addressed.

COMMENT: No response.

RESPONSE: *No revisions were suggested.*

Appendices

QUESTION: Please provide any comments on the content, presentation, etc. of the included appendices.

COMMENT: *No response provided.*

RESPONSE: *No revisions were suggested.*

Annotated Comments on the Profile

COMMENT: Line 304: Beryllium has been identified in at least 540 hazardous waste sites that have been proposed for inclusion on the EPA NPL. It may be worth indicating whether this represents contamination of background levels present in nature.

RESPONSE: *The sentence the peer reviewer has quoted is found in Section 1.1 (Overview). In response to the suggestion, the following sentences have been added: "Measurements in water and soil at these sites are generally higher than background levels. Therefore, individuals living near these sites may be at risk of exposure to higher levels of beryllium."*

COMMENT: Line 308: In inhalation exposures, the lung appears to be the deposition spot from which Be is distributed throughout the body. This appears to be the first use of scientific notation for beryllium. Should define or be consistent.

RESPONSE: *Updated "Be"* as "beryllium*" in Section 1.2 and remainder of the text.*

COMMENT: Line 2344. …beryllium and its compounds are poorly absorbed after oral and dermal exposure, although dermal exposure can result in beryllium sensitization (BeS). I would avoid this abbreviation since it could be misinterpreted as a sulfide of beryllium. Indeed Chapter 1 is often the only one read especially by the general public thus you should avoid overzealous use of abbreviations (e.g., BeS, CBD, ABD) that reduce readability – especially for the general public (e.g., see: Plavén-Sigray P, Matheson GJ, Schiffler BC, Thompson WH. The readability of scientific texts is decreasing over time. Elife. 2017;6:e27725).

RESPONSE: *Updated BeS to "beryllium sensitization" in Chapter 1. We also removed ABD and CBD acronyms in Chapter 1 and replaced with acute beryllium disease and chronic beryllium disease. Additionally, at first use in Chapter 2, BeS, ABD, and CBD are defined.*

COMMENT: Line 324: Other effects that have been observed in individuals with severe cases of CBD include damage to the right heart ventricle, hepatic necrosis, kidney stones, and weight loss; these effects are probably secondary to CBD rather than a direct effect on the tissues. This sentence is a bit confusing – how are you able to differentiate a primary versus secondary effect with confidence?

***RESPONSE*:** *In section 2.6, the following text was deleted: "these effects are probably secondary to CBD rather than a direct effect on the tissues."*

COMMENT: Line 343. Change to: ABD may be an inflammatory and/or immunological response to beryllium, thus suggesting it may be part of the continuum of CBD.

RESPONSE: *Updated the sentence in section 1.2 to state: "ABD may be an inflammatory and/or immunological response to beryllium and has been hypothesized to be part of the continuum of CBD."*

COMMENT: Line 352. In BeS individuals, beryllium in the lungs binds to protein/peptides and elicits a proliferation of T lymphocytes, a release of inflammatory mediators, and an accumulation of inflammatory cells in the lungs. This is a bit confusing since it implies Be binding to proteins only occurs in these patients. It may be clearer to describe the biochemical effects that then lead to the sensitization.

RESPONSE: *The following text is included in Chapter 1, Section 1.2: "When individuals inhale beryllium, it binds to proteins/peptides and elicits a proliferation of T-lymphocytes, a release of inflammatory mediators, and an accumulation of inflammatory cells in the lungs. This causes sensitization that results in the formation of noncaseating granulomas, the accumulation of mononuclear cell infiltrates, and the development of fibrosis."*

COMMENT: Line 356. Change to: BeS is usually diagnosed as more than one abnormal Beryllium lymphocyte proliferation test (BeLPT) result… ALSO no reason to capitalize beryllium. As shown in Table 2.5 many of the occupational studies do not rely on BeLPT to confirm a diagnosis – it may be appropriate to address this in this portion of the document.

RESPONSE: *Section 1.2 sentence now reads: "Beryllium sensitization is usually diagnosed as more than one abnormal beryllium lymphocyte proliferation test (BeLPT) result, and can progress to CBD, but not all sensitized individuals will develop CBD. As shown in Table 2-5 in Chapter 2, many of the occupational studies do not rely on BeLPT to confirm a diagnosis of CBD."*

COMMENT: Line 371. Dogs, who had access to the beryllium-containing diet for one hour per day, showed higher concentrations of beryllium in the gut than rats, who had unlimited access to the diet. This is confusing – were Be concentrations higher in the gastrointestinal tract tissues or GIT contents? Clarify what you mean by gut.

RESPONSE: *Section 1.2, gastrointestinal effects, was updated to read: "Dogs who had access to the beryllium-containing diet for one hour per day showed higher concentrations of beryllium in gastrointestinal tract tissues than rats who had unlimited access to the diet."*

COMMENT: Line 378. Sensitized guinea pigs also developed granulomatous lesions and other delayed hypersensitive reactions following dermal exposure to beryllium sulfate, beryllium fluoride, beryllium oxide, or beryllium chloride (Belman 1969; Marx and Burrell 1973). Were the animals sensitized – if so with which agent (versus this species is more sensitive to dermal effects)?

RESPONSE: *Section 1.2, dermal effects, was updated to now read: "Guinea pigs sensitized with beryllium sulfate also developed granulomatous lesions and other delayed hypersensitive reactions following dermal exposure to beryllium sulfate, beryllium fluoride, beryllium oxide, or beryllium chloride (Belman 1969; Marx and Burrell 1973)."*

COMMENT: Line 381. Change to: Immunological Effects. Beryllium exposure may cause an immune reaction that presents with respiratory or dermal symptoms.

RESPONSE: *Section 1.2, immunological effects was updated to now read**:** "Beryllium exposure may cause an immune reaction that presents with respiratory, dermal, or other symptoms*."

COMMENT: Table 2.1 – here and elsewhere indicate species as Macacus sp unless actual species is known (or use macaque since you are using common names later; e.g., squirrel monkey). Consider using degeneration rather than hypotrophy for adrenal effects. Reporting p values is variable in this table. Muller et al., 2011 reported differences in lung inflammation scores – is this pneumonitis? Are the scores severe enough to be considered a more serious effect? Some concentrations are using M (e.g., 0.06 M) this is unclear (similar concern for Table 2.2) – avoid using when sex has already been identified. I'd also suggest that this be placed in parentheses (e.g., (M)) to avoid confusion that this could represent a molar measure. Chronic Wagner et al rat study (1969) describes the effects as "Inflammation and proliferation in lung" – the nature of the proliferative response should be described here.

RESPONSE: *Table 2-1 inhalation study numbers were updated for monkey to Macaca mulatta or Saimiri sciureus: 1-3; 11-13; 24, 25. No oral or dermal studies were updated.*

ATSDR uses the terminology supplied (atrophy or degeneration) by the publication author to describe adrenal effects. No changes made.

p-values are not always reported in studies. Therefore, readers will see variable reporting of this in Table 2-1.

Muller et al., 2011 states "An inflammation score was determined by 2 independent investigators blinded to the treatment groups and graded on a scale of 1, 2, 3, and 4, corresponding to no inflammation, mild, moderate, and severe inflammation, respectively." No further description provided by Muller to characterize the effect as pneumonitis. Inflammation is typically classified as a LOAEL; not a serious effect. No changes were made.

In Tables 2-1 and 2-2 "M" is footnoted to mean "males". However, concentrations are typically reported in the Dermal Level of Significant Exposure Table (2-3) because studies report the doses differently. When there is an "M" in the "Doses" column, it represents "molar". When "M" is listed in the "Effects" column, it indicates "males". This can be ascertained by the footnotes of Table 2-3. Formatting of Table 2-1 and Table 2-2 are developed as per ATSDR guidelines (i.e., the listing of sex or molar). Therefore, no edits were made.

Inflammation and proliferation in lung tissue is an effect described in the Reeves et al. 1967 study, not the Wagner et al. (1969) rat study. Proliferation is described in the study as "atypical low cuboidal cells lining alveolar walls around respiratory bronchioles" and "Scattered, dust -laden macrophages are present in the alveoli." Added the detail "atypical proliferation with scattered dust-laden macrophages" to Table 2-1.

COMMENT: Table 2.2. Guyatt et al. 1933 dog study – identify site of ulceration (e.g., gastric, multifocal). Same study: it's unclear that testicular atrophy and degeneration meet the described definition for a serious effect.

RESPONSE: *Since the Guyatt et al. 1933 study is in rats and not dogs, ATSDR assumed it was the Morgaridge et al. 1976 study for the clarification. Added "Ulceration in intestine" to the Morgaridge et al. 1976 dog study in Table 2-2.*

Testicular atrophy is classified as serious per ATSDR guidance as it is considered irreversible.

COMMENT: Table 2.3- Marx and Burrell 1973 – corrosion may be inappropriate here – e.g., erosion or ulceration are the likely effects evaluated.

RESPONSE: *Marx and Burrell did not have an effect of corrosion. However, the subsequent study by Strupp et al. (2011a) did have the effect. While text describing the NOAEL for the study was in the draft reviewed by the peer-reviewer, in the subsequent profile draft, ATSDR deleted the effects text for the NOAEL.*

COMMENT: Line 562. 2.2 DEATH The authors should address whether deaths seen in various animal species following beryllium inhalation are due to an immunological response (beryllium sensitization) or due to the inherent toxicity of the inhaled metal (this is more likely).

RESPONSE: *Added text in Section 2.2 to read: "Deaths observed in the different species of animals is potentially due to the toxicity of the inhaled metal at each duration of exposure."*

COMMENT: Table 2.5. The term berylliosis is occasionally used (e.g., Takaro and Firestone 2009) – this appears in consistent with the use of either ABD or CBD. Welch et al. 2004 – specify which test was used (e.g., BeLPT). Duggal et al. 2010 – change to No changes in respiratory flow rates and lung volume observed. Kreiss et al. 1997 specify which blood tests were abnormal).

RESPONSE: *In Table 2-5 added: "(also called CBD)" in Takaro and Firestone 2009; Added "BeLPT" in results column of Welch et al. 2004; Updated results text for Duggal et al. 2010 to: "No changes in respiratory flow rates and lung volume observed"; Added the following text: "abnormal BeLPT" to the Kreiss et al. 1997 results column.*

COMMENT: Line 929 (and elsewhere): Fifteen mg/m3 of bertrandite ore or beryl ore was the TLV for inert dust. I assume that the exposure concentration is not mg Be/M3 – correct – it may be more appropriate to state 15 mg ore/m3. Alternatively provide in the text a clear statement that exposure concentrations not given as mg Be/M3 are for the chemical form used.

RESPONSE: *Added the word "ore" to Chapter 2, "Respiratory Effects in Animals from Chronic Inhalation Exposure to Beryllium."*

COMMENT: Line 1080: Missing space: …and Skill 1934).No bone effects…

RESPONSE: *Section 2.8, Musculoskeletal: Added space*

COMMENT: Line 1332: delete was in: …but there was were no significant…

RESPONSE: *Section 2.14, Immunological: Deleted "was."*

COMMENT: Line 1425 and 1429: identify lymph nodes evaluated in these studies (e.g., tracheobronchial)

RESPONSE: *Section 2.14 text includes the types of lymph nodes: "The tracheobronchial lymph nodes had moderate cortical and paracortical lymphoid hyperplasia resulting from B and T cell activation. The lymph nodes examined 365 days after treatment were characterized by lymphoid depletion, marked congestion, and medullary fibrosis."*

COMMENT: Line 1433: This is confusing – were lymphocytes evaluated in vitro from Be-exposed animals or naïve controls?

RESPONSE*: Updated text in section 2.14 to clarify: "When lymphocytes from naïve controls and Be-exposed animals were exposed in vitro to beryllium salts they showed increased proliferation rates greater than those of the controls (Stiefel et al. 1980)."*

COMMENT: Line 1443 – move period mark.

RESPONSE: *Section 2.14: moved period mark by deleting extra spaces.*

COMMENT: Line 1446: … in the BeLPT test proved toxic to most of the murine cell cultures, indicating that this test may not be a good model for human toxicity. Is this correct – i.e., is the animal model lacking or the test itself (for human toxicity)?

RESPONSE: *The animal model is lacking as the beryllium lymphocyte proliferation test is used in humans. Updated the sentence prior to the line commented on in section 2.14 to clarify: "*Although significant differences in the results of *BeLPT testing were found between the beryllium-exposed mice and controls, the concentration (100 µmol) of beryllium sulfate used in the BeLPT test proved toxic to most of the murine cell cultures, indicating that murine cell cultures may not be a good model for human toxicity."*

COMMENT: Line 1462: Comparing these results to those obtained in mice exposed to fine particles (Muller et al. 2010) suggests that exposure to fine particles resulted in more severe lung damage than exposure to larger particles. This may reflect dosimetric differences in delivery versus an inherent difference (or both).

RESPONSE: *Included text in section 2.14 to clarify: "Comparing these results to those obtained in mice exposed to fine particles (Muller et al. 2010) suggests that exposure to fine particles resulted in more severe lung damage than exposure to larger particles. This is potentially due to dosimetric differences in delivery versus an inherent difference between the toxicity of the two types of particles."*

COMMENT: Line 1511: Change to Developmental effects of beryllium in humans are limited…

RESPONSE: *Section 2.17, Developmental: Changed is to "are."*

COMMENT: Line 1514: Change to: This case study suggests beryllium may be transferred to the infant in-utero or through lactation…

RESPONSE: *Section 2.17, Developmental: Deleted "exposure."*

COMMENT: Line 1624: extraneous period and parentheses punctuation marks

RESPONSE: *Section 2.19, Cancer: Deleted extra period and parentheses from "workers employed for <1 year (Ward et al. 1992)."*

COMMENT: 1730 and 1731 – versus is superscripted

RESPONSE: *Section 2.19, Cancer: Changed to not superscript "versus" in the following: "…*and maximum exposure levels (32.4 μg/m^3 versus 27.1 μg/$m^{3)}$, within the same order of magnitude."

COMMENT: Line 1882: Beryllium is classified as a carcinogen; however, this is based mainly on reports that beryllium metal and beryllium oxide cause lung cancer in rodents after inhalation of the airborne particulates. It is less clear whether beryllium salts are also carcinogenic. This statement is not needed since this section addresses genotoxicity (i.e., nongenotoxic mechanisms for cancer could occur)

RESPONSE: *Section 2.20, Genotoxicity: Deleted the sentence.*

COMMENT: Line 1937 (and elsewhere): No need to state deoxyribonucleic acid

RESPONSE: *Section 2.20, Genotoxicity: Deleted "deoxyribonucleic acid."*

COMMENT: Line 1938. Change to: … however it increases misincorporation…

RESPONSE: *Section 2.20, Genotoxicity: Deleted "was observed to", line reads: "Beryllium sulfate… (Williams et al. 1989); however, it increases misincorporation… (Sirover, 1975)."*

COMMENT: Line 1963: why use chemical abbreviation here (BeSO4)?

RESPONSE: *Section 2.20, Genotoxicity: Replaced BeSO4 with "beryllium sulfate", line now reads: "Beryllium sulfate… a mean of 32.5 -37.4%... after examining 1663 sequence tags."*

COMMENT: 2.21 MECHANISM OF ACTION. This section also includes a description of pharmacokinetics rather than mechanism of action (e.g., lines 1999-2017).

RESPONSE: *Section 2.21, Mechanism of Action: Deleted four paragraphs of introductory text starting with: "Beryllium can be found...(e.g., size, solubility)…[to] Beryllium was detected in CBD…with CBD (IARC 2012; Sawyer et al. 2005)." New paragraph reads: "Beryllium is a highly charged ion, like*

magnesium, it is also implicated in a variety of physiological functions…. the nucleus (Witschi 1970). Beryllium exposure is… respiratory tract… altering normal physiology. Genes associated with receptors like estrogen …particulate beryllium metal."

COMMENT: Line 2075: Mechanisms of Toxicity: The authors should discuss species differences in response since immunological effects/sensitization differs between humans, rodents, and other species.

RESPONSE: *Added the following text to Section 2.21: "A review by the National Research Council elaborates on the animal models of pulmonary immunotoxicity and sensitization, where the authors conclude that the animal models are inadequate when it comes to replicating the symptoms and effects observed in human CBD."*

COMMENT: Line 2080: CBD is a life-long allergic sensitization and subsequent autoimmune-like response to beryllium exposure. There are some reversal studies though that suggest otherwise.

RESPONSE: *In Section 2.21, Mechanisms of Action, Mechanisms of Toxicity Associated with Respiratory Effects: Deleted previous text and new text now reads: "CBD is a life-long immune sensitization and subsequent inflammatory response due to beryllium exposure."*

In Section 6.2, under Chronic-Duration MRLs, the following was added: "Additionally, there is some evidence that BeS may be reversible, but it is unclear if this was due to laboratory test variability, reductions in exposure and/or loss of sensitization over time (Rom et al. 1983). More studies would be needed to understand the relevance of these observations."

COMMENT: Line 2091: largely focuses on pharmacokinetics and provides little evidence that the sensitization is similar in rodents and other animal species examined to date.

RESPONSE: *Deleted sentence on pharmacokinetics in section 2.21, Mechanisms of Action, Mechanisms of Toxicity Associated with Respiratory Effects.*

COMMENT: Line 2333: It's more accurate to state that the primary route of beryllium exposure is inhalation, particularly among occupationally exposed individuals.

RESPONSE: *Section 3.1, Toxicokinetics, Absorption updated to state: "Most beryllium is absorbed via the lungs, particularly among occupationally exposed individuals."*

COMMENT: Line 2369: This may be correct, however, it may also reflect upper respiratory tract deposition with mucociliary clearance followed by ingestion – or mixed exposure.

RESPONSE: *Text updated in Section 3.1, Toxicokinetics, Absorption to read: "However, human ingestion of beryllium is thought to occur inadvertently via hand-to-face activity following dermal handling of beryllium, or as a result of mucociliary transport of inhaled beryllium out of the respiratory tract and to the gastrointestinal tract followed by ingestion or by mixed exposure. In animals, beryllium and its compounds are poorly absorbed from the gastrointestinal tract."*

COMMENT: Line 2380: Did these workers have CBD?

RESPONSE: *Yes, these workers showed CBD and the content (human laboratory exposure, clearance) has been moved to Section 3.1.3, Excretion.*

COMMENT: Line 2382: This is confusing – deposition will differ based on species, airflow, air concentrations and particle size. Is there sufficient data to suggest that "he rate of pulmonary deposition between mice and humans for total particles (Be and BeAl) differed by a factor of 20 with humans having the higher deposition rate." Is this based on experimental data or modeled estimates using available particle deposition models? Table 3.1 should indicate this is modeled data.

RESPONSE: *IRSST 2012 is an experimental study in mice and compares the animal model data to human data. Included the following text in Section 3.1.1:"The rate of pulmonary deposition between mice and humans for total particles (Be and BeAl) differed by a factor of 20 with humans having the higher deposition rate based on experimental data from IRRST (2012)."*

COMMENT: Line 2387: Missing space in: BeO (Table 3 1).The lung

RESPONSE: *Updated Table 3-1 to include space.*

COMMENT: Line 2401: Avoid using "resist" discuss relative sensitivity instead.

RESPONSE: *Text updated in section 3.1.1 Absorption to read: "Males exhibited a greater enlargement of the lymph nodes than females. According to the authors, this indicates that there were sex differences associated with beryllium exposure where males were more sensitive than females (Reeves and Vorwald 1967)."*

COMMENT: Line 2421. Change to: For example, elevated beryllium concentrations were seen in lung tissue taken from subjects in the Beryllium Case Registry more than 20 years…

RESPONSE: *This text was deleted from section 3.1.1 as the citation was not a primary scientific publication.*

COMMENT: Line 2430. Change to: …the respiratory tract (Delic 1992; HSE 1994, Bruce 2011).

RESPONSE: *Text updated in section 3.1.1 Absorption to read: "Studies in guinea-pigs and rats indicate that 40–50%...the respiratory tract (Delic 1992; HSE 1994; WHO 2001)."*

COMMENT: Line 2453: Although beryllium ions are rapidly cleared, billions of beryllium ions may be released in the respiratory tract via dissolution in airway lining fluid (Stefaniak et al. 2012). Using "billions" is inappropriate given the number of ions in a mole of material.

RESPONSE: *Text updated in section 3.1.1 Absorption to read: "The rapid clearance of beryllium ions leads to an increased release in the respiratory tract via dissolution in airway lining fluid (Stefaniak et al. 2012)."*

COMMENT: Line 2459: Be more explicit about the lesions since responses in rodents are not similar (i.e., they do not develop the hallmarks of granulomatous disease, lung fibrosis, and heart enlargement seen in humans with CBD) e.g., see also Table 3-5 and Line 4311.

RESPONSE: *Included information in section 3.1.1 describing the lesions in mice. Updated text to contain: "For example, C3H/HeJ mice exposed to beryllium metal for several months resulted in beryllium lung burdens of generally >20 µg/lung with the development of lesions that had Be-containing macrophages, granulomatous pneumonia, lymphocytic interstitial aggregates, and mononuclear interstitial infiltrates (Finch et al. 1998; Nikula et al. 1997)."*

COMMENT: Line 2461. Change to: Studies suggest that beryllium is unlikely to be systemically absorbed through intact skin because beryllium binds to proteins and nucleic acids of the epidermis, leading to poor dermal absorption.

RESPONSE: *Updated text in section 3.1.1 to: "*Studies suggest that beryllium is unlikely to be systemically absorbed through *...."*

COMMENT: Line 2475: Is this needed here? Also any studies that were underway in 2007 should be completed by now.

RESPONSE: *In section 3.1.1, the following paragraph was reworded to: "The beryllium occupational air standard is intended to protect workers from high inhalation exposures. However, beryllium is also slightly absorbable through the skin, particularly if broken. Skin absorption of beryllium may create skin ulcers and damaged skin can increase the amount of beryllium absorbed as described further below (Kreiss et al. 2007)."*

COMMENT: Line 2478-2485 – this paragraph does not relate to pharmacokinetics and does not belong here (same issue to some extent with the immediately preceding paragraph).

RESPONSE: *We kept the text in section 3.1.1 relating to studies discussing beryllium absorption including: "The beryllium occupational air standard…Kreiss et al. (2007). CBD cases at a copper-beryllium alloy…Tinke et al. (2003)…skin contact with poorly soluble beryllium oxide particles can cause…humans." as it pertains to absorption of beryllium via dermal exposure.*

COMMENT: Line 2512: Extraneous period punctuation marks.

RESPONSE: *In section 3.1.1, the following sentence was updated without additional punctuation marks and now reads: "Accidental ingestion of beryllium… former being more likely (Table 3-3) (Deubner et al. 2001c)."*

COMMENT: Line 2522: Distribution. Cite studies evaluating distribution to the brain – e.g., Drobyshev et al. (2019).

RESPONSE: *Added text to section 3.1.2 to include brain accumulation and it now reads: "Intraperitoneal injection of beryllium sulfate in rats elicited brain accumulation of beryllium in a dose-dependent manner (Drobyshev et al. 2019)."*

COMMENT: Line 2525: Specify species used for the Krachler et al. (1999) study - human.

RESPONSE: *Included "human" in section 3.1.2 to read: "A study by Krachler et al. (1999a)… that beryllium is transferred across the human placenta…."*

COMMENT: Line 2530: Was animals intended to be a subheader?

RESPONSE: *Fixed the text in section 3.1.2 to remove animals, the sentence now reads: "Meehan and Smythe (1967) reported beryllium concentrations in several human organs: 0.21 ppm in lungs; 0.08 ppm in brain; 0.07 ppm in both the kidney and spleen; 0.04 ppm in each of liver, muscle, and vertebrae; 0.03 ppm in heart; and 0.02 in bone."*

COMMENT: Line 2533: Change was provided to were provided.

RESPONSE: *Updated text in section 3.1.2 to: "Further details regarding the source of the organs were not provided."*

COMMENT: Line 2615: Change to: Excretion of absorbed beryllium is generally via urine; whereas unabsorbed ingested beryllium is excreted through the feces (WHO 2001).

RESPONSE: *Updated text in section 3.1.3 to: "Excretion of absorbed beryllium is generally via urine, whereas unabsorbed ingested beryllium is excreted through the feces (WHO 2001)."*

COMMENT: Line 2739: One case report indicates that a child who lived near a beryllium manufacturing facility developed CBD (Eisenbud et al. 1948b). this case report should be evaluated with caution – what was the diagnostic criteria used in the late 1940s?

RESPONSE: *Deleted the sentence from section 3.2.*

COMMENT: Line 2957. Change to: Alveolar macrophages from patients with CBD and BeS demonstrated significantly greater cell surface CD16…

RESPONSE: *Deleted "were", in section 3.2, from sentence written in comment above.*

COMMENT: Line 2962. It is possible that this polymorphism could be related to other adverse effects (e.g. GI lesions), but further research is needed. Why GI lesions since the evidence is largely limited to high dose studies performed in dogs?

RESPONSE: *Deleted GI lesions from section 3.2 sentence; it now reads as: "It is possible that this polymorphism could be related to other adverse effects, but further research is needed."*

COMMENT: Line 3503: Are there data about oral exposure from dental alloys? For example gingivitis/contact dermatitis has been reported (e.g., see: Haberman et al; https://doi.org/10.1111/j.1600-0536.1993.tb03378.x).

RESPONSE: *Included text in section 3.2: "Haberman et al. (1998) examined the use of beryllium dental materials which may cause allergic contact dermatitis in some patients. Signs and symptoms consistent with gingivitis, oral lichen planus, leukoplakia, aphthous ulcers, and pemphigus were observed with exposure to beryllium in dental alloys (Haberman et al. 1998)."*

COMMENT: Line 3776: Earlier a +0 oxidation state was also described.

RESPONSE: *A sentence in Chapter 5 was removed that stated Be(2+) was the only oxidation state identified in a study. Further, a sentence was adapted in section 4.1 and now reads: "It appears in Group IIA of the periodic table and the most common oxidation state is Be(+2), although an oxidation state of (0) has been observed in certain compounds."*

COMMENT: Line 3970. Missing space in reaching a concentration of 29pmol/kg

RESPONSE: *In section 5.5.3. the sentence was revised to read: "However, beryllium concentration increased with depth from 200 to 3,500 m, reaching a concentration of 29 pmol/kg."*

COMMENT: Line 4244: Further study is needed to understand the immune component of effects observed in animals (e.g. GI lesions in dogs). Dogs are very sensitive to some GI "irritants" (e.g., NSAIDs) when compared to people. Is there any reason to suspect that GI lesions seen in dogs are immune-mediated?

RESPONSE: *Deleted GI lesions in dog from Section 6.1 as there was no direct evidence that GI lesions in these dogs were exclusively immune mediated. Added text to section 6.2, immunological header: "Additionally, the EPA Office of Water Scientists indicate epithelial surfaces (e.g., lung, GI tract) appear to have allergenic responses to beryllium exposure and suggest researching whether the FCGR3A gene (as discussed in section 3.2) is linked not only to lung effects but GI lesions as well."*

COMMENT: Line 4246: The organs or systems adversely affected in humans after exposure to beryllium include primarily the lungs but the heart, liver, kidney adrenal and hematopoietic tissue have been reported as target organs. This is confusing since elsewhere in the document some effects, e.g., those on the human heart, have not been attributed to a direct effect due to beryllium exposure.

RESPONSE: *In section 6.1, "heart" has been deleted from respective paragraphs. The health effects section indicates that the effects on the heart are not thought to be direct effects.*

COMMENT: Line 4344: Change to: …incidence data do not show a statistically significant effect…

RESPONSE: *Section 6.2 sentence was changed to add "do": "The Morgareidge et al. (1976) dog study… as gastrointestinal incidence data do not show a statistically significant effect… when the highest dose is excluded."*

COMMENT: Line 4347: A well-conducted chronic inhalation study in rats and mice using several exposure levels would add confidence to the database and eliminate uncertainties due to the flaws in the existing studies. It's not clear whether the flaws warrant an additional chronic bioassay – this could be strengthened by describing critical flaws that lower confidence in the existing studies. Meta-analyses of human and animal cancer data may also be appropriate.

RESPONSE: *In section 6.2, replaced text with: "A well-designed chronic inhalation study in rats and mice which includes lower doses of exposure would fill database gaps and mitigate uncertainties associated with the current body of literature."*

COMMENT: Line 4598: Additional comparative toxicokinetics studies regarding distribution, absorption, and excretion of inhaled beryllium would be helpful to determine the use of the appropriate animal model to study ABD and CBD. I disagree fundamentally the issue of developing an animal model for ABD and CBD is analogous to long-standing challenges of developing animal models that replicate skin sensitization seen in humans. Laboratory animals poorly mimic this response and PK studies are unlikely to shed new light on developing an appropriate animal model.

RESPONSE: *Updated text in section 6.2 to include: "Additional comparative toxicokinetics studies regarding distribution, absorption, and excretion of inhaled beryllium could be used to study ABD and CBD, with the help of in vitro, organ on chip models using human lines."*

Comments provided by Peer Reviewer #2

ATSDR Charge Questions and Responses

Chapter 1. Relevance to Public Health

QUESTION: Do you agree with those effects known to occur in humans as reported in the text? If not, please explain why and provide a copy of additional references you would cite and indicate where (in the text) these references should be included.

COMMENT: The effects known to occur in humans as listed in the text of Chapter 1 appear to be supported by empirical findings as reported in published literature used to develop the profile. No additional references were found that would warrant the inclusion of additional effects known to occur in humans.

RESPONSE: *No revisions were suggested.*

QUESTION: Are the effects only observed in animals likely to be of concern to humans? Why or why not? If you do not agree, please explain.

COMMENT: It is unclear with respect to gastrointestinal effects (GI). It is indicated that no human data were located regarding GI effects and the effects listed were reported in dogs and rats. Dogs experienced GI ulceration and inflammatory lesions from ingestion of beryllium-containing diets but rats did not. These differences were ascribed to differences in eating patterns, but this is somewhat confusing. The dogs had access to the beryllium-containing diet for one hour/day whereas the rats had unlimited access to the diet. Therefore, the dogs potentially had a bolus exposure whereas the rats potentially had a consistent level of exposure through out the dosing period. Could this difference be more due to the frequency or exposure dose than the eating pattern? If rats were given a bolus, such as on a dosing wafer, would they be anticipated to experience similar lesions? "Eating pattern" does not appear to be the reason for the difference in effects but to the frequency of the exposure dose.

Suggestion: It is recommended that this be clarified or at least acknowledged that eating pattern could reflect differences due to the frequency of beryllium exposure doses.

RESPONSE: *Included text in Section 1.2: "The difference in observed gastrointestinal outcomes between dogs and rats may be associated with the difference in the frequency of beryllium exposure due to different eating patterns."*

QUESTION: Have exposure conditions been adequately described? If you disagree, please explain

COMMENT: In this chapter, exposure conditions appear to be described as only general population or occupational and adequate information is provided to explain these exposure conditions. For purposes of this general and introductory chapter, the exposure conditions appear to be adequately described.

RESPONSE: *No revisions were suggested.*

Chapter 2. Health Effects

QUESTION: Do the health effect conclusions made in Chapter 2 adequately reflect the findings in the published literature? If not, please suggest appropriate changes.

COMMENT: The health effect conclusions made in Chapter 2 appear to reflect findings in published literature.

Suggestion: This profile does not consistently include summative sections as have been included in some other Toxicological Profiles written by the Agency. For example, prior to Figure 2.1, it would help to have a summary of the linkages between exposure and health outcomes identified by epidemiological studies and a summary of findings from animal studies. These summative sections make it easier for the public health community to make note of potential health effects that may arise from beryllium exposure. Similarly, some other profiles provide overview paragraphs at the start of each health endpoint discussed to give the reader a shortened summary of the findings to be reported in the longer overview. This is done in this profile only in some sections and not all sections.

RESPONSE: *Added summary statements where needed in sections 2.2 to 2.14 as follows:*

- *2.2 Death: More human studies indicate an increase in mortality after inhalation exposure. Furthermore, an increase in mortality is observed in animal studies after inhalation exposure. In animal studies after oral exposure, mortality was observed, but was contingent on the compound being tested.*
- *2.3 Bodyweight: Changes in body weight have been observed in humans and animals after inhalation and oral exposure to beryllium or its compounds. No studies were located regarding body weight effects in humans or animals after dermal exposure to beryllium or its compounds.*
- *2.4 Respiratory: Human and animal studies indicate that the respiratory tract is the primary target of beryllium toxicity following inhalation exposure. Beryllium exposed people may present with acute* beryllium disease (ABD) or chronic beryllium disease (CBD) after inhalation exposures. These diseases are caused by immune system reactions targeting the lungs. Epidemiological evidence in human studies are summarized in Table 2-5.
- *2.5 Cardiovascular: The database is not robust enough to make any conclusionary remarks concerning potential cardiovascular effects. A single monkey species and a qualitative human study have suggested heart effects. It is possible that these effects are secondary to the respiratory effects, rather than direct toxicity to the heart.*
- *2.6 Gastrointestinal: It is unclear whether gastrointestinal effects result from oral exposure to beryllium as only two animal species have been tested and have conflicting results. Effects observed in dogs were at a non-environmentally relevant dose level (a higher level than found in the general environment).*
- *2.7 Hematological: Potential hematological effects from beryllium exposure in humans have not been well studied. Anemia was observed in animals after inhalation and oral exposures.*
- *2.8 Musculoskeletal: Irregularities in bone morphologies were observed in rats after oral exposure to beryllium carbonate (30-345 mg/kg/day). However, dog and rat studies using beryllium sulfate (1-31 mg/kg/day) did not find any musculoskeletal effects. No effects were observed in humans.*
- *2.9 Hepatic: Limited human studies and conflicting results in animal studies for hepatic effects from beryllium exposure preclude conclusive remarks regarding hepatic effects.*
- *2.10 Renal: Monkeys that were acutely exposed had renal effects from high amounts of inhaled beryllium (≥8.3 mg/m^3) or from the combination of pre-sensitization and lower dose exposure (≥0.184 mg/m^3). Intermediate and chronic exposure at doses up to 0.62 mg beryllium/m^3 did not result in renal effects for monkeys, rats, or hamsters. Limited human studies showed potential renal effects.*

- *2.11 Dermal: Occupational studies indicate dermal eruptions from beryllium exposure; however, the studies often have multiple exposure routes (e.g., inhalation, dermal) and therefore cannot be attributed to just one route. No studies were located regarding dermal effects in humans after oral exposure to beryllium or its compounds. Skin lesions were observed in humans and animals after dermal exposures (Table 2-3).*
- *2.12 Ocular: There is limited information on ocular effects in humans and animals. Conjunctivitis has been noted to occur after a splash burn or in association with contact dermatitis of the face (VanOrdstrand et al. 1945). No studies were located regarding ocular effects in humans after oral exposure to beryllium or its compounds.*
- *2.13 Endocrine: There are limited studies on the potential endocrine effects from beryllium exposure. A single occupational study and monkey studies observed adrenal gland changes after beryllium inhalation exposure. No effects were observed in the endocrine system after oral exposure in human and animals.*
- *2.14 Immunological: Alterations in lymphocytes and inflammatory responses were consistently observed in humans and animals after inhalation exposure to beryllium and its compounds. Potential immune effects from oral beryllium exposure has not been addressed. Dermal beryllium studies also indicate immune responses for humans and animals (Table 2-3).*

QUESTION: Were adequately designed human studies identified in the text (i.e., good exposure data, sufficiently long period of exposure to account for observed health effects, adequate control for confounding factors)? Were the major study limitations sufficiently described in the text without going into lengthy discussions? If study limitations were not adequately addressed, please suggest appropriate changes.

COMMENT: It appears as if adequately designed human studies were identified in the text and limitations of studies also appear to have been included. Reasons for not including specific epidemiological studies also were listed at the beginning of Chapter 2.

RESPONSE: *No revisions were suggested.*

QUESTION: Were adequately designed animal studies identified in the text (i.e., adequate number of animals, good animal care, accounting for competing causes of death, sufficient number of dose groups, and sufficient magnitude of dose levels)? If not, does the inadequate design negate the utility of the study? Please explain.

COMMENT: It does not appear as if experimental design considerations for animal studies were included in the text, so it is not possible to determine if inadequate design negates the utility of specific studies. Occasional comments are inserted about specific studies, for example "exact concentrations were not clearly specified" but qualitative assessments of study design do not appear to be a major component of the text except in the section on cancer endpoints evaluated in epidemiological studies.

Suggestion: If assessments of the adequacy of individual studies in the database for beryllium are an important part of the toxicological profile, more information is necessary in the current version of the profile. For example, language concerning the appropriateness of the design of animal studies presented in the profile needs to be included.

RESPONSE: *ATSDR is currently phasing in systematic reviews as part of the Toxicological Profile development process. However, this update of the Beryllium Toxicological Profile did not undergo a systematic review. ATSDR recognizes the importance of systematic reviews and anticipates the incorporation of this methodology in new and future updates of existing toxicological profiles. A systematic review will result in consistent statements on the quality of the evidence.*

QUESTION: Were the animal species appropriate for the most significant toxicological endpoint of the study? If not, which animal species would be more appropriate and why?

COMMENT: There does not appear to be a discussion of appropriateness of species for understanding the potential for beryllium exposure to affect human health endpoints (there does, however, appeart to be some discussion of species relevance in Chapter 3 related to animal-human extrapolations).

Suggestion: If a discussion of the appropriateness of animal species is an important part of the profile, it needs to be included. As the one MRL derived is based on epidemiological findings, this may not be relevant. However, if identified data gaps can be filled by data from experimental animal models, the appropriateness of various models should be clearly stated. There is some discussion of species relevance in Chapter 3 related to animal-human extrapolations.

RESPONSE: *The toxicological profile discusses Animal-to-Human Extrapolations in section 3.1.5. Additionally, section 6.2 indicates: "Determining an appropriate animal model and further incorporation of in vitro, organ on chip models that use human lines would help elucidate pathogenesis."*

QUESTION: Has adequate attention been paid to dose-response relationships for both human and animal data? Please explain.

COMMENT: There appears to be acknowledgement of dose-response relationships for human and animal data in some sections of Chapter 2 but not all.

RESPONSE: *No revisions were suggested. There is a lack of dose response relationships for the genotoxicity of beryllium. This is mentioned in Section 6.2, Identification of Data Need, and Appendix A, Oral Chronic MRL Worksheet. In Section 2.20, the following sentence addresses the issue: "Furthermore, while beryllium chloride and beryllium sulfate were found to be mutagenic, the dose-response relationship was weak when the compounds were tested with Escherichia coli (Taylor-McCabe et al. 2006; Zakour and Glickman 1984)."*

QUESTION: Are you aware of any studies that are not included in the profile that may be important in evaluating the toxicity of the substance? Please provide a copy of each study and indicate where in the text each study should be included.

COMMENT: It appears as if the profile includes relevant studies.

RESPONSE: *No revisions were suggested.*

QUESTION: Are you aware of any studies that are not included in the profile that may be relevant to deriving MRLs for any of the substance isomers? Please provide a copy if this is a new reference.

COMMENT: It appears as if the profile includes relevant studies.

RESPONSE: *No revisions were suggested.*

QUESTION: Were all appropriate NOAELs and/or LOAELs identified for each study (both in the text and the Levels of Significant Exposure (LSE) tables and figures)? If not, did the text provide adequate justification for excluding NOAELs/LOAELs including, but not limited to, citing study limitations? Please suggest appropriate changes.

COMMENT: It appears as if the profile identified appropriate NOAELs and LOAELs for the studies within the profile.

RESPONSE: *No revisions were suggested.*

QUESTION: Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables? If not, please explain why and suggest appropriate changes.

COMMENT: It appears as if the serious category includes death, weight loss greater than about 8-10%, disease (emphysema, pneumonitis, granulomas, cancer) and the less serious includes other endpoints. This seems consistent with "serious" effects being those that evoke failure in a biological system that can lead to morbidity or mortality and "less serious" effects being those that are not expected to cause significant dysfunction or death or those whose significance to the organisms is not clear.

RESPONSE: *No revisions were suggested.*

QUESTION: Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain. If citing a new reference, please provide a copy and indicate where (in the text) it should be included.

COMMENT: Separate sections on "mechanism of action" and "mechanisms of toxicity" exist in the profile. It appears as if the "mechanisms of action" section concerns ways in which beryllium can interact with physiology and the "mechanisms of toxicity" section concerns respiratory system-specific molecular pathways that are perturbed and that lead to adverse health outcomes. This is a little bit confusing. Note that the diagrams included in the section on "mechanisms of toxicity" are very helpful for understanding how beryllium affects the lungs.

Suggestion: Adjust the titles of these sections. They both concern mechanisms of toxicity but the section titled "mechanisms of toxicity" should be titled "Mechanisms of toxicity specific to respiratory effects."

RESPONSE: *Mechanisms of toxicity is a sub-heading in Section 2.21 Mechanism of action. The subheading has now been labeled as: "Mechanisms of toxicity associated with respiratory effects" for clarity.*

QUESTION: Are the conclusions appropriate given the overall database? If not, please discuss your own conclusions based on the data provided and other data provided to you but not presented in the text.

COMMENT: The conclusions appear to be appropriate given the overall database.

RESPONSE: *No revisions were suggested.*

Chapter 3. Toxicokinetics, Susceptible Populations, Biomarkers, Chemical Interactions

QUESTION: Is there adequate discussion of absorption, distribution, metabolism, and excretion of the substance? If not, suggest ways to improve the text.

COMMENT: The toxicokinetic summary at the start of the section is a nice addition. The remainder of the section appears to contain an adequate discussion.

Note: Line 2529 begins "Animals Meehan and Smythe (1967)…" The word "animals" appears to be extraneous.

RESPONSE: *Fixed the text in section 3.1.2 to remove animals, the sentence now reads: "Meehan and Smythe (1967) reported beryllium concentrations in several human organs: 0.21 ppm in lungs; 0.08 ppm in brain; 0.07 ppm in both the kidney and spleen; 0.04 ppm in each of liver, muscle, and vertebrae; 0.03 ppm in heart; and 0.02 in bone."*

QUESTION: Have all available pharmacokinetic/pharmacodynamic models and supporting data been presented? If not, please explain.

COMMENT: It does not appear as if PBPK models have been developed for beryllium. This is noted in the profile.

RESPONSE: *No revisions were suggested.*

QUESTION: Is there adequate discussion of the differences in toxicokinetics between humans and animals? Is there adequate discussion of the relevance of animal toxicokinetic information for humans?

COMMENT: This section appears to be relatively sparse on details. In the text (3.1.1-3.1.3) , there appears to be little discussion about differences in toxicokinetics between humans and experimental animals. This may be due to the a) lack of PBPK models and b) lack of animal models for chronic beryllium disease.

Suggestion: Please state reasons for why the profile lacks details about differences in toxicokinetics between humans and experimental animals.

RESPONSE: *Animal studies demonstrate a similar immunological response but do not adequately reproduce features of human CBD. More detailed studies need to be done to better understand the species related differences. Currently, animal studies cannot reliably predict exposure-response effects of beryllium exposure in humans (e.g. development of CBD).*

QUESTION: Are there any data relevant to child health and developmental effects that have not been discussed in the profile and should be? Please provide any relevant references.

COMMENT: There do not appear to be additional studies/data to add to this section.

RESPONSE: *No revisions were suggested.*

QUESTION: Is there a discussion of populations at higher risk of susceptibility? Do you agree with the choice of populations? Please explain and provide any additional relevant references.

COMMENT: The discussion of populations at higher risk of suscpebtility is detailed and provides additional data beyond a National Research Council report on health effects of beryllium exposure published in 2008. The choice of populations appears appropriate.

RESPONSE: *No revisions were suggested.*

QUESTION: Are the biomarkers of exposure specific for the substance? Please explain.

COMMENT: It appears as if the biomarkers of exposure to beryllium are measurement of beryllium concentrations in excreta, urine, blood, hair follicles, and/or tissues. There do not appear to be other biomarkers of exposure other than measurement of beryllium. This is specific to beryllium and as beryllium is not metabolized, appropriate.

RESPONSE: *No revisions were suggested.*

QUESTION: Are the biomarkers of effect specific for the substance? Please explain.

COMMENT: It appears as if biomarkers of effect specific for beryllium are beryllium sensitivity and chronic beryllium disease. Diagnosing beryllium sensitivity can be determined from a beryllium-specific lymphocyte proliferation test (BeLPT) but chronic beryllium disease is more challenging to determine due to similarities with sarcoidosis. This section contains a detailed analysis of the diagnostic tools used for chronic beryllium disease, including strengths, weaknesses, and specificity. This is a particularly good section of the profile.

RESPONSE: *No revisions were suggested.*

QUESTION: Is there adequate discussion of the interactive effects with other substances? Does the discussion concentrate on those effects that might occur at hazardous waste sites? Please explain and provide any additional references.

COMMENT: It appears as if several of the interactive effects listed concern agents co-administered to reduce toxicity of beryllium (i.e., to explore new chelation therapies). It is therefore unclear why these agents were included as they are unlikely to be encountered at hazardous waste sites or in environmental/occupational exposure scenarios (these include ferric ammonium citrate, aurine tricarboxylic acid, tiron, and 2,3-dimercaptopropane sulfonate).

Suggestion: Indicate in the text that some interactions with other chemicals have been intentionally performed to see if these interactions can reduce beryllium toxicity, possibly through a chelation effect, or other reason(s) as apporpriate.

It also appears as if a section includes the effects of beryllium on simian adenovirus transformation (lines 3258-3261). The relevance of this sectin is unclear.

Suggestion: Better explain the relevance of the information in lines 3258-3261 or remove.

RESPONSE: *In section 3.4, the following text was added: "Most studies involving chemical interactions were performed to assess whether a substance could ameliorate beryllium toxicity."*

Sentences with simian adenovirus were deleted from Section 3.4.

QUESTION: If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions? Please explain and provide any additional references.

COMMENT: If known, if appears as if the mechansisms of interactions of beryllium with other agents are discussed.

RESPONSE: *No revisions were suggested.*

Chapter 4. Chemical and Physical Information

QUESTION: Are any of the values or information provided in the chemical and physical properties tables wrong or missing? Please explain and provide any additional references.

COMMENT: The values or information provided in the chemical and physical properties tables appear to be correct and complete.

RESPONSE: *No revisions were suggested.*

QUESTION: Is information provided on the various forms of the substance? Please explain.

COMMENT: No information is provided on dimethyl beryllium. It may be worthwhile to mention that beryllium, like other metals, can form organometallic complexes. Otherwise, the information appears to be complete.

RESPONSE: *Added a sentence in section 4.1 that states: "*Beryllium, like other metals, can form organometallic complexes.*"*

Chapter 5. Potential for Human Exposure

QUESTION: Is the information on production, import/export, use, and disposal of the substance complete? Please explain and provide any additional relevant references.

COMMENT: The information on production, import/expourt, use, and disposal appears to be complete.

RESPONSE: *No revisions were suggested.*

QUESTION: Has the text appropriately traced the substance from its point of release to the environment until it reaches the receptor population? Does the text provide sufficient and technically sound information regarding the extent of occurrence at NPL sites? Do you know of other relevant information? Please provide references for added information.

COMMENT: The information on point of release into the environment until it has reached the receptor population appears to be appropriate as does the information regarding extent of beryllium occurrence at NPL sites.

RESPONSE: *No revisions were suggested.*

QUESTION: Does the text cover pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media? Do you know of other relevant information? Please provide references for added information.

COMMENT: The information relative to movement of beryllium across environmental media appears to be appropriate.

RESPONSE: *No revisions were suggested.*

QUESTION: Does the text provide information on levels monitored or estimated in the environment, including background levels? Are proper units used for each medium? Does the information include the form of the substance measured? Is there an adequate discussion of the quality of the information? Do you know of other relevant information? Please provide references for added information.

COMMENT: The information relative to levels monitored appears to be complete.

RESPONSE: *No revisions were suggested.*

QUESTION: Does the text describe sources and pathways of exposure for the general population and occupations involved in the handling of the substance, as well as populations with potentially high exposures? Do you agree with the selection of these populations? If not, why? Which additional populations should be included in this section?

COMMENT: The information relative to sources and pathways of exposure appears to be complete.

RESPONSE: *No revisions were suggested.*

Chapter 6. Adequacy of the Database

QUESTION: Do you know of other studies that may fill a data gap? Please provide any relevant references.

COMMENT: There do not appear to be additional studies, not already considered in the profile, that may fill a data gap.

RESPONSE: *No revisions were suggested.*

QUESTION: Do you agree with the identified data needs? Please explain.

COMMENT: The identified data needs appear to be fairly comprehensive.

Suggestion: In the section on immunological data needs (lines 4412-4424), additional data linking systemic toxity to demal exposure is a data gap that does not appear to be identified. For example, Anderson and Meade (2014) note that the skin may play an important role in the etiology of chronic beryllium disease.

Reference: Anderson SE and Meade BJ. 2014. Potential health effects associated with dermal exposure to occupational chemicals. Environ. Health Insights. 8:51-62.

RESPONSE: *Added the following sentence to Section 6.2: "Dermal beryllium exposure caused by occupational exposure could potentially have systemic effects in humans and needs to extensively be examined (Anderson and Meade 2014)."*

QUESTION: Are the data needs presented in a neutral, non-judgmental fashion? Please note any bias in the text.

COMMENT: The data needs appear to be presented in a neutral, non-judgmental fashion. No bias was noted.

RESPONSE: *No revisions were suggested.*

Chapter 7. Regulations and Guidelines

QUESTION: Are you aware of any additional regulations or guidelines that should be included? Please provide citations.

COMMENT: There do not appear to be additional regulations or guidelines to be included.

RESPONSE: *No revisions were suggested.*

QUESTION: Are there any that should be removed? Please explain.

COMMENT: There does not appear to be a need to remove any of the included guidelines.

RESPONSE: *No revisions were suggested.*

Minimal Risk Levels (MRLs)

QUESTION: If no MRLs have been derived, do you agree that the data do not support such a derivation? Please explain.

COMMENT: For the MRLs that were not derived (Inhalation-Acute; Inhalation-Intermediate; Oral-Acute; Oral-Intermediate; Oral-Chronic), it does not appear as if sufficient/appropriate data are available. Agree with the decision not to derive MRLs for these exposure routes and durations.

RESPONSE: *No revisions were suggested.*

QUESTION: If MRLs have been derived, do you agree with the proposed MRL values? Explain. If you disagree, please specify the MRL value that you would propose.

a. Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose.

COMMENT: One MRL was derived for Inhalation-Chronic and it was based on data from epidemiological studies. The critical effect was beryllium sensitization, which is a fairly well-established precursor for chronic beryllium disease; this effect was associated with both a no observed adverse effect level (NOAEL) and a lowest observed adverse effect level (LOAEL) in the study identified as the principal study. The LOAEL of the principal study was consistent with LOAELs reported in other published epidemiological studies. The rationale for selection of the endpoint and principal study were clearly explained.

Only two uncertainty factors were applied: one for variability among humans (10) and one for database uncertainty (3). As the study from which the point of departure was derived was a chronic epidemiological study, these uncertainty factors appear to be appropriate.

RESPONSE: *No revisions were suggested.*

QUESTION: Please comment on any aspect of our MRL database assessment that you feel should be addressed.

COMMENT: No additional comments.

RESPONSE: *No revisions were suggested.*

Appendices

QUESTION: Please provide any comments on the content, presentation, etc. of the included appendices.

COMMENT: The Appendices appear to contain appropriate content and are presented in a clear and transparent manner.

RESPONSE: *No revisions were suggested.*

Annotated Comments on the Profile

None provided.

Comments provided by Peer Reviewer #3

ATSDR Charge Questions and Responses

Reviewer 3 included these comments with the charge questions and responses, comments annotated in the profile are addressed under the annotated section:

I have attached to this e-mail by tract changes to the Toxicologic Profile on Beryllium. Some of the specific comments I have made in the manuscript are:

COMMENT: Line 855 – I have suggested a different way of organizing the reversible respirable effects of beryllium

RESPONSE: *Text of section 2.4 changed to: "Physiological abnormalities in lung function were observed in 57% of the surveillance-identified subjects compared to 93% of the clinically identified subjects."*

COMMENT: Line 1376 – I have quoted from Curtis 1951 reference the data on skin testing in normal.

RESPONSE: *Added the following text to section 2.14: "This demonstrated that patch testing could potentially sensitize individuals to beryllium."*

COMMENT: Line 2085-2097 – I have made multiple changes to the section on mechanisms of toxicity to eliminate some prior hypothesis and to make it more accurate.

RESPONSE: *See annotated comments for section 2.21, below.*

COMMENT: Line 4237 - I have added two references (already in the biblio) to this section to emphasize the importance of dental technician exposure

RESPONSE: *See annotated comments for section 5.7, below.*

COMMENT: I would like to say that there are numerous references to the Cummings 2009 manuscript that would like to claim that ABD is really an acute form of CBD. I think that this is a mistake and while one can have an acute hypersensitivity reaction to beryllium if one is sensitized, to say that all of ABD is due to hypersensitivity is a mistake.

RESPONSE: *The comment about ABD and CBD above is addressed in the first response to Chapter 1, below. Additionally, the text in section 2.21.1 now reads: "Early research on ABD suggested that it was an inflammatory response to beryllium, but new evidence suggests that acute inflammatory reactions to beryllium may also be an immunological response and part of the continuum of CBD (Cummings et al. 2009), although this is not fully established."*

In addition, I think that some mention in the manuscript about ways to protect workers from a hypersensitivity reaction may be different than the way to protect workers from a toxicity. If there is one operation that confers risk, with a toxicity if all the workers are rotated thru this operation, then no workers would receive a high enough dose to get sick. However, for a hypersensitivity reaction, only a subpopulation (in the case of beryllium probably 5-10%) will get sick. Thus if only 50 workers are needed for a certain operation, only 2.5 – 5 workers will get sick instead of 25-50 workers if all 1000 workers are rotated thru the operation. I think this concept should be part of the Profile, but I am not sure where is should go.

RESPONSE*: Occupational populations that work with beryllium are at higher risk for exposure to beryllium and therefore have greater potential for CBD development. ATSDR is not a regulatory agency though OSHA is a regulatory agency. OSHA and NIOSH focus on workplace safety measures that include reducing worker risk. Section 3.2 on susceptible populations does discuss the genetic basis for susceptibility and begins with the paragraph stating: "There are strong data to suggest that there is genetic susceptibility factor that may predispose certain individuals to development of CBD….not all individuals with beryllium hypersensitivity will develop CBD…. whether an individual is able to present beryllium to a T cell and mount a proliferative response (Maier 2002)."*

COMMENT: Below I have copied the chapter heading and my specific comments if any.

RESPONSE: *No response necessary.*

Chapter 1. Relevance to Public Health

QUESTION: Do you agree with those effects known to occur in humans as reported in the text? If not, please explain why and provide a copy of additional references you would cite and indicate where (in the text) these references should be included.

COMMENT: I agree with the effects in human. The only comment I would like to make refers to the suggestion that ABD may be an acute form of CBD (see above). While I agree that this can happen, I think that ABD should be reserved for an acute toxic effect of beryllium on the respiratory tract and not confused with an acute hypersensitivity reaction in someone sensitized to beryllium and exposed to high concentrations.

RESPONSE: *Section 1.2 states that: "Occupational exposure to higher concentrations of soluble beryllium compounds can result in acute beryllium disease (ABD), while exposure to relatively low concentrations of soluble or insoluble beryllium compounds can result in chronic beryllium disease (CBD). ABD is characterized by inflammation of the respiratory tract tissues and is usually resolved within several months of exposure termination and has been reduced by control measures implemented in the workplace."*

QUESTION: Are the effects only observed in animals likely to be of concern to humans? Why or why not? If you do not agree, please explain.

COMMENT: Most of the animal data refers to effects due to the toxicity of beryllium rather then effects due to the hypersensitivity that can be induced in a subpopulation. The toxicity effects require high doses of beryllium and under current conditions, this type of exposure would be extremely rare in humans Animal models that can reproduce the hypersensitivity have only just been developed and the effects in these models will probably have more conern for humans

RESPONSE: *The following text has been added to section 1.2: "Studies in different species of animals demonstrate a similar immunological response as humans as well as other toxicity. However, there are deficiencies in these studies; they do not adequately reproduce features of human CBD. Therefore, these studies cannot reliably predict exposure-response effects of beryllium exposure (NRC 2008). Humans are exposed to lower concentrations of beryllium than levels used in most animal studies, hence it is pertinent to examine the physiological changes happening at those lower doses. It is potentially likely that prior sensitization in humans is exacerbating the toxic effects."*

QUESTION: Have exposure conditions been adequately described? If you disagree, please explain

COMMENT: Yes I think they have.

RESPONSE: *No revisions were suggested.*

Chapter 2. Health Effects

QUESTION: Do the health effect conclusions made in Chapter 2 adequately reflect the findings in the published literature? If not, please suggest appropriate changes.

COMMENT: Yes the health effects reflect the findings in the published literature

RESPONSE: *No revisions were suggested.*

QUESTION: Were adequately designed human studies identified in the text (i.e., good exposure data, sufficiently long period of exposure to account for observed health effects, adequate control for confounding factors)? Were the major study limitations sufficiently described in the text without going into lengthy discussions? If study limitations were not adequately addressed, please suggest appropriate changes.

COMMENT: Yes adequately designed human studies were described

RESPONSE: *No revisions were suggested.*

QUESTION: Were adequately designed animal studies identified in the text (i.e., adequate number of animals, good animal care, accounting for competing causes of death, sufficient number of dose groups, and sufficient magnitude of dose levels)? If not, does the inadequate design negate the utility of the study? Please explain.

COMMENT: Yes adequately designed animal studies were described.

RESPONSE: *No revisions were suggested.*

QUESTION: Were the animal species appropriate for the most significant toxicological endpoint of the study? If not, which animal species would be more appropriate and why?

COMMENT: The animal species were appropriate for the toxicologic endpoints. However, the newer models of beryllium hypersensitivity should give more data on CBD.

RESPONSE: *Relevant studies that examine the animal models on CBD are included in the text, however, animal models do not reliably predict exposure-response effects of beryllium exposure and reproduce feature of human CBD. The reviewer did not suggest additional studies. Therefore, it was assumed this comment is referring to studies that may be published in the future.*

QUESTION: Has adequate attention been paid to dose-response relationships for both human and animal data? Please explain.

COMMENT: Yes adequate attention has been paid to dose-response relationships.

RESPONSE: *No revisions were suggested.*

QUESTION: Are you aware of any studies that are not included in the profile that may be important in evaluating the toxicity of the substance? Please provide a copy of each study and indicate where in the text each study should be included.

COMMENT: No I am not aware of additional studies that should be included.

RESPONSE: *No revisions were suggested.*

QUESTION: Are you aware of any studies that are not included in the profile that may be relevant to deriving MRLs for any of the substance isomers? Please provide a copy if this is a new reference.

COMMENT: I am not aware of additional studies that may be relevant to deriving MRLs

RESPONSE: *No revisions were suggested.*

QUESTION: Were all appropriate NOAELs and/or LOAELs identified for each study (both in the text and the Levels of Significant Exposure (LSE) tables and figures)? If not, did the text provide adequate justification for excluding NOAELs/LOAELs including, but not limited to, citing study limitations? Please suggest appropriate changes.

COMMENT: I think that all appropriate NOAELs and LOAELs were identified but this is not my area of expertise.

RESPONSE: *No revisions were suggested.*

QUESTION: Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables? If not, please explain why and suggest appropriate changes.

COMMENT: I agree.

RESPONSE: *No revisions were suggested.*

QUESTION: Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain. If citing a new reference, please provide a copy and indicate where (in the text) it should be included.

COMMENT: As indicated above I have made some changes in the mechanisms of health effects.

RESPONSE: *Please see responses provided in the "Comments Provided by Peer Reviewer 3" pages above and the annotated comments that are included further below.*

QUESTION: Are the conclusions appropriate given the overall database? If not, please discuss your own conclusions based on the data provided and other data provided to you but not presented in the text.

COMMENT: I think that the conclusions are appropriate.

RESPONSE: *No revisions were suggested.*

Chapter 3. Toxicokinetics, Susceptible Populations, Biomarkers, Chemical Interactions

QUESTION: Is there adequate discussion of absorption, distribution, metabolism, and excretion of the substance? If not, suggest ways to improve the text.

COMMENT: I think the discussion is adequate.

RESPONSE: *No revisions were suggested.*

QUESTION: Have all available pharmacokinetic/pharmacodynamic models and supporting data been presented? If not, please explain.

COMMENT: I believe so.

RESPONSE: *No revisions were suggested.*

QUESTION: Is there adequate discussion of the differences in toxicokinetics between humans and animals? Is there adequate discussion of the relevance of animal toxicokinetic information for humans?

COMMENT: I believe that the limits of the animal studies with reference to human disease has been adequate.

RESPONSE: *No revisions were suggested.*

QUESTION: Are there any data relevant to child health and developmental effects that have not been discussed in the profile and should be? Please provide any relevant references.

COMMENT: I an not aware of any such studies.

RESPONSE: *No revisions were suggested.*

QUESTION: Is there a discussion of populations at higher risk of susceptibility? Do you agree with the choice of populations? Please explain and provide any additional relevant references.

COMMENT: A discussion of the genetic susceptibility to CBD is provided and the risks involved.

RESPONSE: *No revisions were suggested.*

QUESTION: Are the biomarkers of exposure specific for the substance? Please explain.

COMMENT: Except for the BeLPT I do not know of any biomarkers that are specific for exposure.

RESPONSE: *No revisions were suggested.*

QUESTION: Are the biomarkers of effect specific for the substance? Please explain.

COMMENT: I do not know of any biomarkers that are effect specific for beryllium except for maybe the BAL BELPT. The granulomatous reaction is not specific and the biomarkers are for a granulomatous reaction and are not specific for beryllium.

RESPONSE: *Section 3.3.2 Biomarkers of Effect extensively discusses the use of BeLPT to detect effects from exposure to beryllium.*

QUESTION: Is there adequate discussion of the interactive effects with other substances? Does the discussion concentrate on those effects that might occur at hazardous waste sites? Please explain and provide any additional references.

COMMENT: I am not aware of interactions with other substances.

RESPONSE: *No revisions were suggested.*

QUESTION: If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions? Please explain and provide any additional references.

COMMENT: Not applicable.

RESPONSE: *No revisions were suggested.*

Chapter 4. Chemical and Physical Information

QUESTION: Are any of the values or information provided in the chemical and physical properties tables wrong or missing? Please explain and provide any additional references.

COMMENT: I think that the information provided is correct.

RESPONSE: *No revisions were suggested.*

QUESTION: Is information provided on the various forms of the substance? Please explain.

COMMENT: Yes, the various forms of beryllium are described.

RESPONSE: *No revisions were suggested.*

Chapter 5. Potential for Human Exposure

QUESTION: Is the information on production, import/export, use, and disposal of the substance complete? Please explain and provide any additional relevant references.

COMMENT: To the best of my knowledge this is complete.

RESPONSE: *No revisions were suggested.*

QUESTION: Has the text appropriately traced the substance from its point of release to the environment until it reaches the receptor population? Does the text provide sufficient and technically sound information regarding the extent of occurrence at NPL sites? Do you know of other relevant information? Please provide references for added information.

COMMENT: I think that this discussion is adequate.

RESPONSE: *No revisions were suggested.*

QUESTION: Does the text cover pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media? Do you know of other relevant information? Please provide references for added information.

COMMENT: I think this discussion is adequate.

RESPONSE: *No revisions were suggested.*

QUESTION: Does the text provide information on levels monitored or estimated in the environment, including background levels? Are proper units used for each medium? Does the information include the form of the substance measured? Is there an adequate discussion of the quality of the information? Do you know of other relevant information? Please provide references for added information.

COMMENT: I think this discussion is adequate.

RESPONSE: *No revisions were suggested.*

QUESTION: Does the text describe sources and pathways of exposure for the general population and occupations involved in the handling of the substance, as well as populations with potentially high exposures? Do you agree with the selection of these populations? If not, why? Which additional populations should be included in this section?

COMMENT: Yes, I think that the text describe the sources and pathways for exposure adequately

RESPONSE: *No revisions were suggested.*

Chapter 6. Adequacy of the Database

QUESTION: Do you know of other studies that may fill a data gap? Please provide any relevant references.

COMMENT: I know of no additional studies.

RESPONSE: *No revisions were suggested.*

QUESTION: Do you agree with the identified data needs? Please explain.

COMMENT: Yes I agree with the identified data needs.

RESPONSE: *No revisions were suggested.*

QUESTION: Are the data needs presented in a neutral, non-judgmental fashion? Please note any bias in the text.

COMMENT: I think that the data needs are appropriately stated.

RESPONSE: *No revisions were suggested.*

Chapter 7. Regulations and Guidelines

QUESTION: Are you aware of any additional regulations or guidelines that should be included? Please provide citations.

COMMENT: I am not aware of any additional regulations or guideline that need to be included.

RESPONSE: *No revisions were suggested.*

QUESTION: Are there any that should be removed? Please explain.

COMMENT: No.

RESPONSE: *No revisions were suggested.*

Minimal Risk Levels (MRLs)

QUESTION: If no MRLs have been derived, do you agree that the data do not support such a derivation? Please explain.

COMMENT: I agree that the data do not support the derivation of an MRL.

RESPONSE: *No revisions were suggested.*

QUESTION: If MRLs have been derived, do you agree with the proposed MRL values? Explain. If you disagree, please specify the MRL value that you would propose.

a. Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose.

COMMENT: *No response provided by the reviewer.*

RESPONSE: *No revisions were suggested.*

QUESTION: Please comment on any aspect of our MRL database assessment that you feel should be addressed.

COMMENT: *No response provided by the reviewer.*

RESPONSE: *No revisions were suggested.*

Appendices

QUESTION: Please provide any comments on the content, presentation, etc. of the included appendices.

COMMENT: No comment.

RESPONSE: *No revisions were suggested.*

Annotated Comments on the Profile

COMMENT: What about individuals who work in airplane manufacture and maintenance (airplane bushing are made of beryllium) and also dental hygenists who make bridges and crowns.

RESPONSE: *This comment refers to the discussion in section 1.1 (Overview and U.S. Exposures) surrounding populations at greater risk of beryllium exposure and general population exposure. The following paragraph now reads: "Although beryllium is found in water and soil, most human exposure to beryllium and its compounds occurs primarily in the workplace. People who work in beryllium manufacturing, fabricating, and reclaiming industries have a greater probability of inhalation exposure than non-occupational groups. The general population can be exposed to trace amounts of beryllium through inhalation of air, consumption of food, water, and incidental soil ingestion, and skin contact with air, water, or soil that contains beryllium. Dental technicians who work approximately 8 hours/day are exposed to beryllium through inhalation exposure (Stark et al. 2014). People working in aeronautics and aircraft industries are exposed to beryllium as they are exposed to it through altimeters, braking systems, bushings and bearings for landing gear (Kreiss et al. 2007)."*

COMMENT: The following text in section 2.4 had the comment- Not exercise capacity but should be physiologic abnormalities: "*Alterations in exercise capacity were observed in 57% of the surveillance-identified subjects compared to 93% of the clinically identified subjects had alteration in lung function."*

RESPONSE: *Text of section 2.4 was changed to: "Physiological abnormalities in lung function were observed in 57% of the surveillance-identified subjects compared to 93% of the clinically identified subjects."*

COMMENT: It would be good to organize this section [2.4] into three sections 1. Studies involving ABD, 2. Studies involving patientis with BeS or CBD. 3. Beryllium workers without known ABD or BeS or CBD

The original description of ABD described patients having a compete recovery by 6 months. In CBD there has only been improvement in patients treated with steroids. The study by commings should probably be listed under CBD rather than ABD. Finally the Sprince study is looking at beryllium workers without a diagnosis of beryllium disease.

RESPONSE: *The section is organized according to the ATSDR guidelines by route and duration of exposure. The Cummings et al. (2009) study is discussed in section 2.4 with amended text as follows: "However, new evidence resulting from a detailed review of case reports in workers exposed to beryllium by Cummings et al. (2009) suggests that ABD may be an immunological response to beryllium, rather than irritative, and as such ABD may be part of the continuum of CBD and may occur at exposure levels lower than previously reported, however this theory is not completely accepted in the field."*

Added clarifying language to Section 2.4 about the Sprince study: "Sprince et al. (1978) conducted health surveys (including measurement of lung function and x-rays) in 1971 and 1974 in beryllium workers without a diagnosis of beryllium disease."

COMMENT: Would delete this last sentence as it is not appropriate for the discussion of skin lesions.

RESPONSE: *The reviewer suggests deleting from section 2.11 (Dermal), the sentence: "The authors suggest that there is an immune component to the ABD observed, and ABD and CBD represent a continuum of disease." This sentence was removed.*

COMMENT: This reference could also be added to the section on reversible respiratory effects.

RESPONSE: *The reviewer suggests referencing Aronchick et al. 1987 in the section on reversible respiratory effects, which is in section 2.4 (Respiratory). The following text was added to the section: "Additionally, therapy that controls the immune response (i.e., corticosteroids) can improve pulmonary function (Aronchick et al. 1987)."*

COMMENT: In the 1951 Curtis study, 16 individuals with no prior exposure to beryllium were patch tested. All were negative were evaluated at 48-72 hours. Eight developed flare ups at the test sites 6-16 days later. Seven agreed to be retested and all were patch test positive. This demonstrated that patch testing could sensitize individuals to beryllium.

RESPONSE: *Included "This demonstrated that patch testing could potentially sensitize individuals to beryllium." in the text in Section 2.14.*

COMMENT: ABD has been virtually eliminated today due to environmental controls at the workplace.

RESPONSE: *While the comment was made to section 2.21, the introductory sentences were deleted based on another reviewer's comment. However, the following was added to section 1.2: "Adherence to environmental controls in the workplace have now made the occurrence of ABD rare."*

COMMENT: And has been observed to have a latency of 20 years or more (Kreibel, D, Brain JD Sprince NL, Kazemi H. the pulmonary toxicity of beryllium. Am Rev Respir Dis 1988;137:464-473)

RESPONSE: *The Kriebel citation was included in Section 2.21 along with the following text: "The disease may appear after removal from exposure and has been observed to have a latency of 20 years…."*

COMMENT: While it may have been postulated that beryllium acts as a hpaten, this is no longer thought to be true.

RESPONSE: *Deleted "acting as a hapten" from section 2.21; the sentence now reads: "Beryllium interacts with antigen presenting cells in the lungs…class II molecule (Newman 1996b…)."*

COMMENT: EM studies which will be discussed later suggest that beryllium is not binding to peptides but binding to MHC molecules that change the electrostatic charge and the subsequent peptides that they can bind.

RESPONSE: *Added the following text to section 2.21: "While Day postulated that beryllium interacted with antigens, it is now thought that beryllium may bind to MHC molecules (Dai et al 2010). Canine alveolar macrophages indicate similar results (Day et al. 2005)."*

COMMENT: Now I think it is Materion.

RESPONSE: *This comment refers to the discussion of beryllium production by Brush Wellman Inc. in Section 5.2.1 (Production). In response to this comment, the profile has been updated with information found about Materion in USGS sources. Brush Wellman Inc. likely became Materion. Currently ATSDR has no updated information on the process that Materion uses to produce beryllium and beryllium alloys. However, text was adapted to remove Brush Wellman, generalize the process known in 1978, and state that it is unknown whether this is the current process. The text now reads as follows:*

"Information on beryllium process production is from Balance et al. (1978). Through 1977, beryllium metal was produced by a couple of U.S. companies using the Schenzfeier-Pomelee purification process. The process starts with beryllium hydroxide and forms intermediates with the use of heat and reduction by magnesium. Water leaching or electro-refining further purifies the metal product."

"Beryllium oxide was produced by dissolving technical-grade beryllium hydroxide in sulfuric acid, precipitating out hydrated beryllium sulfate, which is then calcined at 1,150–1,450 °C (Ballance et al. 1978). Copper-beryllium alloy is produced from beryllium oxide, carbon reduction in the presence of molten copper and an arc-furnace set at 1,800–2,000°C. Other beryllium alloys start with a copper beryllium alloy and melt in other metals (Ballance et al. 1978). It is unclear whether there are newer processes for producing beryllium metal, beryllium oxide, and beryllium alloys."

COMMENT: Again it is Materion

RESPONSE: *This comment refers to the following sentence in Section 5.2.1 (Production): "Brush Wellman, Inc. of Elmore, Ohio is the only processor of beryllium ores in the United States." In response to this comment, the following paragraph was updated to read: "In 2017, Materion produced beryllium hydroxide, beryllium metal, metal-matrix composites, ceramics, and beryllium strip and bulk products at plants in Elmore, Ohio, Fremont, California, Tucson, Arizona, and Shoemakersville, Pennsylvania (USGS 2020). IBC Advanced Alloys Corp. produced beryllium-aluminum alloys, beryllium-copper alloys, and its own proprietary alloys at plants in Franklin, Indiana, New Madrid, Missouri, Royersford, Pennsylvania, and Wilmington, Massachusetts (USGS 2020). Beryllium alloys were also produced by Belmont Metals Inc. in Brooklyn, New York and by NGK Metals Corp. in Sweetwater, Tennessee (USGS 2020). Beryllium oxide ceramic components and compound materials were manufactured in Haskell, New Jersey by American Beryllia Inc., and beryllium metal sheets and foil were manufactured in Los Angeles, California by American Elements (USGS 2020). Recent production and mine shipments have decreased from 270 metric tons of beryllium content in 2014 to an estimated 170 metric tons of beryllium content in 2018 (USGS 2019)."*

COMMENT: Is a Japanese company with Manufacturing facilities are located in Sweetwater, Tennessee; Nagoya, Japan; and Coueron, France.

RESPONSE: *This comment refers to NGK Metals Corporation in the following sentence in section 5.2.1 (Production): "NGK Metals Corporation in Reading, Pennsylvania is also a major U.S. manufacturer of beryllium alloys." In response to this comment, this sentence has been deleted and replaced with the following: "Beryllium alloys were also produced by Belmont Metals Inc. in Brooklyn, New York and by NGK Metals Corp. in Sweetwater, Tennessee (USGS 2020)."*

COMMENT: This is now a Japanese company and is not located in Reading, PA. They have Manufacturing facilities are located in Sweetwater, Tennessee; Nagoya, Japan; and Coueron, France.

RESPONSE: *This comment refers to NGK Metals Corporation in the following sentence in section 5.2.1 (Production): "NGK Metals Corporation in Reading, Pennsylvania is also a major U.S. manufacturer of beryllium alloys." In response to this comment, this sentence has been deleted and replaced with "Beryllium alloys were also produced by Belmont Metals Inc. in Brooklyn, New York and by NGK Metals Corp. in Sweetwater, Tennessee (USGS 2020)."*

COMMENT: I believe this should be included here.

RESPONSE: *The peer reviewer is referring to their edit to a sentence in Section 5.5.3 (Water), which they changed from: "In Australia, had an average beryllium concentration of 0.05–0.08 µg/L (Meehan*

and Smythe 1967)" to: "In Australia, rainwater and streams had an average beryllium concentration of 0.05–0.08 µg/L (Meehan and Smythe 1967)." The change was accepted.

COMMENT: Two references that can be added here are:

1. R M Kotloff 1, P S Richman, J K Greenacre, M D Rossman, Chronic beryllium disease in a dental laboratory technician, Am Rev Respir Dis. 1993 Jan;147(1):205-7.

2. Elisabeth Fireman 1, Mordechai R Kramer, Israel Priel, Yehuda Lerman, Chronic beryllium disease among dental technicians in Israel, Sarcoidosis Vasc Diffuse Lung Dis. 2006 Oct;23(3):215-21.

RESPONSE: *The peer reviewer suggests adding these two sources to the discussion of dental technicians, beryllium exposure, and chronic beryllium diseases in Section 5.7 (Populations with Potentially High Exposures). The sentence was updated from: "It is likely that dental technicians who work with beryllium-containing dental alloys without using appropriate handling safeguards may be exposed to higher levels of beryllium than the normal population (Stark et al. 2014)" to: "Dental technicians who work with beryllium-containing dental alloys without using appropriate handling safeguards may be exposed to higher levels of beryllium than the normal population (Stark et al. 2014) and can develop CBD (Kotloff et al. 1993; Fireman et al. 2006)." These changes were accepted.*

COMMENT: The reviewer inserted the following sentence in Chapter 6 (Immunological) in the profile. "In addition, since BeS and CBD is an immunological reaction that only a subpopulation can develop, studies are needed to determine whether limiting the numbers of workers with potential exposure to beryllium is useful rather then rotating all workers thru areas with potential beryllium exposure."

RESPONSE: *It is outside the purview of ATSDR to suggest specific workplace preventive interventions and/or policy changes that may impact workers. NIOSH is the research agency that studies worker safety and health and empowers employers to create safe and healthy workplaces.*