EPA's Response to Selected Major Interagency Comments on the Interagency Science Consultation Draft IRIS Toxicological Review of Libby Amphibole Asbestos

August 25, 2011

Purpose:

The Integrated Risk Information System (IRIS) assessment development process of May 2009, includes two steps (Step 3 and 6) where White House offices and other federal agencies can comment on draft assessments. The following are EPA's responses to selected major interagency review comments received during the Interagency Science Consultation step (Step 3) for the draft IRIS Toxicological Review of Libby Amphibole Asbestos (dated May 2011). All interagency comments provided were taken into consideration in revising the draft assessment prior to posting for public comment and external peer review. The complete set of all interagency comments is attached as an appendix to this document.

For a complete description of the IRIS process, including Interagency Science Consultation, visit the IRIS website at www.epa.gov/iris.

Topic #1: Terminology - *NIOSH commented on several issues regarding the current terminology and definitions of terms relevant to asbestos. A key comment was the need for clarity in the use of the term "Libby Amphibole asbestos" for the mixture of mineral fibers that forms the basis of this assessment.*

> **EPA Response:** EPA agrees with the need to use clearly defined terminology when discussing asbestos and related mineral fibers. The terminology of asbestos and related mineral fibers is an ongoing issue in the field of asbestos research. Usage of the term 'asbestos' depends in part on the framework or context: commercial use, regulatory, geologic (hand samples), mineralogic (composition), and analytical (size aspect ratio, regulatory). EPA has included in the text clarification of the terminology when used, and has added a glossary of asbestos terms to the Toxicological Review to clarify how the definitions of the asbestos-related terms are used in this assessment. For the purposes of this document, EPA uses the term "Libby Amphibole asbestos" to identify the mixture of amphibole mineral fibers of varying elemental composition (e.g. winchite, richterite and tremolite, etc), which have been identified in the Rainy Creek complex near Libby, MT as described in Section 2.2 of the Toxicological Review. A geological description

of this mixture is available in Meeker et al. (2003). EPA has explained this at first usage of the term "Libby Amphibole asbestos" in each section of the Toxicological Review and has included it in the glossary of asbestos terms used in the assessment.

Topic #2: Cohort Selection for Derivation of the Reference Concentration (RfC) - *NIEHS requested further clarification on the decision to use a subcohort of the Marysville,OH worker cohort for derivation of the RfC. NIEHS stated that the Marysville, OH worker cohort is well described and scientifically supported for use as the basis of the RfC derivation, and was not aware of any other populations with sufficient data to support an RfC for Libby Amphibole asbestos. However, NIEHS stated that the use of the truncated cohort for the RfC was not clearly explained. NIOSH also requested clarification and more consistency in the discussion of the cohort selection.*

EPA Response: EPA acknowledges that there are advantages and disadvantages to both the full cohort and subcohort analyses. The key issue is the tradeoff between the use of the smaller subcohort (less statistical power, but better exposure information) compared to the full cohort (more statistical power but lack of exposure measurements prior to 1972).

Although EPA has chosen to use the results from the analysis of the subcohort to derive the RfC, EPA also included analysis of the full cohort as a supporting analysis. EPA has included a detailed charge question for the external peer review panel on the merits of each modeling approach (Charge Question IIIA3).

In addition, EPA has included a charge question to elicit comment from the external peer review panel on the methodology of the exposure reconstruction including the methods for estimating pre-1972 exposures (Charge Question IIIA1).

Topic #3: Characterization of the Critical Effect for RfC Derivation – *OMB questioned the characterization of pleural thickening as an adverse effect, while NIOSH requested that EPA strengthen the characterization of the severity of pleural thickening and its association with pulmonary function and chest pain. ATSDR and NIEHS agreed with the selection of localized pleural thickening as the critical effect.*

EPA Response: The critical effect for RfC derivation is the observation of localized pleural thickening (LPT) on standard radiographs. The radiographic classification of

LPT (ILO, 2000) includes pleural lesions associated with chronic chest pain, decreased lung volume, and decreased measures of lung function. LPT is an irreversible pathological change. EPA considers LPT to be an adverse effect and an appropriate endpoint for RfC derivation. The dataset from the principal study does not include an index of severity or measure of the extent of pleural thickening, although it should be noted that the extent of the lesion determines its severity (Sec 5.2.2.3 of the Toxicological Review). An analysis was done which considered other critical effects (i.e., all pleural thickening, diffuse pleural thickening or small opacities, as well as different benchmark response responses for the more severe health endpoints (Section 5.3.8). EPA also evaluated the presence of bilateral LPT versus unilateral LPT as a rough approximation of increased severity. The text was clarified with respect to characterizing the critical effect.

Topic #4: Uncertainty Factors (UFs) - *CEQ, ATSDR, and NIEHS agreed with the application of UFs (intraspecies UF of 10 for human variability and database UF of 10). DOD and OMB questioned the selection of the database UF due to the extensive database available for asbestos, in general, and because the selected critical effect is the most sensitive endpoint observed. OMB recommended reducing the intraspecies UF stating that applying a 10-fold factor —where the extrapolation is from low level exposure in presumably healthy adults to even lower levels of exposure for general population — was incongruous with the amount of uncertainty that would be introduced in extrapolating from animals to humans.*

EPA Response: Although there is a large database for asbestos in general, only three study populations exist for Libby Amphibole asbestos specifically: the Marysville, OH worker cohort, the Libby worker cohort and the ATSDR community screening (which includes some Libby worker cohort participants). Limitations of these studies are described in Section 5.2.4 of the Toxicological Review.

Another factor that was considered in the application of a 10-fold UF for database deficiencies relates to the time from first exposure to time of observation for the critical effect. Data on the critical effect from the subcohort are only available for approximately 30 years from first exposure to the time of observation. However, the RfC is representative of a full lifetime of exposure. A review of the general literature on asbestos indicates that pleural thickening progresses with time from first exposure, even after cessation of exposure. However, no data are available for assessing the incidence of

pleural thickening for a full lifetime. Therefore, this is considered to be a gap in the current database.

An intraspecies UF of 10 was applied to account for human variability and potentially susceptible individuals in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of Libby Amphibole asbestos in humans. Only adults sufficiently healthy for full-time employment were included in the principal study and the study population was primarily male and, as such, does not represent a susceptible population. As stated in EPA's *A Review of the Reference Dose and Reference Concentration* (U.S. EPA, 2002), reduction of the intraspecies UF from a default of 10 is generally only considered if data are representative of the exposure-response data for susceptible subpopulations.

The discussion of UFs in Section 5.2.4 of the Toxicological Review has been revised for clarity. EPA has also augmented the general charge question related to the application of UFs (Charge Question IIIA6) to focus more specifically on the issues related to the database UF.

Topic #5: Use of Linear Low-Dose Extrapolation for Cancer - *DOD and OMB commented that EPA should present both linear and non-linear low-dose modeling for the observed cancer effects of Libby Amphibole asbestos. They stated that there is significant biological support for a non-linear extrapolation based on sufficient information that general asbestos, acting as a fiber, acts through a mode of action that is due to the presence of inflammation and oxidative stress. OMB specifically requested that a charge question be included regarding the choice of linear versus non-linear modeling for the low-dose region of the exposure-response curve.*

EPA Response: It is EPA's judgment that the data are insufficient to establish that non-linearity exists in the exposure-response curve at low doses based on the available mode of action data for cancer effects following exposure to Libby Amphibole asbestos. EPA interprets "significant biological support" as meaning enough information to identify key events and to have reasonable confidence in the sequence of events and how they relate to the development of tumors in both a temporal and dose-related manner. Key events have not been identified for any mode of action for Libby Amphibole asbestos, and exposure-response and temporal relationships have not been established. Therefore, a non-linear extrapolation approach was not further considered. Research on various types of mineral fibers supports the role of multiple biologic responses following exposure to

asbestos (i.e., chronic inflammation, generation of reactive oxygen species, direct genotoxicity, and cytotoxicity and cellular proliferation) in the carcinogenic response to mineral fibers. However, the complexities of fiber toxicity make it difficult to define modes of action for asbestos, in general (as reviewed in Aust et al., 2011; Mossman et al., 2011; Huang et al., 2011; Bunderson-Schelvan et al., 2011; Broaddus et al., 2011). Further, limitations in early study design and presentation of the results hinder understanding of the mode of action for specific fiber types. Additional information has been added to Section 4.6.2 of the Toxicological Review. Charge Question IIB2 has been augmented to better reflect this issue.

Appendix

Memo to: Environmental Protection Agency

From: NCEH/ATSDR, Centers for Disease Control and Prevention

Regarding: Interagency review of EPA's Draft Toxicological Review for Libby Amphibole asbestos

Date: June 9, 2011

General comments

- The document could benefit from a good editor. Many typos decrease the readability of the document. The document also tends to repeat parts as if several contractors put different pieces together. The Table of Contents does not match actual page numbers, references are listed differently in the text and References section, and the Introduction has boilerplate text regarding RfDs and RfCs that is not applicable or is incorrect in the case of asbestos.

- The document is very thorough and does a good job of presenting the work although some sections contain extraneous and/or unnecessary material and could be simplified to be more readable.

Major concerns

- Implementation – background. It may not be possible to separate natural background levels of asbestos fibers from very low levels of fibers resulting from anthropomorphic contamination. If so, this will impact implementation of the RfC (1×10^{-5}, or 0.00001, PCM fibers/cc for continuous exposure). Some areas of the country (e.g., El Dorado Hills, CA) have naturally occurring asbestos with amphibole background levels (as measured by EPA reference stations) of approximately 0.0008 f/cc, exceeding the RfC even in the cleanest areas of El Dorado County. The RfC also exceeds many Libby areas that have already been cleaned. WHO (1988) reported studies that showed the median level of asbestos in the US of 3 x 10-4 f/cc, which exceeds the proposed RfC for Libby Amphibole.

- The RfC is orders of magnitude lower than typical detection limits for asbestos analyses (around 0.001 f/cc in EPA's results reported in Chapter 2). Analytical costs to reach a 0.00001 f/cc detection limit could be very high. Even more cost will be incurred if analyses attempt to determine distinct contributions from Libby Amphibole and background asbestos.

- The development of a specific Libby Amphibole RfC used for Libby and former vermiculite processing plants, may lead to concerns about asbestos levels in homes with vermiculite attic insulation (VAI). EPA may need to address concerns about VAI in homes.

- The model developed by Peto and others and used in the EPA IRIS document for mesothelioma was not used here but instead a Poisson distribution with an MCMC Bayesian approach was used. The rationale for this is questionable given the following:

    - EPA's own review (Region 9, San Francisco) found that the Peto model adequately describes meso epidemiological data sets.

- Only 18 cases of meso in Libby were available for model fitting the Libby data while 100's of meso cases were well fit to the Peto model.
- The exposure data for the Libby cohort is poor, possibly worse than midget impinger data. The document states, (pg 5-58) "…..derivation of specific exposure concentrations may be subject to a sizable measurement error".
- The Bayesian approach removes the age-related or residence time-weighted influence of younger age exposures on mortality. Although the document states earlier, "Unlike many chemicals that are rapidly metabolized in the body and excreted, asbestos fibers are durable and some may remain in the body for years. Fibers that remain in the lung may continue to damage lung cells and tissue until they are removed or cleared (Section 3.2). Similarly, fibers that translocate to the pleura may damage cells as long as they remain in this tissue. Therefore, a fiber exposure may not only damage tissue during the exposure, but fibers may remain in these tissues, with cellular and tissue damage accumulating over time." It seems most improbable that LA, even if more toxic than other amphibole, acts by a mechanism of action that is so different from other amphiboles that LA does not have an age-related mesothelioma effect.

At a minimum this document should perform the same analysis using the Peto model so the results can be compared.

- A life-table analysis was performed using the mesothelioma and lung cancer data and models from the Libby specific data. However, the life-table data came from the whole US. It is not known how comparable Libby mortality is to the US as a whole. This assumption is probably acceptable but this uncertainty should be acknowledged.

Non Cancer Toxicity of Libby Amphibole Asbestos

This portion of the review focuses on those sections of the EPA Toxicological Review and the Fact Sheet that describe the hazard and dose-response assessment of chronic inhalation exposure to Libby Amphibole asbestos. Overall, these sections are well written and EPA has clearly synthesized the scientific evidence and presents a non cancer hazard assessment of this chemical that is logical, transparent, and concise.

In these draft documents EPA proposes an RfC of 1 X 10^{-5} fibers/cc. The critical effect that was selected as the point of departure (POD) was localized pleural thickening as identified by radiographic analysis. The POD for this critical effect was $BMCL_{10}$= 0.076 fibers-yr/cc. The uncertainty factor (UF) applied was 100 (10 for intraspecies variation and 10 for database uncertainty). In deriving the RfC, the POD was divided by 60 years (lifetime of 70 years minus 10 years to account for lagged exposures) and then divided by the UF of 100. The RfC is based upon the Marysville, OH worker cohort exposure to Libby Amphibole asbestos {Lockey et al., 1984; Rohs et al., 2008}). The end point selection, the benchmark dose analysis methodology and assumptions, and the uncertainty factors applied in the derivation of the proposed RfC appear appropriate given the available data. The implementation of the proposed RfC will be a challenge.

Specific comments.

Draft Charge to Peer Reviewers

Pg 1-3. The sentence "Libby Amphibole asbestos is a potential concern for former vermiculite processing and waste disposal sites which may have handled vermiculite mined in Libby, MT" is misleading. Although Libby Amphibole is a concern for the above mentioned population, it is also definitely a concern for Libby residents, which are not mentioned (and should be)in the background paragraph.

Draft Toxicological Review
The IUR and RfC, the main things most cleanup managers and risk assessors will use, are buried in the text and very difficult to find. Our reviewers only found the RfC in one place (page 5-24 after many pages of detailed modeling), and the IUR in two places (pages 5-88 and 6-17). We feel these values need to be highlighted in an executive summary or another easy-to find place.

Pg 1-1, line 34. NMRD should be spelled out the first time it is used.

Pg 4-20, line 21. Suggest substituting "Radiographic anomalies" for "Radiographic abnormalities."

Pg 4-20, lines 30-31. "International Labor Organization 1981 classification system" should read "International Labor Office 1980 classification system."

Pg 4-81, lines 18-20. It would be advisable to provide a reference for the following statement: "Because pulmonary function (volume and rate of breathing) decreases with age, increased deposition of fibers in the lung from exposures in later lifestages is unlikely."

Page 4-81, lines 30-33: The following statement is problematic: "Due to the natural increase of non-cancer health effects among older adults, it is likely that older individuals exposed to Libby amphibole at some point in their lives will have elevated rates of disease. Radiographic tests among those exposed to Libby amphibole show that older age is one of the factors most associated with pleural or interstitial abnormalities". Older individuals in Libby may have a higher incidence of nonmalignant respiratory diseases because of longer latency from initial asbestos exposure, not because of a "natural increase of non-cancer health effects among older adults", since the outcomes reported here are fairly specific of asbestos exposure. Although this fact is addressed later on in the document, we suggest modifying the preceding statement.

Page 5-13, first paragraph: The statement "Pleural thickening does not progress to parenchymal changes." could be omitted, since this document is directed to a scientific audience.

Page 5-33, lines 16-20: "However, a recent study by Larson et al. (2010b) examined serial radiographs conducted on a group of Libby vermiculite workers with pleural or parenchymal changes. They found that among those workers with localized pleural thickening, all cases were identified within 30 years, and that the median time from hire to the first detection of localized pleural thickening was 8.6 years." Although the statement is true, it should be noted that the different methodology used (i.e., retrospective assessment of serial radiographs) may have been responsible for increased sensibility to detecting pleural abnormalities. Although presence of pleural plaques is definitely a sensitive health outcome endpoint, further analysis could be performed using "severity" of pleural plaques, which could be measured by existing classifications (e.g. Bourbeau J, Ernst P, Chrome J, Armstrong B, and Becklake MR. The relationship between respiratory impairment and asbestos-related pleural abnormality in an active work force. Am Rev Respir Dis 1990; 142:837-842). The spectrum of pleural disease can vary considerably and small pleural plaques are unlikely to cause deleterious effects on pulmonary function

and therefore have little clinical significance. These comparisons would enhance EPA's ability to evaluate if health outcomes that are more important from the functional and clinical perspective are associated with certain levels of exposure. Nevertheless, since the presence of pleural plaques increases the risk of malignant asbestos-related diseases, this endpoint should not be dismissed at all.

Pg 5-51, lines 3-16. This paragraph is extremely confusing. Needs to be rewritten.

Pg 5-55. *While*

16 mesothelioma is known to have an average latency as long as 55 years among selected
17 occupations (e.g., Bianchi and Bianchi, 2009), several mesothelioma deaths in the cohort
18 occurred within 30 years from the start of the exposure, suggesting a shorter latency period in
19 this population

This statement implies that Libby Amphibole is more toxic because the time to meso period (latency) is only 30 years in those exposed to LA. Lanphear and Buncher (1992) calculated a mean latency period (reviewing 1,105 cases) of 32 years. Very much in line with Libby; suggesting the above conclusion may be invalid.

Pg 2-11, line 25. The word "also" should be major.

Pg2-13, lines 3-20. This would be a good place to introduce "transitional fibers"

Pg 2-19, lines 20-21. Resolution limits of PCM should be discussed here.

Pg 2-21 section 2.4. Rail lines and studies around rail lines need to be discussed.

Pg 2.25, line 12. The claim that "There are reports" needs references.

Pg 3-1 figure. The two-headed arrow from "Dust in inspired and expired air" is not consistent with the legend. Expired air should be a clearance mechanism and a dashed line. Two arrows instead of a double headed arrow are needed.

Pg 3-8, line 18. Biopersistence is not the right choice of words. Translocation followed by rapid excretion may result in low biopersistence but still result in fibers that are easily translocated. "Durability" would be a better choice.

Pg 5-49, line 10. Need a timeframe reference. Was this until the plant closed? The workers retired? After 1960 until when?

Pg 5-51, lines 1-2. This reads as much too definitive. The exposure estimates around these workers had huge uncertainty associated with them.

Page 6-22: The text states that both the RfC and IUR are in units of fibers-yr/cc. This is not correct, and not the same as in IRIS, as stated. On page 5-24, the RfC is listed with correct units, 1×10^{-5} fibers/cc for continuous exposure. On pages 5-88 and 6-17, the IUR is listed with correct units, 0.169 per fiber/cc, or $(\text{fiber/cc})^{-1}$.

Page 6-22—6-23: Today, PCM can resolve diameters smaller than 0.4 □m. The Framework for Investigation Asbestos-Contaminated Sites recommends PCMe to include diameters between 0.25 □m

and 3.0 □m. Because today's definition of PCM and the definition used to define the IUR/RfC are different, this will cause confusion in applying the IUR/RfC. Do investigators need to analyze a subset of PCM or include only fibers greater than 0.4 □m in calculating PCMe? This needs to be clarified in the text.

Draft Fact Sheet

This does not seem like a fact sheet for the public. The purpose and audience of the document needs to be clear, and we suggest including more detailed description if the intended audience is the general public. This document also needs to be proofread for typos.

Page 2. Incorrect units for the inhalation unit risk (IUR) in the table. The units should be $(\text{fibers/cc})^{-1}$.

Page 2, footnotes. Again, the units for IUR are incorrect. They should be $(\text{fibers/cc})^{-1}$.

Comments on "NCEA Interagency Communication #120 - Transmission of science consultation draft assessment for Libby Amphibole asbestos"

Prepared by Greg Miller
White House Council on Environmental Quality
6/10/11

Thank you for the opportunity to review the Interagency draft *Toxicological Review of Libby Amphibole Asbestos*. The level of detail and analysis in this document is very impressive. I strongly agree with the decision to base the cancer assessment on the available epidemiologic data and support the derivation of a linear cancer IUR. Thank you and good luck with your revisions.

Does the IUR adequately protect children? - Section 6.1.5

I agree with the conclusion that the available data are not sufficient to establish a mode of action for Libby Amphibole asbestos; thus, the linear extrapolation method is warranted (without the application of the ADAFs). However, the Tox Review should make a greater effort at addressing the question of whether the IUR adequately protects children. Because the modeled cancer data do not indicate an increase risk in a supralinear fashion over time, the selected linear cancer model is not expected to underestimate early-lifetime or less than lifetime risk. While a great deal of effort has clearly been put in to crafting a well-written assessment of the available children's exposure and toxicity studies, the Section 6.1.5 does not offer an explicit statement that the selected linear model should be protective of children's exposures – specifically because the data are not expected to be supralinear. The following statement from EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (2005) would support the conclusion that the derived IUR is expected to be protective of children who have experienced early life exposures. Please include it as part of the discussion in Section 6.1.5.

> "It is the Agency's long-standing science policy position that use of the linear low-dose extrapolation approach (without further adjustment) provides adequate public health conservatism in the absence of chemical-specific data indicating differential early-life susceptibility or when the mode of action is not mutagenicity."

Uncertainty Factors

The Libby amphibole assessment lacks information on childhood exposure-response and adverse noncancer outcomes in children. Thus, the full intraspecies uncertainty factor of 10 is justified. As stated in the Tox Review, the database uncertainty factor of 10 is justified by the lack of information on the potential for autoimmune disease and rheumatoid arthritis and the lack of information to extrapolate to a full lifetime of exposure with the data set used to derive the POD. I support the selected uncertainty factors.

Minor comment

The Table of Contents in the May 2011 draft is not accurate.

Department of Defense Comments on Libby Amphibole asbestos IASC draft 5-13-11.pdf		
Comments submitted by: Chemical Material Risk Management Directorate	Organization: Department of Defense	Date Submitted: 6/9/2011

*Comment categories: Science or methods (S); Editorial, grammar/spelling, clarifications needed (E); or Other (O). Also please indicate if Major i.e. affects the outcome, conclusions or implementation of the assessment.

Comment No.	Section	Pages	Comment	Suggested Action, Revision and References (if necessary)	*Category
1	Table of Contents	Global	The "Contents" Section (e.g., Sections 4.5) does not always match up with the "Section Titles" or page numbers in the draft document and thus, it and the entire draft document need careful editing. For example, "Chronic Inflammation" is Section 4.5.5.1, not 4.5.1.1, which does not exist. Section titles also may be on the page indicated in the "Contents" but may be different than what is stated in the "Contents." Section 4.6.2.1.1, page 4-73 refers the reader to Section 4.5.1.1; Section 4.6.2.1.4, page 4-75 refers the reader to Section 4.5.1.2, which although called out in the "Contents" Section, also no longer exists in this version of the draft.	We recommend careful review and editing of this draft prior to release for public comments. More importantly we also recommend a systematic technical review of the data and how it are used together to derive conclusions. This would ensure internal consistency, accuracy, transparency, and completeness of the document.	S
2		Global	We suggest that asbestos would be an excellent case to implement section 3.3.4 of EPA's 2005 cancer guidelines. This section, "Nonlinear Extrapolation to Lower Doses" states (emphasis	DoD suggests that, per EPA's guidelines, a nonlinear, as well as a linear extrapolation, be evaluated and that this evaluation be clearly presented to the end user (i.e., the risk	S/M

			added): "Nonlinear extrapolation having a significant biological support may be presented in addition to a linear approach when the available data and a weight of evidence evaluation support a nonlinear approach, but the data are not strong enough to ascertain the mode of action applying the Agency's mode of action framework. If the mode of action and other information can support chemical-specific modeling at low doses, it is preferable to default procedures."	manager). As discussed in later comments, we believe there are sufficient data to evaluate a mode of action and that, even if the data are not strong enough to ascertain the mode of action, the biological weight of the evidence is sufficient to implement this section of EPA's guidelines.	
3		Global	There were sufficient inconsistencies with regard to the methods and data used for analysis that it is not clear if all of the following comments are relevant. In particular, we spent time commenting on procedures or evaluations that were contradicted by other parts of the document.	DoD recommends that the IRIS documents receive a better quality review prior to their release outside the agency. The number of errors and internal inconsistencies in this document (see comments #1 and # 15 for examples) makes it very difficult to perform a high quality review of the document in the limited amount of time provided.	S
4	4.4.2 Genotoxicity	4-57	As discussed extensively by experts in mutagenicity at the external peer review of EPA's IRIS toxicological evaluation of hexavalent chromium, the data required to determine that a chemical is mutagenic have become more detailed and restrictive. Much of that which would have been considered a demonstration of mutagenicity in the past is no longer sufficient. In particular, these experts were concerned about the conflation of mutagenicity and	We suggest that EPA update its consideration of mutagenic activity (and the related concept of genotoxicity) in light of recent advances in epigenetics and genomics, e.g., as discussed in the referenced external peer review. It would not be beneficial for this document to receive the same criticism of an IRIS document that was just reviewed, nor would it be useful to have IRIS documents that had obviously inconsistent evaluations of similar data. Our	S

			genotoxicity that had also occurred in the draft document they were reviewing. In particular, one of the reviewers who had published on bacterial and cell culture data declared that those data should no longer be used to determine mutagenicity, and that they were, at best, just an indication that the chemical might be mutagenic if tested appropriately. For example, in the late 1970's, the Ames test was used first as an indicator of both mutagenicity and carcinogenicity, as all carcinogens were assumed to act through an initial mutation (see, for example, EPA's 1986 cancer guidelines). By the early 2000's, however, the test was no longer considered a firm indication of an ability to cause mutations in eukaryotes, much less a carcinogens for mammals (see, for example, EPA's 2005 cancer guidelines). By the criteria discussed by the experts in genetic toxicology at EPA's external peer review for hexavalent chromium, neither indirect mutagenicity via reactive oxygen species (ROS) nor physical intercalation into the DNA helix, i.e., the two most likely methods for interaction of asbestos with DNA, are considered mutagenic effects for a chemical.	evaluation would be that asbestos would not be considered a mutagenic chemical, although it might be considered genotoxic.	
5	4.5.5. Mode-of-Action Information (non-cancer)	4-68	While we agree that the "precise mechanism" of noncancer effects is not known, we reference EPA's 2005 cancer guidelines to make the distinction between "mode of action" (MOA) and	We suggest that EPA attempt evaluation of this or a similar MOA. With the amount of data available, and recognizing that surrogate data from other types of asbestos can be used, such	S

			"mechanism of action". The EPA's 2005 cancer guidelines defines the *"mode of action"* as a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation. It clearly distinguishes between a "mode of action", where precise mechanisms need not be known, and a "mechanism of action" where these processes would be more defined. As outlined in the section headings in this part of the document, EPA has not only provided key events for an MOA, but has also provided data demonstrating that these events occur: Exposure to relevant size of asbestos; 4.5.5.1. Chronic Inflammation; 4.5.5.2. Cytotoxicity and Cellular Proliferation; and 4.5.1. Pleural Thickening.	an attempt would either demonstrate an MOA or clearly define what data would be required to do so. Not attempting such an analysis is a disadvantage to stakeholders who might be interested in establishing an MOA. Further, as many, if not all, of the key events have been delineated for this chemical, the absence of such an analysis – without clearly demonstrating where necessary data might be absent and what data might fulfill the data gap – might suggest that EPA has not determined how much and what type of data would be sufficient to establish a mode of action for a chemical. Without such criteria, decisions regarding a mode of action are neither transparent nor clear.	
6	4.6.2. Mode-of-Action Information	4-72	As with the noncancer MOA, EPA has outlined a potential MOA for cancer in its section headings. This MOA would be: 4.6.2.1.2. Reactive oxygen and nitrogen species production; 4.6.2.1.1. Chronic inflammation; and 4.6.2.1.4. Cytotoxicity and cellular proliferation. Given the lack of mutagenicity that is discussed in comment #7, we think that this MOA is quite likely to have sufficient data to be "determined" per EPA's 2005 cancer guidelines.	We suggest that EPA attempt evaluation of this or a similar MOA. With the amount of data available, and recognizing that surrogate data from other types of asbestos can be used, such an attempt would either demonstrate an MOA or clearly define what data would be required to do so. Our analysis also strongly suggests that such an MOA would clearly determine that the dose-response function is nonlinear at low doses. As this determination would substantially affect the quantitative risk assessment of this substance, not attempting	S

				such an analysis is a disadvantage to interested stakeholders.	
7	4.6.2.1.3. Genotoxicity/mutagenicity	4-74	As stated previously, experts in this discipline distinguish genotoxicity and mutagenicity. As EPA's cancer guidelines reference both mutagenicity and a mutagenic mode of action, EPA's analysis should clearly make this distinction. Our analysis of the data presented is that they are all evaluations of genotoxicity, and should be so labeled.	For scientific accuracy, we highly recommend that EPA distinguish between genotoxicity and mutagenicity, especially as these studies are likely to be considered evaluations of genotoxicity, not mutagenicity.	S
8	4.6.2.2	4-76	We agree that this chemical does not have a mutagenic mode of action for carcinogenesis	No action necessary	S
9	5.2.1.6. Selection of Critical Effect	5-13 to 5-15	We are confused by the nomenclature. On page 5-14, EPA states that the critical effect is "localized pleural thickening" which corresponds to the data presented in Table 5-3. In contrast, Figures 5-2 and 5-3 have no such term, but apparently use "discrete pleural". The table references the same studies as the text, and the figures have no associated reference.	While we are assuming that "localized" and "discrete" are the same, EPA should clarify the nomenclature to avoid confusion. Moreover, if these figures were generated by EPA, the nomenclature should be consistent with the reference from which the data were derived. If not, the reference should be provided.	S
10	5.2.2.1 Exposure data choice of exposure metric	5-16	The adjustments from the reported statistic of "cumulative years" is not justified or referenced, as will be discussed below. Moreover, as each adjustment is based on one or more *ad hoc* assumptions, the adjustments <u>unnecessarily increase the uncertainty of the risk estimate</u>. 1. The analysis states, *"Each worker's*	We recommend that EPA perform its analysis in the metric presented by the study, i.e., cumulative years. Uncertainty introduced too early in the analysis will be perpetuated and magnified through the rest of the analysis. If EPA wants to convert the results to another metric, it should do so at the end of the analysis, so that the effect of such a conversion	S/M

			cumulative exposure was then adjusted to a cumulative human equivalent exposure for continuous exposure (CHEEC; fibers-yr/cc) to represent exposure 24 hours/day and 365 days/year (assuming that any exposure off site was zero).". Yet earlier (5.2.1.1. Evaluation of Exposure in Candidate Studies), EPA notes that peak or average exposures would be preferable *("Each of the studies provided estimates of cumulative Libby Amphibole asbestos exposure (in fibers-yr/cc), rather than mean or peak exposure.").* We agree that some measure of intensity, such as peak exposure, is likely to be the appropriate metric. EPA's adjustment errs in the opposite direction, averaging over periods of time when exposures did not occur. This "adjustment" may be a default procedure, but it is neither justified nor appropriate for asbestos, given that peak exposures, i.e., accumulation in the lung due to overwhelming of the lung's defense systems, is the likely MOA of lung cancer. The process merely serves to artificially increase the potency by asserting the lower "averaged" exposure is responsible for the effect. 2. The report also states, "*Adjustments for different inhalation rates in working versus nonworking time periods were incorporated in this analysis."* As exposure would only occur during working time periods, we are not clear why other inhalation rates were used to	on the cancer risk can be clearly and transparently determined by all of the stakeholders without having to repeat EPA's quantitative procedures. 1. EPA's text should be consistent as to what is believed to be the appropriate metric in the exposure and the toxicology sections. In particular, for this substance, EPA should justify averaging over non-exposure periods, especially if peak exposures are considered most relevant. 2. The second "adjustment" has no apparent relevance to the estimation of exposure and internal dose. Thus, it should either be more clearly explained or deleted as it will introduce more *ad hoc* assumptions and therefore unnecessary uncertainty into the analysis.	

			determine rate of exposure		
11	5.2.2.2. Datasets for Modeling Analyses	5-17 to 5-18	EPA states that *"1. The data from Lockey et al., (1984), n = 513 and Rohs et al. (2008), n = 280 were combined, n = 793"* Adding the Lockey et al. (1984) and Rohs et al. (2008) is not logical, as the latter is stated to be a follow-up of the same individuals as the former. This will result in double-counting the same individuals with cancer. Note that this procedure was not used for evaluating the noncancer effects, i.e., the later study of Rohs et al. (2008) was used (see Table 5-3). There are more appropriate, statistical methods for combining these data to include the (presumably) increased number of cancers due to the longer latent period assessed in the later evaluation. These would not double-count individuals.	EPA has faced this issue previously, and to the best of our knowledge, has never added the results of a follow-up study to the results of the earlier study of the same cohort. In this case, the later study had fewer participants. Nevertheless, published, statistical methods are available to accommodate such data, we believe that the data should be reanalyzed. Furthermore, if EPA continues to add the results of these studies, it should explain why it used a different procedure for the non-cancer effects.	S
12	5.2.2.3.1 Statistical model evaluation	5-21	It is unclear how "Different exposure lags (0, 5, 10, 15, and 20 years)" were evaluated, as the combined Lockey and Rohs data had different times of observation. For example, assuming the data were gathered about 20 years apart, a 5-year lag for the Rohs data would be a 25-year lag for the Lockey data.	If the lags were applied before the data/results were added, the process for doing this should be explained. If not, lags "applied" to the summed results have no logical interpretation. The effect of adding the results is compounded by adjusting the latent period for results that have differing internal lags from the exposures. We recommend that the statistical analyses be corrected or clarified before the document is released for external peer review and public comment.	S
13	Figure 5-5.	5-24	Given that EPA has data well below the ED01	Consistent with EPA guidance the POD at the	S/M

			response level, selection of the BMDL10 as the point of departure (POD) appears unreasonably high. Relevant procedures for selecting a POD from Benchmark dose modeling can be found in the EPA's 2005 cancer guidelines that states that the POD should be near the low end of the data. (Other EPA guidance on benchmark dose modelling, which is not yet final, also states that the POD should be near the low end and that it may be below (or sometimes above) the ED10.) The Toxicological Review shows 2 of the 4 data points are below the selected POD.	ED10 should be reported but we suggest that lower levels also be considered.	
14	5.2.3 RfC Derivation - Uncertainty Factors	5-25	It is not clear why EPA used an uncertainty value of 10 for database deficiencies. EPA's rationale is stated here: *"An UF value of 10 was applied to account for deficiencies in the database (UFD) based on lack of data on effects other than in the respiratory system, limitations of the principal study design, other observed effects (cardiovascular disease and autoimmune effects) that have not been well-studied, and uncertainties in time from first exposure."* The information presented indicates that protecting for effects in the respiratory system would protect for other effects as well.	DoD suggests that the extensive data on other forms of asbestos should be used to confirm the described observation and reduce the uncertainty factor for database deficiencies unless EPA can demonstrate that the missing tests are likely to be positive and more sensitive than the effects on the respiratory system. We believe that the database uncertainty factor may be reduced below 10.	S/M
15	5.4.2.1 Description of Libby Worker Cohort	5-37	The description of the data used for the cancer potency analysis in this section, i.e., *"For the purposes of this assessment, vital status follow-up was completed by NIOSH through 2006 using*	The document needs to be further reviewed for inconsistencies and inaccuracies.	S

			the National Death Index (NDI-Plus; Bilgrad, 1995).", is completely different than the description of the methodology described earlier in the chapter and as discussed in comments #11 and #12 above. It is difficult to provide an adequate review when a document contains internal inconsistencies that substantially affect the evaluation of the analyses presented.		
16	5.4.3 Exposure-Response Modeling	5-55	Although not stated explicitly, all of the dose-response models selected assume a continuous function through the origin, i.e., assume that no threshold exists for asbestos carcinogenicity. As stated above, our analysis of MOA suggests a nonlinear, i.e., threshold, dose-response function.	We suggest that sufficient information exists to determine that asbestos has a threshold for carcinogenicity, and that EPA should explore this possibility based on the data presented in this document. If EPA performs an explicit MOA analysis that agrees with our analysis, they could further develop a POD and an RfD for cancer, as was done for noncancer effects.	S
17	5.4.5.3 IUR Derivation for Combined	5-88	The document gives the IUR value as "0.169 per fiber/cc". We expect that one, or at most two, significant figures can be justified	The IUR should be reported as 0.17 per fiber/cc.	S

NIEHS Comments for the IRIS Toxicological Review of Libby Amphibole Asbestos

In general, EPA did a very good job in presenting the needed information with sufficient clarity and detail to support this Toxicological Review of Libby Asbestos. Our main concerns involve, 1) the choice of a subcohort of the Marysville data-set versus the entire cohort and, 2) the less health protective Libby site specific IUR (versus the current IRIS IUR) given the confounding, instability, and uncertainties associated with the Libby worker cohort. Our specific comments are outlined below. We applaud EPA for this effort to understand asbestos exposures and risks for the Libby community and to develop a site specific IUR and the first RfC to protect individuals from adverse non-cancer health effects.

1. Inhalation Reference Concentration (RfC) for Libby Amphibole Asbestos

With respect to the RfC developed using the Marysville, OH cohort. The Marysville, OH worker cohort is well described and scientifically supported for use as the basis of the RfC derivation. We are not aware of any other populations with sufficient data to support an RfC for Libby Asbestos. Also, the use of localized pleural thickening as the critical effect for the RfC is scientifically justified as these findings represent irreversible pathology (highly specific to asbestos exposure) that has been associated with symptoms, physiologic impairment, and slow progression which may be associated with worsening clinical sequelae. With respect to Libby Asbestos exposure in particular, studies have shown markedly elevated prevalence of pleural disease among workers and non-occupationally exposed individuals with progressive loss of pulmonary function both radiographically and functionally. Larson et. al., also reported what appears to be shortened latency times and the progression of circumscribed pleural disease to diffuse pleural disease, further underpinning the physiological and clinical relevance of radiographically identified “localized pleural thickening” in this population.

The modeling appears to be well described and appropriately conducted. The benchmark response of a 10% increased risk of localized pleural thickening is scientifically reasonable and appropriate for the derivation of the RfC given the size of the study cohort and background prevalence of this effect. Also, the study limitations and uncertainty factors are thoughtfully discussed and appear reasonable. With that said, our main concern regards the use of a truncated cohort, instead of the full Marysville cohort, for purposes of the RfC derivation. Given the apparent quality and available information regarding the workplace and cohort, the decisions underpinning the use of the truncated cohort for the RfC are not clearly explained or appear to be scientifically supported. An updated exposure reconstruction, of previously peer-reviewed reconstructions, developed by the University of Cincinnati (UC) for exposures prior to 1972 included extensive efforts by these investigators to evaluate the worker exposures and pre-1972 conditions. These efforts included (as described in Appendix E) extensive document and data evaluations, interviews with OM Scott management, additional employee interviews, highly detailed examination of workplace process and employee information, and re-evaluations of manufacturing processes and usage of vermiculite and raw materials. Additionally, UC investigators detailed their exposure reconstruction to further ensure accuracy and robustness

of exposure estimates (e.g., adjustment for working and non-working periods and inhalation rates, accounting for overtime and reduced hours, etc.).

While, pre-1972 exposures were not quantified, there do not appear to be any substantive issues or indications of unaccounted for work process changes that would invalidate the previous peer-reviewed approaches taken by UC investigators to back extrapolate from post-1972 exposures, nor the more extensive exposure reconstruction used for development of the RfC. Inclusion of this data should be evaluated in sensitivity and uncertainty analyses to enhance the quality and strength of the data set. For example, the effects of pre-1972 exposure misclassification on the RfC appears to be inconsequential as sensitivity analysis (Appendix E, page 15) reports little effect on the RfC in association with an estimated doubling of exposures between 1967-1972 as compared to no estimated doubling. The effect of truncating the cohort (use of post-1972 employment data only) is even more obvious in Figure E-3 with the clear loss of the well-established time-from-first-exposure variable as compared to the full data set. Larsen, et al.(2010), reported findings of decreasing cumulative dose and increasing latency between time from first exposure and signs of disease among Libby workers. Thus, modeling of the much smaller sub-cohort does not accurately reflect the exposure-response relationship that has been scientifically determined among Libby workers and in other cohorts. Also, truncation of the data set to only those employees first exposed after 1972 as a basis for the RfC, is not consistent with the EPA discussion (Section 5.2.1.5) of the selection of the Marysville cohort as the principal study in large part due to the longer time from first exposure (an important factor in the development of the health effect). Thus, EPA's explanation for this choice to reduce the available data-set about 80% (12 versus 61 cases) with the associated increase in uncertainty, based upon *"longer follow-up time and additional covariate information"* is not clearly described or scientifically supported by the available information.

2. Carcinogenicity of Libby Amphibole Asbestos

We support the designation of the Libby Amphibole Asbestos as "carcinogenic to humans" by the inhalation route of exposure. We agree that the cancer weight of evidence characterization is clearly described in the document. While establishment of the mode-of-action of carcinogenic response would further inform the establishment of the Libby Amphibole as being carcinogenic to humans, a full understanding of the mode-of-action by which the carcinogenic endpoint occurs is not necessary in order to make such a determination. However, it would be helpful if the document were to recommend studies that would be useful for the purpose of informing the carcinogenic mode of action.

The document is transparent in the explanation of uncertainties and limitations in the methodology. That said, we believe that the cancer risk estimates should be scientifically strengthened and the associated uncertainties reduced by considering and incorporating the following considerations and recommendations:

The selection of the occupational cohort of vermiculite miners and millers is a reasonable, but not ideal, study population for the determination of the IUR. Uncertainties and confounding factors associated with this cohort call into question the accuracy of the IUR derivation. For example:

a) It is established that many miners and millers at the Libby operations died of non-malignant, asbestos related diseases before the expected latency associated with lung cancer or mesothelioma (Sullivan 2007). Deaths or non-malignant disease that would prematurely remove workers from the cohort, or any missed cases of mesothelioma, would cause an underestimation of the number of cancer and/or mesothelioma cases resulting in a significant underestimation of the cancer/mesothelioma risks. Due to the relatively small number (n=7) of mesothelioma deaths recorded in the cohort, any additional uncounted mesothelioma deaths would increase the absolute risk estimate markedly. We believe this is a significant oversight.

b) Considering the expected latency period for mesothelioma coupled with the decision to count only cancer mortality and not incidence. It is expected that workers in the subcohort who may not yet have succumbed to their disease or who will develop this fatal disease in the future were not included in this evaluation. Due to the relatively small number (n=7) of mesothelioma deaths recorded in the subcohort, any additional uncounted mesothelioma deaths would increase the absolute risk estimate markedly. We believe this is a significant oversight.

c) Due to the remoteness of the Libby mining operations, there is enhanced concern that many cases of cancer and mesothelioma that may have occurred due to exposures at the site went unnoticed as such. Upon occurrence of disease, many miners are likely to have sought medical care outside of the Kootenai Valley as far away as Salt Lake City. While the assessment discusses and attempts to account for misclassification of disease, it does not address site-related mortality that is likely to have occurred remotely. Such cases would increase the cancer/mesothelioma risk estimates for the site.

d) Non-occupational asbestos exposures in this community can be very high, even exceeding occupational standards, and are not insignificant with respect to exposures and cancer mortality. Whitehouse et.al. (2008) reported 11 cases of mesothelioma among non-mine workers. Thus, inability to account for non-occupational exposures in this cohort can result in significant exposure misclassification and confounding.

Additionally, the exposure-response modeling used in the development of the IUR should include quantitative assessment of the full fiber distribution. Employment of the older light microscopic techniques for exposure assessment to the exclusion of available information on full fiber distribution represents loss of an important opportunity to further public health protection from fiber exposure and greatly enhance nation-wide understanding of fiber toxicology. Recent work by Dement et al *(Dement, J.M. et al. (2011) Estimates of historical exposures by phase contrast and transmission electron microscopy for pooled exposure-response analyses of North Carolina and South Carolina, USA asbestos textile cohorts. Occup. Environ. Med http://www.ncbi.nlm.nih.gov/pubmed/21217162)* demonstrates the value and importance of such comparative analyses. Both historical and more recently collected information on the details of

fiber size distributions are available for the Libby site. Analysis of this information relative to both malignant and non-malignant asbestos disease in Libby would enhance the present analyses as well as a general understanding of fiber exposure-response nationwide.

3. The charge questions for external reviewers should include an open ended question, for both the RfC and IUR, to solicit any additional comments or concerns from the reviewers. The current structuring of the questions limits reviewers ability to comment on other issues and concerns relevant to the documents and achieve the best input and product from this process.

Informal Comments of the National Institute for Occupational Safety and Health on the May 2011 Interagency Science Consultation draft *Toxicological Review of Libby Amphibole Asbestos*
June 9, 2011

The National Institute for Occupational Safety and Health (NIOSH) reviewed the U.S. Environmental Protection Agency (EPA) May 2011 Interagency Science Consultation draft ***Toxicological Review of Libby Amphibole Asbestos*** prepared in support of summary information on the Integrated Risk Information System (IRIS). The following comments are intended to assist EPA in assessing hazards from Libby Amphibole asbestos.

Comments on the overall document:

1. This Toxicological Review has numerous issues on terminology and definitions, all of which should be resolved.. NIOSH recommends a careful edit of the draft document be done with experts familiar with discipline-specific terminology.
    a. The first term of concern is "asbestos", which appears as early as the title. Asbestos has been clearly defined in Federal Regulations, but it is not used in that strict sense in this document. Defining asbestos as asbestiform and asbestiform as being like asbestos is circular reasoning and should be avoided. Prismatic and acicular are also vague, descriptive terms in mineralogy, and one geologist's "prismatic" can easily be another geologist's "acicular". Asbestos itself tends to defy categorization, and asbestos can be found to grade into material that some geologists would not consider "asbestiform". Under the optical microscope it is often impossible to know if one is viewing a single prismatic crystal, a bundle of asbestos fibrils, or a cleavage fragment. The dimension-based definitions of a fiber in Occupational Safety and Health Administration (OSHA) regulations and by NIOSH and the World Health Organization (WHO) have some advantages because they are not sensitive to vague terminology, however, they do not differentiate on particle habit.
    b. Use of the term "Libby Amphibole Asbestos":
        i. U.S. Federal agencies and other national and international organizations have defined "asbestos" to include the six commercially used asbestos minerals – the serpentine mineral chrysotile, the amphibole minerals amosite (cummingtonite-grunerite asbestos), crocidolite (riebeckite asbestos), actinolite asbestos, anthophyllite asbestos, and tremolite asbestos. Lines 11-14 on page 2-13 state the amphibole minerals that are found in the vermiculite deposit from Rainy Creek near Libby, Montana have been appropriately identified to include the fibrous amphiboles winchite (84%) with lesser amounts of richterite (11%) and tremolite (6%). Given that agencies do not currently classify the amphibole minerals winchite and richterite as an "asbestos" mineral, consideration should be given to deleting the word "asbestos" when describing this complex mixture of amphibole minerals found in the Libby, Montana vermiculite deposit. Terminology consistent with that stated on page 2-11 (lines 20-21) "For purposes of this document, the

material from this mine will be called Libby Amphibole" may be a more appropriate mineralogical description.

ii. The composition of the fibrous amphibole mineral fibers associated with Libby vermiculite is quite complex mineralogically. Given mineralogical nomenclature changes for the amphiboles in recent decades, it is even more complex when viewed through the published historical scientific literature. Rationale for use of the term "Libby Amphibole asbestos" should be provided early in the document. One way to do this would be to avoid using the term "Libby Amphibole asbestos" in the Foreword and use it first in Introduction, where a single parenthetical sentence could be inserted to refer readers to the explanatory appendix for a detailed rationale for use of the term. Care should be taken not to use two different terms (as is currently the case in the draft) "Libby Amphibole asbestos" and "Libby Amphibole" unless a clear difference in these two terms is established and justified in the document.

c. NIOSH recommends defining the terms fiber and fibrous in or prior to the Introduction, as they are used many times in the Introduction. Since most literature definitions of fiber and fibrous are inadequate, the document should include its own. A fiber made up of a bundle of smaller fibers is often also termed a fiber. A fibril should be defined as an individual crystal of very high aspect ratio and thickness in the sub-to-low micrometer range. Geology recognizes crystalline and non-crystalline (amorphous) forms only. "Fibrous" is a crystal habit and fibrous minerals are crystalline. It is possible to define asbestiform as a special case of the fibrous habit when the length, thickness, and consequent flexibility of the fibers make them either a material that could be sold as asbestos or appear similar to such (e.g., when zeolites or other minerals are termed asbestiform). Given the different ways that disciplines and this draft use the term "fiber" (e.g., sometimes in the "mineralogical" sense and other times in the "regulatory" sense), NIOSH recommends clarification of the definition. It would help to include all definitions for "fiber" as it is variously used in this document in an appendix. In key areas where specificity would be helpful, use a modifier with "fiber" to clarify its use (e.g., "mineralogical fiber(s)", or "regulatory fiber(s)"). This definitional issue relating to "fiber(s)" is broached, but not comprehensively dealt with, in the paragraph at the top of Page 2-4.

d. - NIOSH recommends using the ILO classification of "abnormalities" instead of "changes." Use of the term "changes" (as jargon for [radiographic] abnormalities): The term "changes" implies a longitudinal assessment of changes comparing two x-rays taken at two different times in an individual. To avoid misleading readers, even when the original investigators of a published study used the jargon "changes," NIOSH

recommends all occurrences of "changes" used in the context of chest x-ray findings be replaced by "abnormalities"—the term used in the ILO classification system.

2.. The review refers incorrectly to electron microscopy as a fiber-counting tool for a risk assessment based on optical fiber counts. While fiber counts based on only electron microscopy may have value in remediation or other efforts, it is currently not possible to assign risks based on such measurements as is clearly recognized in the document.

Page 6-22 line 31: "Although some historical data do exist providing TEM analysis of airborne fibers from the Libby, MT mill operation (McDonald et al., 1986a; Langer et al., 1974), these data are not sufficient to provide an alternative set of exposure measurements in TEM units for the Libby worker cohort, or provide a PCM to TEM conversion across the various work environments."

This statement is correct, and thus difficult to reconcile with the statement on 6-23, line 3: "…measures of exposure may be done with methods such as TEM and then adjusted through fiber-counting rules to estimate the number of PCM-countable asbestos fibers. Site-specific environmental conditions should be considered in determining how to best identify PCM-countable asbestos fibers in relevant air samples for exposure assessments used in conjunction with this health assessment to yield estimates of risk." Based on the statement in 6-22 line 31 there is no basis on which this can be carried out and so, of course, there is no attempt to present a procedure. An enormous amount of data is presented in Appendix B regarding TEM methods and results. The relevance of this Appendix to the Toxicological Review and reason for its inclusion is unclear, except that it may appear to support an inappropriate comparison between PCM and TEM data as noted above. The appropriate methodology where a risk assessment is based on PCM data is detailed clearly in NIOSH Method 7402, the use of TEM to adjust a PCM count (PCMe). Other criticism could come from comparing the Marysville, Ohio and Libby materials for consistency in fiber dimensions by electron microscopy (4-30 and C-4), when equivalent optical microscopy of airborne fibers might not be so consistent.

3. Attributing all disease observed among Marysville workers to the Libby amphibole is problematic. EPA points out that some of the Marysville, Ohio workers were exposed to vermiculite from at least several sites, including Palabora, South Africa, Virginia Vermiculite, (Louisa, VA), and Enoree, South Carolina (contains amphibole fibers). Depending on the area being mined at any location, there may have been more, or less, amphibole asbestos fibers contaminating vermiculite.

4. Overall, the document is very confusing, because it discusses numerous analyses and modifications that have no impact on the final result. Suggest paring it down to less than 500 pages and include only relevant material and relevant material from the appendices in the text. Clearly tell the reader what EPA did to arrive at the RfC and do not discuss what EPA decided not to do. As presented now, it raises the question: is the final model correct or with more work would another analyst obtain a more satisfactory model and more attractive RfC? Copyedits

Comments on (Table of) Contents:

General: NIOSH recommends that the numbered outline of contents correspond to the numbered outlined followed in the body. The numbered outline of contents does not correspond to the numbered outline followed in the body of the report.

Minor comments

3.2.3: To matchheadings used for 3.2.1. and 3.2.2, consider replacing "Dermal" with "Dermal Contact".

4.1.2.1: Replace "Geographic-Based Mortality Analysis" with either "Geography-based Mortality Analysis" or "Geographic Mortality Analysis".

4.3: Hyphenate "…ENDPOINT-SPECIFIC…"

4.3.1.1: Delete "the" as follows…. "Hazard Characterization for ~~the~~ Libby Amphibole Asbestos Fibers"

5.4.2: "—with Rationale and Justification" seems redundant. One or the other alone is sufficient.

6: Hyphenate "…EXPOSURE-RESPONSE…" for consistency with its hyphenation in 6.2, 6.2.2, and 6.2.4.

Comments on List of Tables

List of Tables, 4-6, 4-8, and 4-9: For consistency with clinical usage, replace "Pulmonary" with "Chest" when referring to chest radiography.

List of Tables, 4-9: Insert "Marysville, " before OH for consistency with 4.1.

List of Tables, 4-13. Resolve redundancy, perhaps as follows… "Incidence and mortality results for breast cancer and prostate cancer ~~cancers~~ in…"

Check page numbers; some do not correspond with location of the table, particularly Chapter 4's tables.

Comments on List of Figures

Check page numbers; some do not correspond with location of the figure.

Comments on List of Abbreviations and Acronyms

NIOSH suggests enough information be provided to ensure that readers and reviewers understand the meaning of technical terms. The list of abbreviations and acronyms is helpful and a big improvement from previous versions. However, more informative definitions are still needed for some terms. For example, what is the difference between RfC and RfD? Describe briefly how a POD is identified and how it is used. Does its application assume a zero intercept? The reader should not have to find and obtain a background document to understand the risk assessment. What is an IUR? Instead of listing only the words (i.e., inhalation unit risk) that

correspond to the initials, state the meaning of the term. Is it the risk associated with inhaling one unit of an agent? If so, that would be the slope and should be stated on page xiii and again in chapters 5 and 6. While these terms may seem obvious to those who conduct EPA IRIS risk assessments, they are obscure to many readers of this document.

"FVC" is "forced vital capacity" (not "force vital capacity").

"International Agency for the Research of Cancer" (IARC) is "International Agency for Research on Cancer".

"Nf2" is "neurofibromatosis type 2" (not "neurofibromatous 2")

"NIOSH" is "NIOSH National Institute for …" (not "NIOSH National Institute of …".

$PM_{2.5}$: should be an "m" after "μ".

"SAS" should probably not be listed. "SAS" is a trade name (see http://www.sas.com/presscenter/guidelines.pdf) and it is inappropriate to spell it out as "Statistical Analysis Software".

"SEER" should be spelled out with an additional comma, as "Surveillance, Epidemiology and End Results" (see http://seer.cancer.gov/about/SEER_brochure.pdf and line 8 on page 4-11 of the draft).

"SHHF" should be spelled out without hyphenation as "spontaneously hypertensive heart failure".

"SIR" is "standardized incidence ratio" (not "standard incidence ratio").

"SPF" should perhaps be spelled out with additional hyphens as "specific-pathogen-free".

"WKY" would be better spelled out as "Wistar-Kyoto" (not "Wistar Kyoto rat").

"XRCC" would be better listed as "XRCC1" and spelled out as "X-ray repair cross-complementing protein 1".

Comments on the Foreword:

The Foreword (page xv) states that Chapter 6 will cover non-cancer endpoints and reference concentration. However, the lists of tables and figures, and the table of contents of Chapters 1-5, are limited to the cancer assessment. The non-cancer endpoint assessment appears to be added on, even though it is the basis for the RfC.

First paragraph, line 4: Suggest changing "the vermiculite mine <u>in</u> Libby, Montana" to "the vermiculite mine <u>near</u> Libby, Montana"

Comment on Authors, Contributors, and Reviewers

The periods used for punctuating the terminal degrees of two of the individuals listed (Christensen and Kopylev) should be deleted for consistent formatting.

Comments on Chapter 1 Introduction

Minor comments:
Page 1-1, line 33 to Page 1-2, line 1: This sentence would be clearer with a single parenthetical example ("NMRD") without the additional complexity of the unclear phrase "potentially cardiovascular disease". Suggested edit: "There are potential risks of mortality from noncancer disease (e.g. NMRD~~, potentially cardiovascular disease~~)."

Page 1-1, line 34: In citing potential mortality risk from noncancer disease, suggest using asbestosis as an example, rather than NMRD. Rationale: the relative risk of asbestosis associated with the Libby amphibole is much greater than the relative risk of NMRD. Further, smoking-related NMRD will be discounted as due to other cause.

Page 1-3, line 5: "phased" should be "phase"

Page 1-3, line 12: So that it will more logically follow the "pleural and pulmonary" order established on line 11, suggest reordering the parenthetical listing, as follows…. "…~~asbestosis,~~ pleural plaques, asbestosis, reduced lung function…"

Page 1-3, line 15: Define "potency factors." Are these slopes?

Page 1-3, line 18: Add "for lung cancer and mesothelioma respectively" or other explanation for the two lifetime risk estimates.

Page 1-3, line 20: "…and the age of onset of exposure…" should be "…age at onset of exposure…".

Page 1-3, lines 22- 24: Suggest telling the reader how to interpret the IUR (inhalation unit risk)—i.e., "An IUR of 0.23 can be interpreted as a 23% increase in lifetime risk of dying from mesothelioma or lung cancer with each 1 fiber/cc increase in continuous lifetime exposure."

Page 1-4, line 3: Suggested clarifying edit: "…on workers ~~in mines without~~ who mined and processed ore with no significant amphibole fiber ~~contamination~~ content."

Page 1-4, line 6: Suggested edit: "…exposures to ~~asbestos~~ fibers…".

Page 1-4, lines 18-19 "to other amphibole mineral fibers": The definition of mineral fiber in this statement is unclear, since the preceding sentence refers to "a complete range of morphologies from prismatic crystals to asbestiform fibers". Does fiber in this context then include "prismatic crystals" or only "asbestiform fibers"?

Table 1-1. Is this table showing total deaths/100,000 from the cause, or total excess deaths/ 100,000?

Comments on Chapter 2 Geology, Use, and Exposure Potential

Minor comments:

Chapter 2 In discussing the composition of the Libby vermiculite in this chapter, acknowledge the presence of quartz (Meeker et al., 2003).

Page 2-1: Suggest that the 2nd and 3rd paragraphs on this page be ordered so that the processes are described in the order they occurred. Exfoliation should be described at the end of the processes.

Page 2-1, line 14: Suggest editing to make clear that asbestosis is a type of NMRD.

Page 2-1, line 14: Suggest replacing "pleural anomalies" with "pleural abnormalities". While the former term is not wrong in this context, the latter term is used in the ILO classification system for characterizing pleural findings seen on chest radiographs.

Page 2-1, line 20: The primary commercial product from the Zonolite operation was vermiculite concentrate. Ore was taken from the mine, but not sold as such. In the mill, the ore was ground or crushed into concentrate (also releasing fibers through the mill stack, contaminating the town), sized in the screening plant, and concentrate of various sizes was sold. For the most part, the concentrate was loaded onto railroad cars and sent to other locations for exfoliation. Some vermiculite was exfoliated in Libby as well.

Page 2-1, line 24: The word "contaminated" is misleading. Also, at this point in the process one is not talking about "product." Suggested edit: "Since the vermiculite ~~product was contaminated with~~ ore contained fibers…"

Page 2-1, lines 25-27: Here again, it is misleading to suggest that "contamination of the finished product" was the result of release of fibers during the expansion of vermiculite. Also, fibers were released by more than just the thermal expansion process. Suggested edit: "…fibers were released during this ~~energetic~~ and other kinetic processing of the ore and product, ~~potentially~~ exposing workers. Because fibers remained in the processed ore, ~~in and resulting in asbestos contamination of~~ even the finished product sold to consumers contained Libby Amphibole asbestos."

Page 2-1, lines 31-33: NIOSH recommends clarification. The "then" in line 33, following as it does a paragraph that focuses on exfoliation, implies a temporal sequence in which the vermiculite was all exfoliated in Libby before shipping. But, as the rest of the sentence makes clear, most was shipped before exfoliation. In any editing of this sentence, it could be made clear that some of the product was exfoliated in Libby for local use, but most was "loaded onto railcars and transported across the country and elsewhere to expansion plants where it was exfoliated and distributed locally." Note the suggested "and elsewhere" because substantial quantities were shipped elsewhere in North America (and apparently even to Hawaii per a later table in this document).

Page 2-1, line 33 to Page 2-3, line 12: this sentence needs grammatical editing.

Figure 2-2 (page 2-2), legend: suggested clarifying edits… "Expanded vermiculite (a) ~~used as a soil conditioner (a) or~~ and vermiculite attic insulation (VAI) shown in place between ceiling joists (b)."

Figure 2-3 (page 2-3) legend: format (use of upper case lettering) is not consistent with legends of other figures.

Page 2-4, line 3: suggested edit: "…the mineral fibers ~~specific to~~ in Libby Amphibole asbestos." (Not necessary to imply that interest should be focused only on fibers specific to Libby Amphibole asbestos, rather than on the complex of fibers in Libby Amphibole asbestos, including those that are not specific to Libby Amphibole asbestos.)

Page 2-4, lines 18-20: sentence needs knowledgeable editing (i.e., what isn't said here is that ~95% of the Earth's crust is represented by igneous rocks and that sedimentary and metamorphic rocks also contain silicate minerals. Is this what the writers attempted to convey?)

Page 2-4, line 19: "mean" should be "means"

Page 2-4, lines 21-22: the first sentence states that some silicates are insoluble. The second sentence goes on to state that (even in acid) they are not easily soluble, meaning they are not entirely insoluble. Suggestesolving the apparent conflict between these two statements.

Page 2-4, line 25: what is a "hard" silicate?

Page 2-4, lines 25-26: mention of "secondary silicates" warrants mention of primary silicates so that readers who are unfamiliar with this terminology will gain a basic understanding.

Page 2-6, lines 15-17: Suggested edit…. "Chrysotile is also a sheet silicate, ~~but can~~ presenting with an asbestiform morphology ~~where~~ with the sheets ~~role~~ rolled into fibrils, forming asbestiform fibers." (This suggested edit fixes the inappropriate homophone "role", but more importantly, makes clear that the rolled-sheet form is the form in which chrysotile occurs, differentiating it from, for example, non-asbestiform lizardite and similar serpentines.

Page 2-6, lines 15-18: The phrase "such as fibrous versus crystalline" inappropriately implies that "fibrous" and "crystalline" are mutually exclusive terms. Fibrous minerals (even cleavage fragments) are always crystalline.

Page 2-7, lines 19-28: To avoid potential reader confusion, should all occurrences of "solution series" be replaced with "solid solution series"? (Otherwise, the reader is confronted with two terms —"solution series" and "solid solution series" — and does not know what distinguishes them.)

Page 2-7, lines 24 and 26: For clarity, suggest replacing "mineral content" with "elemental composition".

Figure 2-5 (page 2-8) would benefit from color.

Figure 2-6 (page 2-9): Is vermiculite ore sample what the writers meant to convey? NIOSH recommends clarification.

Page 2-9, line 11: The phrase "crystalline or massive form" inappropriately implies that "crystalline" and "massive" forms are mutually exclusive.

Page 2-9, line 12: NIOSH recommends clarification. "The long, slender, hairlike fibers of commercial asbestiform minerals are visual to the naked eye". Individual crystal fibers of asbestos (sometimes termed "fibrils") are invisible to the naked eye. These visible (not "visual") fibers are actually bundles. The term fiber, when used interchangeably between microscopic individual crystals and macroscopic bundles of crystals leads to confusion.

Page 2-9, lines 12-17: NIOSH recommends defining "fiber" and "fibril." First, "visual" should be replaced by "visible" and this and the subsequent sentence could be edited for clarity. Some (bundled) fibers of commercial asbestos are visible to the naked eye, but not all fibers of commercial asbestos. In fact the more slender the fiber, the less likely it is to be visible to the naked eye.

Page 2-9, line 17: temperature and pressure are only two of the parameters that may affect crystalline habit. Others are the local stress field and solution chemistry including gradients of concentration and pH in the fluid from which the crystals form. NIOSH recommends mentioning other parameters.

Page 2-9, line 18: should explicitly state here or earlier that chrysotile asbestos is a serpentine mineral.

Page 2-9, line 18: Suggested edit…. "The morphology of ~~A~~amphibole fibers ~~morphology~~ is more complex than that of serpentine ~~asbestos~~ fibers.

Page 2-9, lines 19-20: The wording "…a crystalline structure (massive) or is fibrous…" seems to inappropriately imply that "crystalline" and "fibrous" forms are mutually exclusive.

Page 2-9, line 21 to page 2-10, line 1: Again, the wording "…including not only the asbestiform, but also, fibrous, acicular, and prismatic" is confusing and warrants knowledgeable editing.

Page 2-9, line 20 "a crystalline structure (massive) or is fibrous": again, fibrous is crystalline.

Page 2-9, line 21 "not only the asbestiform, but also, fibrous": Asbestiform has already been stated to be comprised of fibers, so therefore must be "fibrous".

Page 2-10, lines 4 through 10: although these definitions are from a geology textbook, they should be avoided. Both "acicular" and "fibrous" refer to "needlelike". "Asbestiform" is defined as "fibrous" (or, worse, like asbestos, which is the circular reasoning already referred to). The overlapping nature of the three definitions of three terms is not helpful.

Page 2-10, line 13 “Fibers, crystals, and cleavage fragments”: again fibers are crystals. What is meant here is “Fibrous, prismatic and acicular crystals, and cleavage fragments”.

Page 2-10, lines 3-18: these two paragraphs could benefit greatly from editing by a subject matter expert.

Page 2-10, line 15: replace “fibers” with “particles”.

Section 2.2.2 (begins on page 2-10): note that a vermiculite particle on edge could look like a fiber under the optical microscope.

Page 2-11, lines 20-21 state “For the purposes of this document, the material from this mine will be called Libby Amphibole.” This statement warrants editing to make clear that what is referred to here is not all material from this mine, but rather the amphibole material from this mine. Also, it is not clear why the authors of the draft did not use “Libby Amphibole asbestos” rather than “Libby Amphibole” in this sentence. “Libby Amphibole” rather than “Libby Amphibole asbestos” is used on Page 2-14, lines 11 and 17. (Also see comments in first section “Comments on the overall document”.)

Page 2-11, line 21: for clarity, suggest edit… “Libby Amphibole asbestos is in the tremolite subgroup <u>of amphiboles</u> and historically…”

Page 2-12, line 11 and elsewhere: suggest consistency in using (single word) “endmember” or (two-word) “end member” or (hyphenated) “end-member”. (At least two of these three alternatives are used in the draft document.)

Page 2-12, line 15: “International Mineral Association’s” should be “International Mineralogical Association’s”.

Page 2-12, lines 11 to page 2-13, line 4: for clarity, it may be helpful to replace “the solid solution series” with “the three solid solution series” to clarify that what is being referred to in the context of Libby amphibole is not a single series but several series. (Right?)

Page 2-13, line 8: suggest inserting a comma after “fiber”.

Page 2-13, line 9: replace “Leaky” with “Leake”.

Page 2-13, line 16: replace “Meeher” with “Meeker”.

Page 2-13, line 29: for clarity, consider replacing “individual fibers” with “individual fibrils”.

Page 2-13, line 30: for clarity, consider replacing “fiber types” with “fiber morphologies”.

Page 2-14, line 13: suggest hyphenating “winchite richterite” as “winchite-richterite” in this context.

Page 2-14, line 7: suggest being less absolute in this statement, perhaps along the lines of… "…~~all~~ an overwhelming majority of these fibers are respirable".

Page 2-14, lines 17-18: NIOSH recommends clarification. Did the Marysville plant use Libby grade 3 ore? If so, this point should be included.

Page 2-14, line 23: replace "Appendix F" with "Appendix C". (Suggest rechecking to assure that, throughout the document, cited appendices are the appropriate appendices to cite.)

Page 2-14: The Marysville, Ohio facility has used vermiculite from various locations from the 1950s until 2000. As documented in Appendix C and elsewhere, we know that the Enoree vermiculite may contain amphibole. Samples from Palabora and Louisa, Virginia obtained in 1980 may, or may not, be representative of samples that might be obtained from another location in these mines in any other year. The amphibole fiber content in vermiculite ore varies not only by mine, but also by area (and depth) within the mine that was being mined when the sample was obtained. While descriptions of the amphibole composition taken from any of the mines (including Libby) are of interest, they should not be used as the basis for an assumption that all asbestos-related disease observed among Libby workers is due to the Libby amphibole. Such an assumption would need to be justified by data showing absence of amphibole fibers in representative samples of all batches of vermiculite (from various locations) used at Marysville over the roughly 40-year period.

Figure 2-9 (page 2-16), legend: suggest replacing the second sentence of this legend with something similar to the clearer sentence on page 2-13, lines 26-28.

Section 2.3 (begins on page 2-19): note that it is not possible to make a comparison between transmission electron microscopy (TEM) counts of structures longer than 0.5 µm and phase contrast microscopy (PCM) counts of fibers longer than 0.5 µm even when the difference in width resolution is taken into account. This is because particles shorter than 5 µm have a low probability of being recognized as fibers in PCM, even when they have a 3:1 aspect ratio. Also note that 0.25 µm is very likely an overestimation of the minimum width observable under PCM. The width limit for visualizing amphibole asbestos under PCM may be closer to 0.05 µm.

Page 2-19, line 31 "PCM fiber counts include nonrespirable fibers". Does EPA want to limit the discussion to respirable fibers? Thoracic-size fibers are generally included in asbestos exposure assessments. Also, this is not very significant. The asbestos cassette operates like a vertical elutriator and generally provides a sample close to the thoracic (or PM 10) convention. Since fiber width generally controls aerodynamic diameter, a width of 3 µm (as in the WHO method) can be used to omit particles that would not reach the thoracic airways, but in practice the percentage of fibers omitted by this method is very small.

Page 2-20, line 2 misses a substantial concern when using PCM. As stated in the NIOSH Asbestos Roadmap (p. 63; the document is cited by EPA): "Individual asbestos fibrils range in width from <10 nm (0.01 µm) for chrysotile up to 40 nm (0.04 µm) or more for amosite. Thus, individual asbestos fibrils are not likely to be visible by PCM. Early studies suggested that asbestos particles of 3:1 aspect ratio and longer than 5 µm are not usually individual fibrils but fibrillar bundles that are much wider than fibrils [Hwang and Gibbs 1981; further data cited in

Walton 1982], so that the number of particles meeting these criteria counted under PCM were not generally found to differ greatly from the number of particles meeting the same criteria counted under the electron microscope [Lynch et al. 1970; Hwang and Gibbs 1981; Marconi et al. 1984; Dement and Wallingford 1990]. However, more recent studies suggest there is a substantial difference between counts of particles seen by PCM and TEM [Dement et al. 2009], and the importance of these differences in developing new methods to be used routinely for industrial hygiene surveys will be important to reconcile with the particle characteristics important in disease causation." So, although PCM has been used for asbestos exposure assessment, it is not necessarily a good surrogate because the ratio of countable to non-countable particles varies depending on the source, and thus the actual risk may be under- or over-estimated by PCM.

Sections 2.4.1 (Libby Community) through 2.4.3: these sections describe results of airborne fiber exposure assessments taken in Libby, Montana and other communities where Libby vermiculite was used and an assessment of potential exposures from the handling of Zonolite vermiculite attic insulation. Exposures are reported as f/cc "asbestos PCMe fibers". When possible, additional information should be given as to whether fibers were identified (e.g., winchite, richterite, tremolite) when analyzed by transmission electron microscopy (TEM). If no specific mineralogical analysis was performed, an explanation should be given to support the reporting of "asbestos" exposures.

Minor comments:
Page 2-21, lines 20-21: suggested edit: "…consumer products containing vermiculite mined near Libby ~~are contaminated with the~~ contain Libby Amphibole asbestos."

Page 2-21, line 21: NIOSH suggests editing for sentence verb tense. Why write "may have been exposed" when exposures may still be occurring (as mentioned in the subsequent sentence)?

Page 2-21, lines 30-31: insert "more" between "in" and "activities"

Page 2-21 line 35 to Page 2-22 line 1: suggested edit: "…some adult activity patterns, such as gardening and home repair, may also result in increased exposures~~, such as gardening and home repair,~~ where Libby Amphibole asbestos may be present."

Page 2-22 lines 3-4: suggested edit: "…and where available, exposure measurements are given for various exposure environment and activities."

Page 2-23 line 4: replace "states" with "state" (i.e., memoranda … state).

Page 2-23 line 8: replace "from" with "involved in".

Page 2-23, paragraphs beginning on line 9: NIOSH suggests clarification. The subject of this document is "Libby Amphibole asbestos," which may encompass more than what has traditionally been regulated as "asbestos." Here, the document provides asbestos measurements; however, it does not specify whether the measurements are for what has traditionally been regulated as "asbestos" or for what this document refers to as "Libby Amphibole asbestos."

Page 2-26, line 20: suggested edit: "~~while~~ during the period of years when Libby vermiculite was being exfoliated in Marysville."

Page 2-26, line 20: suggested edit: "It is estimated that 80% of the vermiculite used in the United States, ~~and~~ including consumer products ~~include~~ such as Zonolite vermiculite attic insulation (VAI) and potting soil amended with expanded vermiculite, came from the mine in Libby, MT."

Page 2-27, line 3: suggested edit: "in the ~~both the~~ living space of the homes as well as the attic space."

Page 2-27, line 17: suggested edit: "Libby Amphibole ~~asbestos-contaminated~~ asbestos-containing VAI…"

Page 2-27, line 23: regarding "the asbestos-contaminated VAI", see preceding suggested edit.

Section 2-4 tables: whenever concentrations of fibers or structures are presented in any table, the criteria for defining fiber or structure should be include in a footnote. This is important because various criteria are used.

Comments on Chapter 3Fiber Toxicokinetics

Table 3-1 (page 3-5): NIOSH disagrees with the information in this table. Five (5) µm aerodynamic diameter particles can certainly penetrate below the nasopharyngeal region. In addition, a 1986 reference is used when the updated ICRP deposition model of 1994 is available (and referenced in this document). In general, there is no reference to the impact of particle density on the calculation of aerodynamic diameter. For minerals with a density higher than quartz (2.67), a fiber physical diameter of 3 µm is approximately equal to an aerodynamic diameter of 10 µm and a physical diameter of 1 µm is approximately equal to an aerodynamic diameter of 3 µm.

Figure 3-1 (page 3-1): This figure seems to be copied from a dated ICRP report. One minor error that could be readily "fixed" would be to replace "sputum" with "mucus/phlegm" and then place "sputum" above that box with an arrow analogous to the arrow leading to "feces" from the gastrointestinal tract. One does not swallow sputum; rather, one swallows mucus/phlegm or coughs it out as sputum.

Page 3-2, lines 7-8: "…document a large percentage of respirable fibers as well as fibers <5um-long" is unclear. Why is "as well as fibers <5um-long" in this sentence?

Page 3-3, lines 14-17: The basic description of respiratory tract components, described as "upper respiratory tract", "respiratory airways" and "lungs", is confusing. For example, all structures listed as components of the "upper respiratory tract" are, in fact, themselves respiratory airways. Also, the listed components of the "respiratory airways" are not "respiratory" in the sense that, say, "respiratory bronchioles" (which encompass some alveolar structures) are functionally

"respiratory." Finally, bronchioles are included in the draft's description in both "respiratory airways" and "lung" components. Consider alternative ways to describe components of the respiratory tract. One way might be physiological, to include upper (located in the head and neck) and lower (located in the chest) conducting airways and gas-exchange (located in the deep lung) regions. Another way that may be more appropriate to the issue of particle deposition might be the upper conducting airways in the head/neck (nose, mouth, pharynx), the thoracic conducting airways in the chest (trachea, bronchi, conducting bronchioles), and the gas-exchange region of the lung (respiratory bronchioles, alveolar ducts, and alveoli).

Minor comments:
Page 3-3, line 27: Replace "transmitting airways" with "conducting airways". This term is rarely used. A Google search found three "hits" on the former term compared to nearly 3.5 million for "conducting airways."

Page 3-3, line 32: Suggest replacing "to" with "in" and also replacing "conductive airways" (just over 3,000 hits on Google) with "conducting airways" (1000 times more hits on Google).

Page 3-4, line 2: Suggest deleting "the".

Figure 3-1: the "larger branches of the lung" and "smaller branches of lung" seem unnecessarily aimed towards laymen. (The lung, per se, does not have branches.) NIOSH suggests deleting the entire Table 3-1.

Page 3-6, line 6: Suggest inserting "statistical" before "modeling".

Page 3-6, line 24: replace "take" with "takes" (i.e., model takes).

Page 3-6, line 35: suggested edit: "…when ~~reviewing~~ comparing results of inhalation studies ~~between~~ conducted in different species."

Page 3-7, line 2: "branched bifurcations" is redundant. Suggested edit: "…which ~~have branched bifurcations with~~ serially bifurcate into airways of decreasing internal diameters."

Page 3-7, line 4: for clarity, delete "then farther to the".

Page 3-7, lines 6-7: "cause fibrogenesis" is somewhat redundant. Suggested edit for clarity: "…conducive to deposition ~~at~~ in the ~~primary or secondary~~ bronchioles and alveoli can cause ~~fibrogenesis~~ pulmonary fibrosis and…"

Page 3-7, lines 8-9: the parentheses seem illogical in this context and should be deleted.

Page 3-7, line 14: suggest deleting "deep lung". (All alveoli are "deep lung").

Page 3-7, line 15: should "Deposition" be "Alveolar deposition" in this context?

Page 3-7, line 20: should the "tissue" here be "pleural tissue" (or perhaps "malignant pleural tissue") to distinguish it from the aforementioned "lung tissue"?

Page 3-7, line 31: suggested edit: "In general, ~~fibers are expected to share patterns~~ the pattern of deposition for fibers is expected to have some similarities ~~similar~~ to ~~those~~ the well-studied deposition pattern for essentially spherical particles~~ which is well-studied~~."

Page 3-8, lines 2-4: suggested edit: "~~However, although~~ Though this model has not been fully developed for fiber deposition, ~~due to similarities with particle deposition this~~ it can be used to inform deposition of fibers."

Page 3-8, lines 29-30: suggested edit: "Some of these mechanisms, such as dissolution of the fibers~~,~~ or removal via the mucociliary apparatus, may result in…"

Page 3-8, line 33: replace "transbroncheolar space" with "peribronchiolar space".

Page 3-8, lines 33-34: suggested edit… "…and pleura ~~of the lungs~~…". Alternatively, if the intent is to exclude the pleural surface lining the chest wall, "…and parietal pleura ~~of the lungs~~…".

Page 3-9, lines 1-4: "…throughout the pulmonary and extrapulmonary tissues, as well as other organs, including the brain, kidney, liver, and ovaries" is unclear and should be revised. (All the listed "other organs" represent "extrapulmonary tissues.")

Page 3-9, line 4: suggest replacing "is" with "was". (This refers to papers published in the past.)

Page 3-9, line 9: suggest replacing "increased" with "longer" (to avoid the potentially confusing "increased clearance" wording that would have the opposite meaning).

Page 3-9, line 11: delete "range of the".

Page 3-9, line 20: delete "Large" and begin sentence with "Fibers…". (Small fibers deposited in the nasal passages can also be removed by physical clearance.)

Page 3-9, lines 21-35: suggested edit… "When breathing occurs through the nose, many fibers are filtered by the turbulent airflow in the nasal passages, impacting against the hairs and nasal turbinates, as well as becoming entrained in mucus in the upper respiratory tract where they can be subsequently removed by mucociliary action or by reflexive actions such as coughing or sneezing. ~~Fibers can also translocate due to physical forces associated with respiration (Davis, 1989). Fibers with aerodynamic characteristics that cause them to impact at the nasopharyngeal or tracheobronchial regions of the respiratory tree are likely to be quickly removed (in minutes or hours) by the action of the mucociliary escalator.~~ The mucociliary escalator removes fibers through ciliary movement of the sticky mucus lining (Churg et al., 1989; Wanner et al., 1996). Fibers removed from the ~~pulmonary space~~ conducting airways through this mechanism are ~~either~~ coughed out, or ~~subsequently~~ swallowed and enter the digestive tract where they may adversely affect ~~the~~ gastrointestinal tissue, enter the ~~body via the~~ blood stream, or be excreted. Clearance of fibers via ~~this mechanism~~ mucociliary action is rapid and is usually complete within minutes or hours. However, the mucociliary escalator extends only down to the level of the terminal

bronchioles ~~of the respiratory tree~~ and not to the alveoli. Therefore, particles that reach ~~these deeper regions~~ the alveolar region of the lung cannot be cleared through this process. Fibers can also translocate due to physical forces associated with respiration (Davis, 1989)."

Page 3-10, lines 4-6: "Available data indicate prolonged clearance from the lung of longer serpentine chrysotile fibers (>5 μm) or either long (>5 μm) or short amphibole fibers (Coin et al., 1994; Tossavainen et al., 1994)." This statement is complex and potentially confusing. For clarity, it should be revised with a clear focus on clearance of amphiboles (because there is no chrysotile in "Libby Amphibole asbestos").

Page 3-10, line 7: suggested edit for clarity: "…for long vs. short amphibole fibers…".

Page 3-10, lines 10-11: suggested edit for clarity: "…urge caution in excluding, based on their length, any population of fibers ~~based on their length,~~ from consideration as possibly contributing to the disease process…"

Page 3-10, line 12: should "Libby Amphibole" be "Libby Amphibole asbestos"? More importantly, by specifying either of those possible descriptors, this sentence wrongly implies that there is data available from some other type of asbestos fiber "to resolve the issue about short or long fibers". Consider editing carefully the last two sentences in this paragraph.

Page 3-11, line 8: replace "invasive" with "deposited".

Page 3-11, line 9: suggest replacing "bronchoalveolar epithelium" with "alveolar epithelium" (not to say that alveolar macrophages do not transport fibers through the brachial epithelium, but this would occur much less commonly in light of the layer of mucus lining that epithelium.

Page 3-11, lines 18-21: suggested edit: "These processes include death or dysfunction of ~~phagocytes~~ macrophages due to ~~ingestion~~ phagocytosis of an excessive number of particles (often termed "overload") or highly reactive ~~fibers,~~ particles ~~due to a high burden of deposited fibers (overload)~~, or ~~an~~ attempted phagocytosis ~~by the macrophages to engulf~~ of fibers of lengths that exceed the dimensional capacity of the macrophage ~~length~~ (often termed "frustrated phagocytosis") (NIOSH, 2008)."

Page 3-11, lines 24-32: suggested edit… "Fibers that are too large to be easily engulfed by the alveolar macrophage can stimulate the formation of "asbestos bodies." Asbestos bodies are fibers that ~~are~~, during prolonged residence in the lung, have become coated with proteins, iron and calcium oxalate. Due to their iron content, histological stains for iron have long been used to identify them in tissue; thus, they are sometimes called "ferruginous bodies." The mechanisms that result in the formation of asbestos bodies are poorly understood, although most appear to be formed around amosite fibers (Dodson et al., 1996). The iron in the coating, however, is derived from the asbestos fiber, cells, or medium surrounding the fiber and can remain highly reactive (Ghio et al., 1992; Lund et al., 1994). ~~These bodies are sometimes referred to as "ferruginous" bodies because of their affinity for iron-loving histological stains~~. ~~Ferruginous~~ Asbestos bodies can remain in the lung throughout the lifetime of the exposed individual. Asbestos bodies comprise a minor portion of the overall fiber burden of the lung, and, after the fiber is fully

coated, these fibers might or might not participate directly in asbestos disease. The presence of iron in the coating, however, could provide a source for catalysis of reactive oxygen species similar to that observed with fibers." (This edit moves the alternate name (ferruginous body) earlier in the paragraph, right after iron is first mentioned. It mentions that alternative term only once, sticking otherwise to "asbestos bodies." Also, it seems unconventional to present this as a component of the tissue having affinity for the stain. A more conventional way to present tissue staining is that a specialized stain has affinity for a specific component of the tissue, in this case iron.)

Page 3-12, lines 2-3: suggest fixing run-on sentences.

Page 3-12, lines 4-5: "Fibers have been measured in extrapulmonary tissues including lung parenchyma, pleural plaques, and mesothelial tissue…" is confusing. Lung parenchyma is not extrapulmonary; it is intrapulmonary.

Page 3-12, line 32: suggested edit: "…textile and mining workers from South Carolina and Quebec, respectively, to better…"

Page 3-13, line 1: "…number of tremolite fibers [*in what?*] was higher than…?

Page 3-14, line 13: suggested edit: "…oral ~~or~~ and dermal…"

Page 3-14, line 14: suggested edit: "…route of human exposure to mineral fibers…"

Page 3-14, line 19-20: "The deposition location within the respiratory tract and extrapulmonary sites…" should be edited for clarity. Some of the respiratory tract, as correctly described in an earlier section of the document, is extrapulmonary.

Page 3-14, line 21: suggested edit: "Fiber clearance from the respiratory tract can occur through physical ~~mechanisms like coughing and sneezing, or~~ and biological ~~mechanisms including translocation~~." (This edit avoids redundancy. Deleted details are provided later in the paragraph.)

Page 3-14, lines 28-29: suggested edit: "…Multiple fiber characteristics (e.g., dimensions, density, and durability) play a role in the toxicokinetics of fibers ~~(e.g., dimensions, density, and durability)~~."

Page 3-14, lines 30-31: suggested edit: "…and asbestiform tremolite, ~~another~~ an amphibole fiber that comprises part of…"

Page 3-14, lines 4-6: suggested edit: "The adverse health effects observed in humans are supported by results of the available ~~Libby Amphibole asbestos~~ experimental animal and laboratory studies of Libby Amphibole asbestos."

Comments on Chapter 4 Hazard Identification of Libby Amphibole Asbestos

Chapter 4 is very well-written.

Page 4-1, line 17: suggest deleting "the".

Page 4-2, line 25: suggest placing "Metsovo lung" in quotes.

Page 4-3, line 6 states that Sullivan has "updated the National Institute of Occupational Safety and Health (NIOSH) cohort," without having made clear that the earlier Amandus study was the initial NIOSH cohort study.

Page 4-3, line 18: it would be more accurate to refer to the Libby mine as an open pit mine, or a surface mine. Strip mining is another type of surface mining, but different from an open pit mine.

Page 4-3, lines 25-26: "Tank cars were used from 1950–1959 and then switched to enclosed hopper cars in 1960." How important is this information? What type of car was used prior to 1950? Perhaps this sentence can be deleted without losing any critical information.

Page 4-3, line 27: should use past tense, as these operations ended decades ago.

Page 4-3, line 34: suggest deleing "away from the shop area around the mill".

Page 4-3, lines 2 and 4: suggest inserting "ore" before "concentrate" on each of these lines."

Page 4-6, lines 15-16: "…~~phased~~ phase contrast microscopy (PCM)~~, which~~ to visually ~~counts~~ count fibers…" . Also, should the ">3" on line 16 be ≥3" (i.e., greater than or equal to 3, which is the aspect ratio criterion described in the NIOSH REL for asbestos)?

Page 4-6, line 19: "…considered the limit of resolution for fiber width…"

Page 4-8, line 20: correct misspelling ("mineralology" [sic])

Page 4-9, line 2: "…~~phased~~ phase contrast microscopy…"

Page 4-9, lines 5-6: "…having an aspect ratio greater than 3:1 (Edwards and Lynch, 1967; NIOSH method 7400)." In fact the NIOSH criterion for aspect ratio is greater than or equal to 3. (see 18.a(2) under "Measurement" in NIOSH Method 7400.)

Table 4-3 (page 4-9): the title or footnote should specify that these are counted (not all) fibers, and provide the NIOSH Method used in counting.

Page 4-10, lines 33-34 state "a more limited range of diagnostic codes…" Suggest using the phrase "more specific cause of death codes…." instead. First, there are differences between ICD cause of death codes and ICD diagnostic codes. More important, though, is the change of "limited range" to "specific," as restricting the lung cancer analysis to the appropriate ICD cause codes is a strength, not a limitation. Although laryngeal cancer has been associated with asbestos in some studies, there were no laryngeal cancer deaths through 1999 in the Libby

occupational cohort, thus including extraneous causes in the SMR analysis increases the denominator, decreasing the SMR. This makes very little difference in the cancer analysis, but a vast difference in the accompanying non-malignant respiratory disease analysis, as can be seen by comparing McDonald et al. 2004 to Sullivan 2007. Another consideration is pleural cancer, which is a respiratory cancer. Mesotheliomas were often coded as pleural cancer pre-1999. Sullivan analyzed pleural cancer separately from lung cancer. McDonald's SMR analysis included pleural cancer in the respiratory cancer category for the SMR analysis.

Page 4-11, line 1: the years covered by ICD-9 were 1979-1998. The ICD codes used in the Sullivan 2007 publication (1960-2001), a function of the NIOSH LTAS categories for which comparison rates are available, were:

Cancer of the trachea, bronchus, and lung:

ICD-7 1960-1967: 162.0-162.1, 162.8, 163

ICD-8 1968-1978: 162

ICD-9 1979-1998: 162

ICD-10 1999-2001: C33-C34

Pleural cancer:

ICD-7 1960-1967: 162.2

ICD-8 1968-1978: 163.0

ICD-9 1979-1998: 163

ICD-10 1999-2001: C38.4

The analysis considered all respiratory cancers, but the publication focused on respiratory conditions associated with asbestos exposure from which Libby workers experienced excess deaths. There were no deaths attributed to laryngeal cancer during the relevant time period, although that is a condition sometimes linked to asbestos exposure. It would be more appropriate to use mortality data from NCHS, rather than incidence data from NCI, when discussing the effect of including laryngeal cancer mortality in the respiratory (lung) cancer mortality analysis.

Minor comments

Page 4-11, line 4: McDonald et al. [1986a] coded death certificates to ICD-8.

Table 4-4, column 2: McDonald et al. [1986a] did not obtain cause of death from the National Death Index (NDI), although McDonald et al. 2004 did. The NDI began with 1979 deaths. Earlier deaths were coded to ICD-8 by a nosologist, directly from death certificates that had been obtained from the states. They were not obtained from NDI. Punctuation in the table does not make the distinction clear.

Page 4-4, beginning of section 4.1.1.2: very nice description of job exposure matrix development.

Table 4-1, column 1 (page 4-5): ATSDR assembled the cohort from WR Grace records provided by EPA Region 8, rather than from NIOSH records. Their exposure assessment (column 2) was based on Amandus (NIOSH).

Page 4-14, line 13: again, not all cause of death data was obtained from NDI (see above).

Page 4-15, lines 16-17: while the company did obtain some of the smoking data, many of the surveys appear to have been administered by the local hospital—i.e., contractors performing the X-rays. In addition, NIOSH collected smoking data via telephone from families of a few former workers. Check Amandus and Wheeler [1987] to see if they actually attribute all smoking data to company surveys.

Page 4-16, line 1: NIOSH study records available to EPA clearly demonstrate the questions that were used to obtain smoking information.

Page 4-16, line 2: this difference in smoking rates would only be of concern in the internal analyses (McDonald et al. 2004, Sullivan 2007, Larsen et al. 2010) if there were evidence that smoking rates differed with exposure level. In fact, such differences did occur, based on analysis of the existing smoking and exposure data.

Page 4-17, lines 9-10 state "comparison data were based on multiple causes of death data (1960 to 2002)." The dates appear to be inaccurate, particularly given the follow-up accurate statement that comparison data were only available for the period 1999+.

Page 4-17, line 31: remove "et al."

Page 4-17, line 35 to 4-18, line 1. Suggest reexamining the relevant tables. Larson et al. 2010a, Table 4-5, does not demonstrate a plateau in risk estimates for any outcome using the cut-points published in the table. It is questionable if Sullivan 2007 demonstrates a plateau for lung cancer, as the estimators increase monotonically with increasing cumulative exposure and duration of employment. The estimators do not level or decrease; the pattern observed in occupational studies, and frequently attributed to the healthy worker survivor effect, involves a decrease in estimators for the highest exposure group.

Page 4-20, line 25 states that x-rays were taken as part of a study examination. Specify which study took radiographs—i.e., McDonald. Provide citation. Amandus did not take radiographs, rather used existing worker screening films.

Page 4-20, line 21: Suggest replacing 4.1.1.4.3. heading of "Radiographic anomalies" with a more conventional "Radiographic abnormalities". The ILO classification system used for all studies covered in this section (except for the Whitehouse study) uses the term "abnormalities".

Page 4-20, lines 22-23: Suggested edit… "…showing pleural ~~thickening and anomalies~~ and parenchymal abnormalities in the Libby, MT worker cohorts and patients in one clinical practice who were exposed to Libby Amphibole asbestos." (Whitehouse's study was not on a Libby worker cohort.)

Page 4-20, line 30: Suggested edit… "…was independently read by…"

Page 4-20, line 31: Recheck Amandus' paper. It is misleading to state that "consensus readings" were used for any determination if the readings done for the Amandus study were independently done. (In consensus reading, the readers get together decide how to classify the films.) Suggested edit… "~~Consensus readings were~~ For the analysis, classification indicating pleural abnormalities by at least two of the three readers was used ~~for~~ to determine the presence of pleural ~~findings~~ abnormalities, while the median reading was used to determine the profusion category of small opacities."

Page 4-20, lines 33-35: Suggested edit… "In the McDonald et al. (1986b) study, ~~there was 90% agreement among~~ all three readings agreed for about 90% of ~~readers that the on~~ chest x-rays ~~contained~~ that showed evidence of pleural calcification, obliteration of the costophrenic angle, and pleural thickening on the diaphragm. Similarly, ~~and~~ all three readings agreed for about 80% ~~agreement that there was~~ of chest x-rays that showed evidence of small opacities, pleural plaques, ~~and~~ or diffuse thickening."

Page 4-21, line 2: NIOSH suggests clarification "the overall difference of 6% in the prevalence of opacities". Is the difference between categories? More likely between readers (check Amandus' paper.)

Table 4-6 (page 4-21) title: Suggested edit… "~~Pulmonary~~ Chest radiographic studies…"

Table 4-6 content: the Whitehouse study, while of interest, was not scientifically rigorous. Suggest deleting the Whitehouse results under "Average yearly loss (n = 94 with worsening lung function)". The stratification done to obtain this subset of lung function decline results was not on the degree of pleural abnormality, but rather on lung function decline. In this sense, these particular results are rather silly.

Table 4-6 content: regarding the Larson study, "B raters" should be "B readers". Also, did the Larson study really use consensus panel readings? (A "consensus panel" reading would have the readers together come to a single reading.) Or did the Larson study use independent readings, using them to come to a final determination about pleural abnormalities based on whether the independent readings were in agreement in some specified way(s)?

Page 4-22, line 4: suggest replacing "anomalies" with "abnormalities."

Page 4-22, line 16: suggested edit: "…McDonald et al. (1986b)…"

Page 4-22, lines 19 and 21: should the "unit increase in cumulative exposure" be specified?

Page 4-22, line 33 to Page 4-23, line 2: "The subset of 94 patients who experienced a loss of FVC was characterized as the group with worsening lung function. Among this group, the average yearly loss was 3.2% for FVC, 2.3% for TLC, and 3.3% for DLCO. This decline was noted by the author to be greater than seen in other studies of asbestos-exposed patients." As mentioned in a comment above, the Whitehouse study is not a scientific study, but rather an effort by a practicing clinician to describe an aspect of his practice. It is unscientific to stratify a clinical population (i.e., biased to the sick side to begin with) into a subset whose lung function had worsened (i.e., the subset being even more biased with respect to lung function decline than

the entire biased clinical population) and then describe the average functional decline among the subset that experienced lung function decline as being greater than average declines seen in other studies of asbestos-exposed individuals. Those other studies, unless they were equally naïve in their analyses, did not stratify their patients in this manner. In addition to the problem of how the data were stratified, note that independent B readings were not obtained, and all pulmonary function test results but the first and last tests were ignored. Inclusion of the Whitehouse study in the EPA document is appropriate for the sake of completeness, but it would be best to recognize it as a naïve analysis of a some (but not all) of the clinical data from a very selected set of patients in one clinical practice—and keep the description of results of this study to a minimum.

Page 4-23, line 2: Suggest replacing "lesion" with "abnormality".

Page 4-23, lines 5-7: suggested edit: "Three NIOSH B readers independently reviewed each ~~of the available~~ case's x-rays in reverse chronological order to determine the latency…"

Page 4-23, line 10: "…76 did not have at least one x-ray over the span of at least 4 years…" warrants editing for clarification.

Page 4-23, line 11: "…consensus classification was not reached for three…". As mentioned previously, did Larson use "consensus classification", per se? More likely, he used multiple independent readings and then looked for agreement among these readings.

Page 4-23, line 12: suggest replacing "Circumscribed pleural plaque was" with "Pleural plaques were". (In the ILO classification system, pleural thickening can be either circumscribed or diffuse. "Pleural plaque" is a term used to refer to circumscribed pleural thickening. Thus, "Circumscribed pleural plaque" is redundant and is confusing.)

Page 4-23, line 23: suggested edit for clarity: "…seen with increasing exposure to Libby Amphibole asbestos fiber in studies…"

Page 4-23, line 26: suggested edit for clarity: "…of diffuse pleural thickening and pleural plaques…". (Remember, pleural plaques are a [circumscribed] type of pleural thickening.)

Page 4-24, line 25: suggest replacing 4.1.2.2. heading "Community Health Screening" with "Community Screening—Respiratory Health." With this edit the two-line paragraph on page 4-28, lines 13-14 can be deleted as unneeded.

Page 4-24, lines 29-31. Rather than phrasing this sentence in terms of participation rate (which it is not), describe the screening participants more factually. The proportion of current Libby residents participating in the screening is not of interest in this discussion. The number of people eligible to participate in the study would be of interest, if available. The denominator for this discussion is the 7,307 current and former Libby residents/workers who participated in the screening. For example: "The total eligible screening population (lived or worked in Libby for >= 6 months before 1991) was not known. 7,307 current and former Libby residents/workers participated in the screening. Of these, x % had …."

Page 4-24, line 34 to Page 4-25, line 1: "Moderate to severe restriction (defined as FVC <70% predicted value)" describes an unconventional sole criterion for defining restriction; this would most certainly misclassify cases of obstruction (characterized by low FEV1 /FVC ratio) as restriction.

Page 4-26, lines 13-15: "Among individuals with no definable exposure pathways, the prevalence of pleural anomalies was 6.7%, which is higher than reported in other population studies…" To partially explain this, consider pointing out a potential reading bias resulting from Larson's B readers knowing these chest x-rays were from Libby.

Table 4-8 title (page 4-26): Suggested edit… "~~Pulmonary~~ Chest radiographic~~,~~ and other health screening studies…" Also, with this edit, the "Health screening and pulmonary radiographic changes" should be deleted.

Table 4-8 1st paragraph in first cell under "Inclusion criteria and design details": suggested edit: "…and ratio (FEV1/FVC~~=<70% = moderate to severe restriction~~)."

Table 4-8 1st paragraph in first cell under "Inclusion criteria and design details": suggested edit for clarity: "…19 "exposure pathways," ~~included~~ including Libby…"

Table 4-8 1st paragraph in first cell under "Results": suggested edit for clarity: "…(6.7% among those with no specific pathways, 34.6% among those with 12…"

Table 4-8 2nd paragraph in first cell under "Results": suggested edit… "…Moderate to severe ~~FVC1~~restriction (FVC <70% predicted): 2.2% of men >17 years old; 1.6% of women >17 years old; 0.0% of men or women <18 years old."

Table 4-8 last item under "Results": "Association (OR, 95% CI) seen between ≥ 3activities and:
Usual cough 2.93 (0.93, 9.25)
Shortness of breath 1.32 (0.51, 3.42)
Bloody phlegm 1.49 (0.41, 5.43"
Consider whether these results, which are not statistically significant, warrant being included in the summary table.

Page 4-27, lines 9-10: suggested edit for clarity: "…playing at the ball fields near the expansion plant ~~with large piles of vermiculite~~,…" (Thus, not to be confused with playing in or around piles of vermiculite.)

Page 4-27, line 11: suggested edit: "…heating ~~the~~ vermiculite ore to "pop" it…"

Page 4-28, line 6: suggested edit for clarity: "…there was little difference in ~~the association seen~~ odds ratios across".

Page 4-28, lines 23-24: Suggested edit… "…through ~~her work~~ ~~doing the family laundry which included~~ laundering her father's work clothes."

Page 4-28, lines 26-27: Suggested edit… "Medical records were obtained for all 11 patients; ~~P~~pathology reports were obtained for 10 of the 11 patients~~; for the other patient, diagnosis was based on medical records obtained from the patient's physician~~."

Page 4-28, lines 29-31: The Whitehouse reports a case series, rather than a population-based study. We do not know the accurate numerator based on a case series. Some would say that in the absence of asbestos, we should expect no mesothelioma. Nevertheless, EPA needs to critically assess, rather than simply report, Dr. Whitehouse's statement citing 1 in a million as the background incidence rate for mesothelioma. That is an estimate made before mesothelioma mortality rates were available. If U.S. mesothelioma mortality rates since 1999 are considered, we know there have been an average of 2,435 mesothelioma deaths per year, and that the background rate for mesothelioma is approximately 10.7/100,000 person-years—i.e., 1 per 10,000 or 107 per million.

Page 4-28, lines 31-34: "Whitehouse et al. (2008) used information from a W.R. Grace unpublished report of measures taken in 1975 to estimate that exposure levels of 1.1 fibers/cc were found in Libby, and 1.5 fibers/cc were measured near the mill and railroad facilities." This statement warrants editing for clarity. Should the first "measures" be "measurements" (i.e., air sampling)? Or does this refer to measures taken by Grace that altered levels? Also, "to estimate that exposure levels of 1.1 fibers/cc were found in Libby" is both confused and confusing wording. It does not make sense to estimate levels that were found in Libby. The "and 1.5 fibers/cc were measured near the mill and railroad facilities" is also unclear, specifically because of the comma that precedes this clause and sets it apart from the rest of the sentence.

Page 4-29, line 4: given content of section 4-3, yet to come, consider revising the section 4.1.2.4. heading as follows… "Summary of respiratory health effects…"

Page 4-29, line 7: suggested correction… "…and 60-70~~%~~ times higher…"

Page 4-29, lines 13-15: "Data from this study indicate that the prevalence of pleural abnormalities, identified by radiographic examination, increases with the number of exposure pathways, from 6.7% with no specific pathways to 34.6% with 12 or more pathways (Peipins et al., 2003)." This wording is unclear. If the intent is to generalize by inferring from the findings of this study, then… "Data from this study indicate that the prevalence of pleural abnormalities, identified by radiographic examination, increases substantially with increasing number of exposure pathways (Peipins et al., 2003)." Alternatively, if the intent is to report findings of this study, then… "Data from this study showed that the prevalence of pleural abnormalities, identified by radiographic examination, increased with the number of exposure pathways, from 6.7% with no specific pathways to 34.6% with 12 or more pathways (Peipins et al., 2003)."

Page 4-29, line 30: suggested edit: "…the two related studies…"

Page 4-30, line 4: replace "delivered" with "received".

Page 4-30, line 14: "Task-level samples were conducted" should be clarified. Should this be "Task-level ~~samples were~~ air sampling was conducted"?

Page 4-30, line 15: "polarized light microscopy" should probably be "phase contrast microscopy". The former is used to estimate the asbestos content in bulk samples. The latter is used for quantifying airborne concentrations.

Page 4-30, line 18: suggest wording/structuring this sentence along the same lines used for Group II and Group III sentences that follow (i.e., edit this sentence so the parentheses can be deleted.)

Page 4-30, line 19: suggest replacing "1" with "a".

Page 4-30, lines 21 and 28: suggest deleting "for" from each line.

Page 4-30, line 34: suggest clarifying whether or not this "work force" includes the low-exposed workers used as comparison (mentioned in the previous sentence).

Page 4-31, line 9: should specify the two readers read the films independently.

Page 4-31, line 10: "with a consensus reading by a third reader when needed" warrants more detail and clarification. What were the criteria for determining "when needed"? Also, was this really a consensus reading (i.e., all the readers together decided on the classification), or was this third reading an additional independent reading and, if so, how were final determinations arrived at?

Page 4-31, lines 10-12: the sentence spanning these lines is redundant with a sentence earlier in this same paragraph.

Page 4-31, lines 10-12: if the values given are truly cumulative exposures, as stated, then "fibers/cc" should be "fibers-yr/cc".

Page 4-31, line 18: "pulmonary x-ray" should be "chest x-ray"

Table 4-9, title: again, "~~Pulmonary~~ Chest radiographic studies"

Table 4-9, contents: suggested edit for the second paragraph of "Results" for the Lockey studies: "No relation between cumulative exposure and ~~spirometry results,~~ forced vital capacity, forced ~~and~~ expiratory volume ~~tests~~, or ~~carbon monoxide~~ diffusing capacity."

Table 4-9, contents, third paragraph of "Results" for the Lockey study: "Pleural thickening in 10 workers (2%); bilateral, small opacities in 1 (0.2%). Abnormality increased with increasing cumulative exposure." Should clarify which abnormality. Pleural thickening, small (parenchymal) opacities, or both?

Table 4-9, second paragraph of "Results" for the Rohs study: "28.9%" should be "28.7%" (according to Rohs' paper), though arithmetic would suggest that it should be 28.6% (80/280*100=28.57).

Table 4-9, contents: suggested edit for the second paragraph of "Results" for the Rohs study… "cumulative fiber exposure: odds ratios (adjusting for date of hire, body mass index) by exposure quartile ~~of cumulative fibers~~ were…"

Page 4-32, line 19: Suggested edit… "…exposure ~~after~~ outside of work…"

Page 4-33, line 1: As has been done for other studies described in this draft document, should specify that the three readers were B readers.

Page 4-33, lines 2-9: Suggested edit to simplify/clarify… "Radiologists were blinded to all identifiers. ~~Pleural changes that were considered were localized (pleural plaques) and/or diffuse pleural thickening. Localized (discrete) pleural thickening was defined as thickening with or without calcification, excluding solitary costophrenic angle blunting. Diffuse, pleural thickening was pleural thickening, including costophrenic angle blunting, with or without calcification~~. For this study, pleural changes were considered present if the reader identified, with or without calcification, either circumscribed pleural thickening (excluding solitary costophrenic angle blunting) or diffuse pleural thickening (including costophrenic angle blunting). Interstitial changes were ~~defined as~~ considered present if the reader identified irregular opacities~~,~~ of profusion ~~of~~ 1/0 or greater. ~~A radiographic reading was defined as positive when the median classification from the three independent readings was consistent with pleural change and/or interstitial changes~~. For the analysis, a chest x-ray was defined as positive for pleural change and/or interstitial change when the median classification from the three readings was consistent with such changes." For optimal clarity, each "change" or "changes" here (jargon used by Rohs) should be replaced with "abnormality" or "abnormalities" to avoid implying that this study assessed chest x-ray changes over time. That would involve similar replacing of "change" with "abnormality" in the accompanying tables and further text describing this study. This reviewer would encourage the authors of the draft document to follow through on such thorough editing.

Page 4-33, lines 4-6: these sentences as phrased do not appear to differentiate between localized and diffuse pleural thickening. If the presented analysis lumps them together, then it might be better not to describe two types of pleural thickening, just using presence/absence, or perhaps the two types should be defined in terms of parietal or visceral pleura, as on page 4-65. Lines 4-5 should say "without costophrenic angle blunting" as the term "excluding solitary" as used is open to interpretation—i.e., does it mean that more than one costophrenic angle must be blunted? Page 4-33, lines 13-14, the current wording is "Increasing risk of costophrenic angle blunting (an indicator of pleural effusions) (n = 11),…". Suggested edit "Increasing risk of costophrenic angle blunting (associated with diffuse pleural thickening; can also indicate pleural effusion) (n = 11),…".

Page 4-33, lines 13-16, description of the Rohs study findings: "Increasing risk of costophrenic angle blunting (an indicator of pleural effusions) (n = 11), pleural and parenchymal changes (n = 11), or any of these changes (n = 22) were observed with increasing cumulative exposure when assessed by category of workers or by cumulative exposure across all workers." These findings do not appear to be from the Rohs paper. Among other discrepancies, the Rohs paper reported that 8 workers had parenchymal abnormalities, not 11.

Page 4-33, lines 16-19, description of the Rohs study findings…"The prevalence of any radiographic change was 2.8% in Group I, 3.9% in Group II, and 5.8% in Group III. Using the cumulative fiber metric, the prevalence of any radiographic change was 2.4% in the <1 fiber/cc-year, 5.0% in 1–19 10 fibers/cc-year, and 12.5% in the >10 fibers/cc-year groups." Likewise, these findings do not appear to be from the Rohs paper.

Page 4-33: line 17 describes Group I, II, III; line 19 describes three cumulative exposure groups; line 22 describes 4 other cumulative exposure groups. Please define groups I, II, and III. Are the first series of cumulative exposure categories linked with these groups? Which analysis had these groups?

The final model (page 4-33, lines 23-24) includes three correlated variables (Page 4-34, lines 16-17), yet there was no evidence of multicollinearity (pages 4-33, line 15 to page 4-36, lines 1-2)? This is not obvious from what has been presented. What is presented shows that the crude odds ratios by increasing quartiles of cumulative exposure are 1.0, 4.0, 5.4, 15.4; controlling for three covariates (two being highly correlated with the exposure variable), the odds ratios in these quartiles are 1.0, 2.7, 3.5, 6.9. These are the same?

Table 4-10 (page 4-34): it may be more informative to create a table including results that control for relevant confounders, rather than tabulating the crude analysis, or add additional columns to show both crude and final results for cumulative exposure.

Table 4-10, rightmost column: This column does not relate to the title of the Table 4-10. The source of data presented in Table 4-10 is given as Table 3 in the Rohs paper, but the rightmost column in Table 4-10 is not found in Rohs' Table 3.

Table 4-11 (page 4-35): Does this table present results of a single model, or a series of bivariate or univariate models? NIOSH suggests clarification.

Page 4-35, lines 12 and following: "Modeling of odds ratios with cumulative fiber exposure and including various cofactors (age, hired before 1973, or BMI) with the first exposure quartile as the reference was also conducted. …" It seems odd to describe the modeling methods here, when pertinent results from such modeling were already presented back in the last lines on page 4-33.

Page 4-36, lines 19-21: are the types of pleural and parenchymal changes observed at Marysville also evident in the ATSDR radiographic screening in Libby? Explicitly making this link would be a more convincing argument. A single table demonstrating similarities between Marysville and Libby in radiographic outcomes and results for association with cumulative exposure would be informative. Are the outcomes in the Lockey/Rohs studies the same as in the Peipens community study and the Amandus et al. 1987b, McDonald et al. 1986b, and Larsen studies of radiographic abnormalities in the Libby workers?

Page 4-36, line 20: the phrase "administered as a single entity" is open to interpretation. Does this mean one exposure containing a mixture of all chemicals, or a series of exposures each containing one chemical? What about dermal exposure? Were the same workers employed in the fiber-exposed areas and in the area where these chemicals were added or bagging of finished product took place? This argument is not convincing. The information that Marysville workers

were exposed to numerous pesticides, herbicides, other chemicals, and potentially to fibers from Palaboro, Republic of South Africa, Louisa, Virginia, and Enoree, South Carolina, muddies the link to the Libby amphibole. What happens when different exposures are evaluated in relation to the pleural changes (i.e., cumulative exposure to fibers from other sources, or to some of these chemical agents)?

Page 4-36, lines 23-25: Suggested edit… "The prevalence … ~~increased from 2% in 1984 (10/501) to 28.9~~was 28.7% in 2004 (80/280), compared to a 2% prevalence observed in 1984 (10/501). ~~The prevalence of any radiographic change (discrete pleural thickening, diffuse pleural thickening, and/or parenchymal change) was 29.3% (82/280). The~~ This apparent increase in prevalence ~~in the follow-up study~~ is most likely due to the additional time between the two studies giving additional time for the changes to become apparent in conventional x-rays." Also, the "any radiographic change" sentence is distracting in a summary context because it intervenes between the two sentences that describe an apparent increase in prevalence of pleural abnormalities. Any overt statement that the prevalence increases should be avoided, because the chest x-rays from the earlier study were not available for re-reading at the same time and by the same readers of chest x-rays from the follow-up study.

Page 4-36, lines 29-30: suggested edit: "…for ~~discrete~~ pleural abnormalities ~~thickening and more extensive radiographic changes (that is, diffuse pleural thickening and parenchymal change)~~ with …"

Section 4.1.3: some discussion of potential biases would seem informative in discussing the Marysville studies, especially in light of incomplete participation.

Page 4-37, lines 6-28: suggested edit for clarity: "…which would be expected to result in considerable misclassification. As a result, these studies might provide useful information to communities, but more refined study designs are needed to evaluate risk to individuals truly exposed to Libby Amphibole asbestos in their community due to operations at the expansion plants."

Page 4-37, line 28: epidemiology study methods do not evaluate risk to individuals. A clinician evaluates such a risk. Epidemiology is the study of groups. The text might be modified to read "are needed to evaluate risk to groups of exposed workers."

There are two tables labeled 4-10 (pages 4-34 and 4-39), and an additional two tables labeled 4-11 (pages 4-35 and 4-40). Page 4-39, table 4-10b: perhaps this page could be omitted. Page 4-40, table 4-11b: perhaps the information on this page (exposure period and resident population studied) could be included in Table 4-14.

Pages 4-41-42, Table 4-14 presents incidence observed over what time period? Just during 1999+ when ICD-10 was in effect, or earlier? The table reports a statistically significant excess mortality for cancer of the peritoneum, retroperitoneum, and pleura (including some mesothelioma) in Trenton. The table should note that some mesothelioma, not all mesothelioma, is included. Mesothelioma during ICD-9 may have been coded to 164.9 (cancer of the mediastinum), and a large proportion of mesotheliomas were coded to 199 (site unspecified) (Kopylev et al. 2011; Marsh et al. 2001). This should be mentioned in the text around page 4-37,

line 32-33, and the methods should be discussed in more detail. Is there any difference in exposure between this community and the others studied that might explain the findings? Were there other occupational or environmental asbestos exposures in the location? Any evidence of employment of Trenton residents at the Johns Manville asbestos facility 30 miles away? Any shipyard exposures? Asbestos exposure in other Trenton job sites?

References for comment above:

Kopylev L, Sullivan PA, Vinikoor LC, et al. Monte Carlo analysis of impact of underascertainment of mesothelioma cases on underestimation of risk. The Open Epidemiology Journal 2011;4:45-53.

Marsh GM, Gula MJ, Youk AO, et al. Historical cohort study of US man-made vitreous fiber production workers: II. Mortality from mesothelioma. JOEM 2001;43(9):757-766.

Page 4-42, Table 4-14: the excess (Dearborn, Michigan and Edgewater, New Jersey) and deficits in incidence of digestive cancers might be discussed as well as the digestive cancer mortality excess in Trenton. Should these cancers be attributed to the Libby vermiculite or to other workplace exposures, for example metalworking fluid exposure in the auto industry in Dearborn?

Typo near bottom of page 4-42: “wsa”.

Page 4-44, section 4.1.5, case reports: consider the published case report by Al-Ghimlas and Hoffstein [2007] in the Canadian Respiratory Journal:
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2676838/pdf/crj14164.pdf

Page 4-44, line 8: suggested edit for clarity: “…individual who died 50 years…”

Section 4.2.3 page 4-45, line 34 through page 4-46, line 2: “Both studies observed increased inflammation, however, Libby Amphibole asbestos exposure demonstrated minimal inflammation that did not progress in the time points examined. These studies demonstrate that exposure to Libby Amphibole asbestos may lead to inflammation and fibrosis”. This conclusion is not supported by the results of the studies; the absence of any progression of inflammation following intratracheal exposure to Libby amphiboles does not support the statement that there may be a risk for fibrosis. While it is clear that human airborne exposure to Libby amphibole causes pulmonary fibrosis, the reported intratracheal instillation studies with mice do not demonstrate that effect. In fact, on page 4-73, lines 25-27 the uncertainty of the role of inflammation in causing cancer and mesothelioma is described “…however, the role of inflammation and whether it leads to lung cancer or mesothelioma following exposure to Libby Amphibole asbestos is unknown.”

Section 4.2.4 page 4-48, lines 1-4 (includes Table 4-16): “There are no studies currently available in laboratory animals exposed to Libby Amphibole asbestos by inhalation. However, the chronic intraperitoneal injection study in hamsters (Smith 1978; Smith et al. 1979) demonstrates tumor formation following exposure to tremolite obtained from the Libby, MT mine.” The Smith 1978 citation in the bibliography (page 7-28) is incomplete and appears that it

might not be publically available. Also, the Smith et al. 1979 article cited from "Dusts and Disease" does not specifically mention results from tremolite obtained from the Libby, MT mine.

Page 4-52, line 31: Suggested edit… "…described ~~in the pulmonary analyses~~ above (Section 4.1, Table 4-8).

Page 4-53, line 2: how many people reported these conditions? Also, one reading of the results discussed is that the excess is only in rheumatoid arthritis. Thus, it would be helpful if possible to present numbers specific to each condition, avoiding duplication in count.

Page 4-53, line 13: "values" should be deleted or replaced by "value"

Page 4-53, lines 14-15: "In the ATSDR report, a moderate-to-severe restricted forced vital capacity is defined as an FVC <70%." 70% of what? Earlier in this draft indicated that ATSDR defined restriction as FVC< 70% predicted, which would most certainly include cases of obstruction.

Page 4-53, line 15: what significance does the difference in definitions of restriction have? Defining restriction as FVC<70% predicted has low sensitivity if spirometry was used as the sole criterion. But other measures (radiographs) were also available to detect respiratory disease in individual residents (the purpose of the community screening). The definition of restrictive pattern used by Noonan is an accepted epidemiologic definition of restriction, and improves the predictive value of spirometry alone in detecting restriction. The FEV_1/FVC criterion aims to exclude those with obstruction.

Table 4-18, title (page 4-53): This table should be re-titled "~~Pulmonary radiographic, and other health~~ Autoimmune disease studies in the Libby, MT community. With this revision the "Autoimmune Disease" row header could be deleted.

Page 4-65, line 9: Suggested edit… "Pleural thickening that is caused by exposure to asbestos includes…"

Page 4-65, lines 9-10: Suggested edit… "…discrete pleural plaques, ~~in~~ typically involving the parietal pleura, and diffuse pleural thickening, typically involving ~~of~~ the visceral pleura." Note that later in this same paragraph, it is mentioned that "There are reports of discrete plaques in the visceral pleura". Likewise, diffuse thickening can involve the parietal pleura.

Page 4-65, line 18: "ILO B-Reader standards" should be deleted, or at least better specified in this context as a citation. (There is no such reference listed in the draft document.)

Page 4-65, line 21: Suggested edit… "…of the pleural membrane ~~where there are discrete plaques~~." Fusing can occur with diffuse thickening without plaque.

Page 4-65, paragraph beginning on line 25-28: This paragraph is confusing and should be reconsidered and revised. This paragraph is perhaps intended to place radiographic evidence of pleural disease in context of the histo/pathology evidence covered in the preceding paragraph. It might be best to point out that the difficulty in distinguishing diffuse thickening from plaques in

clinical settings first and foremost arises from the fact that, except in unusual cases, tissue is not available for examination. Reliance is thus on radiographic evidence, which is not entirely specific. On page 4-66, line 2, the opening quotation mark is misplaced. The last sentence in this paragraph is a "run-on" sentence and should be separated into two sentences.

Page 4-66: if asbestosis is the most severe nonmalignant asbestos-related disease, what is the rationale for using pleural thickening in standard setting? Is it more common? Does it occur at lower levels of exposure? Is it because of the long latency period for asbestosis?

Page 4-66, line 11: suggested edit: "Asbestosis is generally the most severe nonmalignant disease associated..." After all, some cases of pleural disease are more severe than some cases of asbestosis.

Page 4-66, lines 12-13: "Asbestosis … becomes evident only after an appreciable latency period." Why was no mention of latency was made in the preceding section on pleural disease.

Page 4-66, lines 18 and following into the next paragraph: Suggested edit… ~~"A profusion of irregular opacities at the level of 1/0 is used as the boundary between normal and abnormal. Asbestosis is associated with dyspnea, bibasilar rales, and changes in pulmonary function: a restrictive pattern, mixed restrictive-obstructive pattern, and/or decreased diffusing capacity (ATS, 2004). In one of the earliest studies conducted, about 50% of the asbestos workers presented with a FVC below 80% of predicted (ATS, 2004).~~

Radiographic evidence of small opacities in the lung ~~is direct~~ can represent indirect evidence of scarring of the lung tissue ~~and as the fibrotic scaring of lung tissue~~ in a manner consistent with mineral dust and mineral fiber toxicity. In most studies involving chest x-rays of asbestosis, the x-rays are classified according to ILO guidelines, and a profusion of small irregular opacities at the a level of 1/0 or greater is considered abnormal. The scarring of the parenchymal tissue of the lung contributes to measured ~~changes in~~ impairment of pulmonary function, including obstructive ~~pulmonary deficits~~ impairment from ~~narrowing~~ narrowed airways, restrictive ~~pulmonary deficits~~ impairment from ~~impacting the elasticity~~ scarring of the lung, and ~~as well as decrements~~ impairment in gas exchange (ATS, 2004). ~~However, although data across~~ Results of studies reported in the mineral fiber literature ~~strongly support a finding of~~ indicate that functional deficits ~~where~~ are associated with small radiographic opacities ~~are visible on radiographs~~, the data also indicate that deficits in pulmonary function ~~(~~consistent with interstitial fibrosis~~)~~ ~~are seen~~ can be measured even before ~~these changes are detected by~~ radiographic abnormalities are detected~~examination. Thus changes in lung function may occur before the fibrotic lesions can be detected on standard radiographs~~ (ATS, 2004 and Brodikin et al., 1994)."

Page 4-66, line 23: ATS conducted this study? Use the primary source; perhaps Selikoff et al., 1964?

Page 4-66, line 30 to page 4-67, line 4 is an interesting perspective; however, since pulmonary function tests generally have not been shown to be a specific predictor of asbestosis in individuals (and are not even required for asbestosis diagnosis [ATS, 2004]), more support from the literature should be given to the argument. Do these statements include consideration of

modern methods of imaging, such as HRCT and digital radiography? Do they consider both sensitivity and specificity of the tests? DLCO is not a specific test for asbestosis.

Page 4-66, line 34: should "Brodikin" be "Brodkin"? Neither is listed in the references.

Page 4-66, line 34: "CO_2 diffusion" should be "CO diffusion" or "carbon monoxide diffusion".

Page 4-66, line 35: delete "other types of".

Page 4-66, lines 34 to Page 4-67 line 1: Rather than making the preceding couple of edits, it might be better to just delete "For example, decreased CO_2 diffusion is a sign of reduced gas exchange in the pulmonary region of the lung and is observed in workers exposed to other types of asbestos even when small opacities are absent on radiographs. Similarly, obstructive deficits in lung function may be observed without radiographic signs for fibrotic lesions." These two sentences, which are not supported by citations, repeat what was stated on lines 30-34 of page 4-65.

Page 4-67, lines 3-4: "these data suggest radiographs may not be sensitive enough to protect against adverse effects from parenchymal effects of asbestos exposure." This warrants revision. Radiographs are diagnostic, not therapeutic.

Page 4-67, lines 20-21: Suggested edit… "…and in radiographic ~~changes in the pleura and parenchyma~~ pleural and parenchymal abnormalities among employees…"

Page 4-67, lines 23-28: Suggested edit… "…~~an increase in~~ radiographic pleural and parenchymal abnormalities ~~changes in the pleura and parenchyma~~ among employees of a manufacturing facility in Marysville, Ohio that used Libby vermiculite ore contaminated with Libby Amphibole asbestos. These studies ~~used ILO diagnostic criteria and~~ demonstrated that ~~the increases in prevalence of adverse effects in the lung and pleural cavity are~~ prevalence of pleural abnormalities was positively associated with increased cumulative exposure to Libby Amphibole asbestos."

Page 4-67, lines 28-29: Suggested edit… "…documented ~~an increase in~~ pleural abnormalities…"

Section 4.6.1 Summary of Overall Weight of Evidence page 4-71, lines 4-6: "These results are further supported by animal studies that demonstrate the carcinogenic potential of Libby Amphibole asbestos fibers and tremolite fibers in rodent bioassays". The only animal study that provides some evidence of carcinogenicity is the single intraperitoneal study reported by Smith 1978 (see comment above) and this study is reported (incorrectly?) in the document to have used tremolite obtained from the Libby, MT mine.

Page 4-71, line 19: again, this cited plateau in lung cancer risk may be questioned (see comments above) because both the SMR and SRR increase monotonically with increasing duration and cumulative exposure.

Comments on Chapter 5 Exposure-Response Assessment

I. Overall comments on Chapter 5 methods

The datasets selected for the risk assessments appear to be appropriate. The methods are thorough. Some redundancies are present and some analyses could perhaps be presented more concisely.

Pleural Plaques

Is there a transit time for fiber translocation to the pleura?

Mesothelioma

A simpler method to estimate exposure-response in a study with zero baseline risk (compared with Monte Carlo Markov Chain analysis) is to use the linear relative rate model with the intercept fixed at a small value corresponding to a low probability of observing any baseline cases.

Observing *duration* to be a better predictor than *cumulative exposure* could indicate that design assumptions or exposure assessments are lacking. In this case, it would be appropriate to move directly to the design modification, restricting workers to those hired after 1959 due to the probable exposure misclassification in the earlier period. With the restriction, observing the best fit with a half-life of five years implies a) some reversibility in the damage inflicted, b) possible removal from the population of those who have higher risk (susceptibility), or c) some consequence of residual exposure misclassification. This deserves some discussion.

Lung Cancer

Poisson regression can be specified with time-dependent exposure without requiring the proportional hazards (PH) assumption (page 5-60). It is also based on internal comparisons, but is a more tedious dataset to construct.

Violation of the proportional hazards assumption is not due to time (age) *confounding* rather effect modification (page 5-62). Smoking may also be contributing to the PH violation, as a negative confounder, because the prevalence of smoking may decline with age and with cumulative exposure metrics and smoking is a risk factor for death and conditions leading to employment (exposure) termination. The analyses on COPD to assess smoking confounding actually support this conjecture: negative confounding is observed, although not significantly (page 5-77).

Applying the PH results to the life-table assumes that the baseline risks not estimated in the PH model actually coincide with population risk which, because of healthy worker and other confounding, may not be accurate, but it is probably close.

RfC calculations are derived from the lower 95% limit of the exposure-response estimates; NIOSH uses the central risk estimates in risk assessment.

II. Page-by-page comments on Chapter 5

Page 5-2, last cell of table: "Pleural and parenchymal ~~changes~~ abnormalities assessed using good quality radiographs, independently evaluated by ~~≥1~~ multiple ~~certified B~~ qualified readers according to International Labour Organization (ILO) standards." The intent seems to be to not rely on studies with a single reader. Also, note that some qualified readers may not be certified as B readers (e.g., if they are located outside the United States: the B Reader Program is a NIOSH program, not an ILO program).

Page 5-2 first paragraph: "anomalies" should be "abnormalities"

Page 5-2, last partial paragraph: "Five cohort mortality studies of Libby miners identified increased risk of mortality from non-cancer causes (McDonald et al., 1986a; Amandus et al., 1987b; McDonald et al., 2004; Sullivan, 2007; Larson et al., 2010a). These studies were not considered because mortality is not a preferred endpoint for deriving a reference value. Studies with more sensitive endpoints (i.e. morbidity studies) are preferred to mortality studies." This is a bit confusing. First, why does the first sentence specify "non-cancer" when the cited studies also assessed risk of lung cancer? Second, is it appropriate to discount these studies merely because they assessed mortality? It may be that mortality studies are not ***generally*** preferred and morbidity studies are ***generally*** preferred. But what if a lower RfC resulted from consideration of the lung cancer mortality studies? If so, would it make sense that they would be excluded just because they are mortality studies?

Page 5-3, end of first paragraph: should "the principal study" be "the principal studies"?

Page 5-3, middle paragraph: suggested edit: "…(small parenchymal ~~changes and pulmonary fibrosis~~ opacities)…" The ILO classification describes them as such.

Page 5-3 and Table 5-2: isn't there another available radiographic study of Libby workers, Larson et al. 2010? Should explain why it is not included (e.g., perhaps had a different outcome or was published after draft completed).

Table 5-2 (pages 5-4 to 5-6): NIOSH suggests re-formatting for clarification. Table 5-2's footnote states that exposure was estimated after 2000; however, Appendix F states that the exposures of interest were from 1957 through 2000 (p. 7) and a job-exposure matrix was constructed to describe exposure each year from 1957 to 2000 (p. 2). Need consistency and validity.

Table 5-2 and associated text in Section 5: As mentioned in a previous comment, in the context of describing ILO classifications of chest x-rays, "changes" is jargon for "abnormalities" and "changes" unnecessarily implies observation of a difference between two films on the same individual taken at different points in time. Thus, because what is referred to in this table and associated text on Section 5 is not changes over time, we suggest replacing "changes" with "abnormalities"— the term used in the ILO classification system.

Table 5-2: In the "Outcome assessment" for the Lockey study, a description is lacking about how non-agreement between the two B readings was handled.

Table 5-2: In the "endpoints evaluated" for the Lockey study, "only one small opacity recorded" should be "only one case reported with small ~~opacity~~ opacities recorded".

Table 5-2: In the "outcome assessments" for Amandus, Lockey and Rohs, "certified B readers" is redundant because all B readers are "certified" as such.

Table 5-2: in the "endpoints evaluated" for the Rohs study, a suggested edit: "Diffuse pleural thickening {including thickening with costophrenic angle…". Diffuse pleural thickening did not necessarily include costophrenic angle obliteration.

Page 5-7, last paragraph describes a pair-matched case-control study. Specifically, which citation does this apply to? Lockey et al. 1984?

Page 5-7: Suggested edit near top of first paragraph: "For example, these two studies used different numbers of occupation locations ~~were used~~, and different approaches…".

Page 5-7: Suggested edit near bottom of first paragraph… "…prevalence of radiographic abnormalities was 4% for pleural calcification, ~~10% for small opacities and~~ 13% for pleural thickening and 10% for small opacities." It is more logical to arrange the order such that listing of the two pleural abnormalities is not split by the parenchymal abnormality.

Page 5-7, at end of first paragraph: Replace "anomalies" with "abnormalities".

Page 5-9, top of page: this misses the point of the 1973 date. While it is accurate that exposure levels were uncertain before sampling began at Marysville in 1972, it is also accurate that exposures were much lower beginning in 1974, when additional controls were implemented. Thus, persons hired <=1973 had higher exposure (if less perfectly measured); while those hired 1974+ had lower exposure, and likely less disease (under an assumption of an exposure-response effect). Thus, we might assume that the prevalence rates in non-participants are likely lower than in participants.

Page 5-9, 2nd paragraph: the definitive statement that controlling to time since first exposure (TSFE) is preferable to controlling for age is an opinion that can be disputed because age-related changes may be unrelated to exposure. Less definitive language is suggested.

Section 5.2.1.3: Amandus et al. developed their conversion ratio based on near parallel time periods in which both types of sampling were done—i.e., it was a mathematical conversion formula, rather than based on interviews. Similarly, McDonald et al. also used a mathematical formula, but this was based on geometric mean and uses a method proposed by another researcher.

Page 5-9: in discussion of the NIOSH data supporting the radiographic analysis, it would be better to focus on the Amandus radiographic cohort. Is the % of workers without specific job information among those who terminated before 1955 important to an analysis of workers employed during the period 1975-1982 (i.e., the Amandus radiographic study subjects)? Further, comments on this page regarding how exposure was estimated for early workers are not factually

correct. NIOSH suggests review of the above comments or changing the focus of this section to the NIOSH radiologic study.

Page 5-9, beginning of first full paragraph: suggested edit: "…was a follow-up ~~conducted 24~~ study in which chest x-rays were taken 22 to 25 years after those taken in the original study by Lockey et al. (1984)." The publication dates of the two papers (24 years apart) are of no consequence in this regard.

Page 5-9, end of first full paragraph: insert comma after "covariates".

Page 5-9, middle of last partial paragraph: suggested edit: "However, Table V in Amandus et al. (1987a) ~~showed that different comparisons of dust versus fiber levels in the Libby workplace~~ showed potential values of that factor in the range of 1.2 to 11.5."

Page 5-9, middle of last partial paragraph: Suggested edit… "…resulting in ~~particularly~~ potentially large measurement error…" The more years a Libby vermiculite's worker worked before 1960, the larger the error in the exposure estimate. But if a worker was hired just a few months prior to 1960 and worked until the mine closed, the effect of the pre-1960 estimate would likely be minor, not "particularly large."

Page 5-10, first sentence: delete the beginning of this sentence (before comma), since it is opinion that is not relevant to the document.

Page 5-10. First paragraph text stating "all workers who participated in the Lockey et al. (1984) and Rohs et al. (2008) studies" while accurate, is misleading, assuming Appendix F is correct. Is it only the 280 participants in the Rohs et al. study who had exposure reassessed—i.e., not the full 512 in the Lockey study and, more importantly, not the 413 included in the full cohort analysis for this risk assessment document? Suggest removing "Lockey et al. (1984) and" from this sentence to better convey the exposure assessment described.

Figure 5-1 (page 5-10): Since Marysville continued to use other vermiculite that may, or may not, have been contaminated with amphibole fibers (see Appendix C) during the period 1980-2000, it would be informative to see a similar figure estimating exposure to any amphibole fiber.

Page 5-11, 1st sentence: as written, the text suggests a discrepancy between this discussion and Appendix F about which workers have the newly developed exposure estimates. If exposure was reassessed for workers included only in the Lockey study, and not in the Rohs study, as stated here, then the text in Appendix F stating that exposure was reassessed for 280 workers should be corrected. If exposure was not reassessed for the approximately 133 workers who didn't participate in the Rohs study, then that needs to be acknowledged and discussed here.

Page 5-11, first sentence in 5.2.1.4: replace "≥1" with "multiple". In none of the four studies was only one reader used.

Page 5-11, three lines from bottom of page: "poor" should be "poor quality".

Page 5-11 bottom to page 5-12 top: in the ILO system, "poor" quality is not the same as "unreadable" quality. Based on the rationale as presented, it is potentially misleading to assert that "In the Marysville cohort, radiographic quality was better." As pointed out elsewhere in this

same paragraph of the draft document, Rohs reported 2.3% (7 of 298 per the description in the draft document) films were unreadable compared to 0.4% unreadable films reported by McDonald. A direct comparison of percentages of films that were poor quality would be a more relevant comparison. Importantly, this comment bears on one stated rationale ("limitations in the quality of the radiographs used for outcome assessment" [see end of first paragraph on page 5-11]) for selecting studies of the Marysville workers over studies of the Libby workers for determining the RfC.

Chapter 5 and Appendix F comparison: Appendix F documents new job exposure estimates developed for this survey, stating that fiber estimates for the period 1957-2000 were made for the 280 study subjects who participated in the 2004 radiographic survey. Chapter 5 repeatedly refers to 1959 as the date Lockey estimated fibers were first used, and either suggests or states that new exposure estimates were developed for all workers who participated in either the Lockey or Rohs studies. Consistency between the two parts of this document is suggested.

Page 5-11: how are amphibole fibers from other sources of vermiculite used in the plant 1957-1990 accounted for here? Is it assumed that these amphibole fibers do not cause asbestos-related radiographic changes?

Section 5.2.1.4 at bottom of page 5-11 refers to the Amandus et al. 1987b radiographs as "company radiographs." This may be misleading because these radiographs were taken at the local hospital. Although paid for by the company, they may have remained at the hospital. Suggest contacting Dr. Amandus at NIOSH directly to verify.

It may not be accurate to state that the Marysville radiography quality was better. Quality assessment could be a judgment call and presumably different readers were used at Libby and Marysville.

Section 5.2.1.5 (page 5-12): were the McDonald et al. radiographs available? Did EPA actually review radiographs to determine that quality of Marysville radiographs was better? Apparently Larson et al. 2010 found the Amandus et al. radiographs were of acceptable quality.

The last paragraph in this section nicely states the advantages of the Rohs et al. 2008 study cohort. Among the disadvantages, of course, are the small number of participants, and the fact that the sub-cohort of 280 was self-selected. Much of the previous two pages could be eliminated. Phrasing of the text at the beginning of this paragraph does not clearly state that increased risk of pleural and parenchymal effects were observed at Libby. That Amandus did not find a relationship between cumulative exposure and pleural abnormalities argues against the Libby amphibole being causal at Marysville. However, McDonald did find a positive relationship. Suggest rephrasing.

Page 5-12, bottom of second full paragraph: suggested edit: "…2000 ILO ~~diagnostic~~ criteria…".

Page 5-12, first sentence in section 5.2.1.6: suggested edit to clarify and avoid potentially misleading assertions: "The pleural and parenchymal effects observed in <u>some</u> exposed individuals in the Marysville cohort (Rohs et al., 2008; Lockey et al., 1984) included ~~increased prevalence of~~ pleural thickening (characterized as either discrete pleural thickening or diffuse pleural thickening) and ~~small~~ parenchymal ~~changes (small~~ opacities~~)~~. These effects were determined using conventional radiographs (Rohs et al., 2008). ~~In clinical settings there are~~

~~difficulties in distinguishing between these two lesions in part due to lack of radiographic film diagnostic specificity as well as the ILO definitions for diffuse pleural thickening of the visceral pleura which may result in some variability in reporting of discrete pleural plaques. There are two classifications for pleural thickening in current guidelines (ILO, 2000). Diffuse pleural thickening is currently only determined where there is thickening along significant extent of the chest wall, and this thickening is "in the presence of and in continuity with, an obliterated costophrenic angle" (ILO, 2000). Although previous classification schemes attempted to distinguish between thickening of the parietal pleura and diffuse thickening of the visceral pleura, the ILO states" reading standard x-rays cannot always distinguish between thickening of the visceral or parietal pleura" (ILO, 2000). Thus, all other pleural thickening is now defined as localized pleural thickening (i.e. where there is no costophrenic angle obliteration). Localized pleural thickening on the chest wall, and diffuse pleural thickening may be graded indicating thickness, and the extent of the chest wall impacted, however these data are not always provided in study reports, therefore regardless of extent of the pleural thickening, only presence or absence may be noted.~~

~~The radiographic changes occur in different anatomical locations. Localized pleural thickening may include plaques in the parietal pleura, or thickening of the visceral pleura, where this thickening does not impact the costophrenic angle (angle between the diaphragm and chest wall as viewed on a radiograph). Diffuse pleural thickening is designated when thickening of the visceral pleura extends to blunt/obliterate the costophrenic angle. Pleural thickening does not progress to parenchymal changes.~~ The data on the radiographic changes are presented in Table 5-3, Figure 5-2 and Figure 5-3. …" (The authors of the draft document may be trying to overemphasize the ILO classification of pleural abnormalities with respect to their location vis a vis visceral/parietal. ILO classification cannot do that.)

Page 5-13: the text "Figures 5-2 and 5-3 present the cumulative prevalence of radiographic changes" is somewhat confusing. It might be clearer to say "Figures 5-2 and 5-3 present the prevalence of radiographic changes across categorizes of increasing cumulative exposure."

Table 5-3 and Figures 5.2 and Figure 5.3 do not provide evidence of the plateauing effect discussed in Appendix E and that was incorporated into the analysis of the full cohort, particularly when exposure is logged. Since plateauing was incorporated into the model, it would be interesting to see how sensitive the plateauing effect is to changes in cut points between the exposure categories. How do these figures look if exposure is cut at exposure quartiles of the cases (15 localized pleural thickening cases in each exposure group)?

Figures 5-2 and 5-3 (page 5-14) use the term "discrete" compared to "localized" in Table 5-3 and "circumscribed" in some places in the draft document. While all are fine, it might be less confusing to consistently use a descriptive term. "Localized" would do well.

Page 5-15, top two lines: suggest deleting "(characterized by Lockey et al., 1984 and Rohs et al., 2008 as discrete pleural thickening)" unless there is a reason to keep it and, if there is, did Rohs so characterize things?

Page 5-15, first paragraph: as one rationale for selecting pleural abnormalities for determining the RfC, the draft document gives "specificity [of such abnormalities] for durable mineral fiber

exposure." While such abnormalities are somewhat specific for such exposures, they are by no means 100% specific. Consider whether a discussion of other causes should be included.

Page 5-15, end of first paragraph: suggested edit: "…is ~~attributed~~ attributable to exposure to Libby Amphibole asbestos in individuals who have been exposed to this amphibole mineral."

Page 5-15, second paragraph: suggested edit: "~~Thickening of the parietal pleura (all sites)~~ In the absence of other causes, pleural thickening is an accepted clinical marker of mineral fiber exposures,…" Again, it may be that too much is made of an ILO classification when it comes to visceral/parietal location. Consider more precise wording—in particular distinguishing between radiologic appearance and histopathological findings. See above comment that pleural thickening is not 100% specific for mineral dust exposure. Thus, ATS [2004] recommends that alternative explanations for diffuse pleural thickening be excluded before relying on that finding as a marker of exposure in an individual patient.

Page 5-15: suggested edit: "~~Parietal~~ Pleural plaques are known to ~~induce~~ be associated, on a population basis, with chronic ~~constricting~~ chest pain which increases in severity as the extent of the plaques increases." Not all patients with plaques have pain.

Page 5-15: "HRTC" should be "HRCT" in both locations. Also, add this term to the Abbreviation list at the beginning of the document. In making the case that localized pleural thickening predicts pulmonary function changes, note that Lockey et al. 1984 found no relation between cumulative exposure and spirometry results, forced vital capacity and expiratory volume tests, or carbon monoxide diffusing capacity (see earlier table summarizing Lockey findings in this EPA IRIS document). Dr. Benson's references have not been incorporated into the list of sources—thus, reviewing this section for accuracy is difficult. This page states why pleural thickening is important and is important in the context of the RfC. Suggest that more time be spent on the literature that links these pleural abnormalities with long-term health outcome. How consistent is the data that links these abnormalities to pain, lung volume loss, etc? Is this a linkage from population-based studies, or does this progression occur in individual people over time?

Page 5-15, last sentence: suggested edit: "Thus the radiographic classification of localized pleural thickening (ILO 2000) defines radiographic ~~anomalies~~ abnormalities which, on a population basis, are associated with chronic chest pain~~, decreased lung volume~~ and decreased ~~measures of~~ lung function."

Section 5.2.1.6 Selection of Critical Effect, page 5-15, third paragraph states "Parietal plaques are known to induce chronic constricting chest pain which increases in severity as the extent of the plaques increases." Suggest changing to: Although chronic severe pleuritic pain is rare in patients with asbestos-induced disease, case reports have documented that parietal pleural plaques can be associated with chronic chest pain. Also, the paragraph could be edited to clearly indicate that localized parietal pleural plaques have been associated with small, but statistically significant reductions in pulmonary function; in comparison, diffuse visceral pleural thickening has a much greater (and more clinically significant) effect on pulmonary function . (See American Thoracic Society (ATS) [2004], cited elsewhere in the draft.)

Section 5.2.1.6 Selection of Critical Effect, page 5-15, last paragraph: the proposed RfC is based on an increased risk of pleural and parenchymal effects. These effects, including pleural plaques, are considered by some to be markers of exposure to durable fibers and to a lesser extent of an adverse clinical effect. Thus, it is important that the citations given (Lilis et al. 1991; Miller et al. 1994; Wang et al. 2001; Petrovic et al. 2004; Swartz et al. 1993 and Copley et al. 2001) provide sufficient justification to support the basis of establishing an RfC for exposure to Libby amphibole minerals. These citations are not listed in the bibliography for an independent assessment. NIOSH recommends including these citations.

Figure 5-4 (page 5-16), legend: "Card" should be "CARD".

Page 5-17, second line of text in section 5.2.2.2: delete "by".

Page 5-18, first full paragraph: "The consensus read of the x-rays from three B-readers was used in both studies." This implies that the three B readers arrived at a classification that they all agreed upon, which is not the case. Suggested edit: "The presence/absence of each radiographic abnormality, determined on the basis of the median ~~consensus read of the x-rays from three B-readers~~ of the three independent B readings of each x-ray was used in the analysis in both studies."

Page 5-18, first full paragraph: "Because the ILO criteria were updated in 2000, the reader forms from Lockey et al. (1984) showing pleural changes were evaluated for consistency with the ILO 2000 criteria. No change in diagnosis was found." This is confusing. It not clear what was involved in the evaluation of consistency, and it is not clear what is meant by "No change in diagnosis was found". NIOSH recommends clarification.

Page 5-18, first full paragraph: "In addition, no change in x-ray or film quality was found that would reduce confidence in the Lockey et al. (1984) data." See comment (above, re Page 5-11) concerning "poor" vs. "unreadable" quality.

Page 5-18, third line of last paragraph: "Amphibole" should be "Amphibole asbestos".

Page 5-18: this discussion raises many questions. The methodology described is problematic because it suggests differential ascertainment of disease outcome between high/low exposure groups in the study cohort(s). The Rohs study subjects were self-selected. Those hired later, and with lower exposure, were less likely to have participated in the Rohs study, thus were less likely to have two radiographs. Without the later film, there is no opportunity to detect disease if it exists. Thus, there likely is under-ascertainment of disease in the lower exposure groups. In addition to exposure lagging, for full cohort analysis there should be a minimum latency criteria (e.g., 10 years from first exposure (hired before 1970) for inclusion of workers studied only by Lockey et al. (for whom only 1984 radiographs were available)). That is, the 79+ workers hired fewer than 10 years before the 1980 radiography should be excluded from the analytic cohort. If EPA does not actually do that, some analysis documenting that it would have no impact should be included.

For some workers, were 1980 radiographs used even though they may have worked later? If so, what exposure value was used? 1980? Is this from the 1980 exposure assessment, or is it updated by Lockey to include the recently available exposure information?

There probably should be a latency cutoff for participation in the full cohort analysis, rather than just exposure lagging. A substantial proportion of study subjects did not have sufficient latency to develop the outcome of interest (up to 133/413=32%) at the time the 1980 radiographs were taken. This introduces a lot of uncertainty into the assessment. How is this addressed in analysis and uncertainty discussion? In Appendix F, Lockey states that exposure was reassessed only for 280. So, what was used for exposure for these 133?

Page 5-19: If the only analysis relevant to this document is the sub-cohort of 12/119 workers hired 1972+ and participating in the Rohs study 22-30 years after first exposure, what is the point of discussing all of the other possible cohorts? NIOSH does not recommend introducing the problematic methodology commented on above.

Section 5.2.2.3 ("Statistical Modeling of the Sub-cohort", page 5-19) states that limiting the analytic cohort reduced uncertainty in exposure estimates. What uncertainty is associated with developing an RfC based on the experience of 119 workers (12 cases) who may have been exposed to several different sources of amphibole fiber? Most occupational epidemiologists look for a cohort with a wide range of exposure because this provides the best data to examine exposure-response. EPA sought human data linking health effects with occupational exposure and then did as much as possible to limit the range of exposure, basing risk assessment on very few workers, and very few cases. These small numbers introduce considerable uncertainty because there is not much reason to believe the sub-cohorts are representative of the population experience. Reducing uncertainty in exposure assessment adds to uncertainty about exposure effect. EPA should abandon the assumption that only exposure data comparable to that which would be obtained in a prospective controlled trial (animal experiment) is acceptable for exposure-response analysis. If carefully controlled experimental data is required, workplace data should not be sought to support IRIS recommendations.

Page 5-19: provide a citation for benchmark dose methodology and add all these acronyms to the Abbreviation list at the front of the document.

Page 5-20: please explain what a 10% excess over 1% equals in a cohort of 119 workers. Is that 1 or 2 cases by chance, and 2 cases is a 10% excess? (1% background is 1.19 cases in a study with 119 workers. 1.1% is a 10% excess=1.309 cases. 1 case is < background, and 2 cases is >10% excess? How much uncertainty regarding the health outcome do these numbers imply? Pleural thickening is a specific response to asbestos and other mineral fibers, but is it a specific response to the Libby amphibole? Can it distinguish between Libby amphibole and silica or asbestos from other vermiculite mines? Does considering confounders result in more cells, thus less statistical power?

Page 5-20, end of first full paragraph: "Among military populations, two studies have reported an estimated prevalence of 2.3% (Miller, 1996; Bohnker, 2005)." More description of the military populations' asbestos exposure would be beneficial.

Page 5-20, beginning of second full paragraph: "EPA selected a BMR of 10% extra risk…" Suggest adding a statement to make this risk understandable (i.e., if the background rate is 1% (10 in 1000), a 10% increase would equate to 1 additional case per 1000 exposed.) Is that correct? NIOSH recommends clarification.

Page 5-20, last paragraph in section 5.2.2.3: "For the Marysville cohort, however, individual exposure and health outcome results are available and a more comprehensive analysis is possible. This type of analysis has more statistical power since it benefits from individual information on each study subject and allows for consideration of potential confounders." This paragraph is confusing and should be revised. The "however" seems to be distinguishing the Marysville cohort form the Libby cohort, but the Libby cohort has already been dispensed with in this part of the draft document. Likewise, while it is asserted that "a more comprehensive analysis is possible," it remains unclear what the comparison is. If the Libby cohort, again this has already been dispensed, so why raise it again here? Finally, and similarly, asserting that "This type of analysis has more statistical power" does not make clear which types of analyses are being compared in this context.

Table 5-5 (page 5-23): please define "a" and "b" used in the models. Typo in AIC column?: 7777.0

Page 5-24, section 5.2.3: this listing of steps in deriving the RfC is clear and helpful. However, should the last line on this page read 1.3 rather than 1.2?

Page 5-26, line 2: was continued employment required for participation in Rohs 2008? Particularly in this sub-cohort of late hires, Rohs states there is a higher nonparticipation rate compared with the entire cohort. Self-selection of the sick into the follow-up study (which provided medical screening) is also a possibility.

Page 5-26, line 4: "computer" should be "computed".

Page 5-26, line 5: "tract, which" should be "tract that"

Page 5-26, lines 5-7: it is pointed out that because HRCT is more sensitive than conventional chest radiography, "the technology employed for determining the prevalence of radiographic changes in the Marysville cohort may underestimate the actual prevalence of localized pleural thickening." Why limit to comparing radiographic methods? Neither of these is as sensitive as direct examination of pleural tissue. It is just that the latter is invasive and has a risk to living human subjects.

Page 5-26, line 22: Should "workers exposed" be "workers first exposed"?

Table 5-6 (page 5-27): label columns 3-11 "duration of exposure."

Page 5-28, line 19: use of the term "confounding" in this context in this document seems unnecessarily confusing, unless confounding is demonstrated statistically. Suggest choosing another word. Comments made earlier regarding page 5-18 apply here. The full cohort is plagued by differential case ascertainment by exposure group, and limiting the 1980 cohort to those with at least 10 years latency is suggested.

Page 5-29, lines 13-16: some would differ with this interpretation. The $BMCL_{10}$ are similar because the variability in the sub-cohort is greater due to small numbers, resulting in a wider CI, thus low $BMCL_{10}$. But the BMC_{10} for the full cohort is about 50% of the BMC_{10} for the sub-cohort. Although rounding results in the same value, the calculated RfC for the full cohort is only 70% that of the sub-cohort—i.e., 0.9×10^{-5} vs. 1.3×10^{-5}.

Pages 5-29 to 5-30: EPA discusses four possible RfC values in this section (2.1×10^{-6}, 4.0×10^{-6}, 9.0×10^{-6}, and 1.3×10^{-5}) and chooses the largest (which is 6 times the smallest), even though the wide confidence limits suggest uncertainty. NIOSH recommends reconsideration.

Section 5.3 "Uncertainties in the inhalation reference concentration (RfC)" (page 5-30): this section needs editing with respect both to consistency in the text and missing words/typos that obscure the arguments. What impacts does the small number of workers at Marysville, and in the sub-cohort have on certainty? The uncertainty section should discuss this. Lines 29-34: recall that there were engineering control changes around 1973 that reduced exposure. So, there was factual information that was used to ascertain the conversion factor.

Page 5-31, lines 25-26: If the South Carolina vermiculite was used early before 1960, then the times since first exposure to the Libby amphibole might be later than estimated for some workers.

Page 5-32, lines 1-2: Is it known that these chemicals are not lung carcinogens or that they do not affect pulmonary function? This statement about unlikely effect of the respiratory system is questionable unless the agents are listed. Documentation of respiratory effect of some co-exposures is simple; documentation of lack of effect would take some thoughtful arguments. Need to strengthen discussion of this assumption.

Page 5-32, lines 11-12: "…no increased prevalence of pleural or parenchymal ~~change~~ abnormalities consistent with asbestos exposure has been observed in *[how many?]* examined household contacts…"

Page 5-32, lines 22-23: suggested edit: "For example, one of the workers had a positive X-ray ~~at~~ in 1980 ~~scan~~, but a negative X-ray ~~at 2000s scan~~ more than 20 years later. (~~excluding~~Excluding this worker from the analysis did not change results.)~~:~~"

Page 5-32, lines 23-26: "However, uncertainty in the prevalence of localized pleural thickening in each individual is considered minimal due to the use of a team of highly qualified chest radiologists evaluating the radiographic films and the use of consensus diagnosis." This sentence warrants revision. First, "prevalence … in an individual" makes little sense, particularly since all prior mentions of prevalence referred to prevalence among a group of individuals. Second, "a team" is misleading in the sense that the readers read the x-rays independently and not as a team. As commented on above more than once, consensus readings were not done. (i.e., the three readers did not get together to arrive at a classification; rather, they read the films independently.) Lastly, NIOSH disagrees with the rationale that uncertainty regarding the presence/absence of abnormality would be "minimal" as a result of using the approach used in the studies to arrive at a determination. Granted, use of three "highly qualified" readers is better than using just one qualified reader or three unqualified readers, for example. But the median of five qualified readers would have been somewhat better than three and use of median of seven more qualified readers would have been a bit better still. Further, as previously and subsequently pointed out in this draft document, use of HRCT would have been better than use of conventional chest radiography if one is speaking of trying to minimize uncertainty about the presence/absence of localized pleural thickening (which should not be equated with "diagnosis").

Page 5-32, line 34 to Page 5-33, line 1: "In general, smoking rates have declined between 1980 and 2000s and BMIs have probably increased,…" This should be clarified. Smoking rates among what population? And BMIs could be said to have likely increased in the Marysville group, if only because it represents an aging population.

Page 5-33, first paragraph: much of this is redundant with what was already stated on page 5-20. Suggest editing this content to minimize redundancy.

Page 5-33, line 4: "tract, which" should be "tract that".

Page 5-33, line 20: should "included" be changed to "excluded" in this sentence? Also, this discussion undermines use of a 10-year lag period in the analysis presented here, as Larson found disease at 8.6 years. Some discussion of exposure level in this context might be helpful. Lines 31-32: this argument seems to contradict the argument presented in the paragraph directly above where Larson et al. 2010b is cited. Same section: are there any changes in radiography equipment or reading techniques that might contribute to the detection rate for pleural thickening? If so, that might impact the background for the 2005 radiographs.

Page 5-34, line 24: suggested edit: "…may increase further…"

Page 5-34, lines 31-32: suggested edit: "Therefore, it is likely that the prevalence of localized pleural thickening would be found to further increase ~~if the~~ among individuals hired in 1972 or later ~~were~~ if they are examined in the future."

Page 5-35, line 14: "fibers" should be "fiber exposures".

Section 5.4.1 (starts on page 5-35): this section is clear.

Page 5-35, line 23: As quantitative estimates are being discussed, suggest adding the word "slope" to this discussion, as in "cancer potency (slope) in the studied population." Line 27: Changing the word "collected" to "selected" would be more accurate because EPA did not collect the data.

Page 5-36, line 6: again, define cancer potency as the slope, a term familiar to most. Lines 17-19: rather than justifying use of absolute risk based on rarity, perhaps it should be justified based on the assumption that mesothelioma is caused by exposure to asbestos fibers.

Page 5-36, line 17: "…an absolute risk [*of how much?*] was…".

Page 5-37, lines 20-23: while it is accurate that the data set provided a broad range of exposure, EPA limited analysis to the comparatively few people (and cases) hired 1960+ resulting in a more limited range of cumulative exposure; also, the large cohort mentioned is considerably reduced. That is, some of the strengths of the data set are not taken advantage of in the analysis presented here. That being the case, perhaps these strengths should not be claimed.

Page 5-39, Table 5-7: remove commas from mean year of birth and mean year of hire.

Page 5-41, lines 1-2: specify that the similar rate is 83%, not 12%. Lines 11-12: note that the definition of lung cancer should be more restrictive, omitting 047c from ICD-5, and definitely

omitting 162.2 (cancer of the pleura) from ICD-7. ICD-5 is not relevant to the analysis EPA presents (1960+). ICD-5 (verify ICD-5 codes, as different sources list different cancer codes)

47
47a Cancer of the larynx and trachea
47b Cancer of the lung and pleura
47c Cancer of unspecified respiratory organs

ICD-7:

162 Malignant neoplasm of bronchus and trachea, and of lung specified as primary

162.0 Trachea

162.1 Bronchus and lung

162.2 Pleura

162.8 Multiple sites

163 Malignant neoplasm of lung, unspecified as to whether primary or secondary

Page 5-46, line 8: "There was one important limitation of the NIOSH JEM." This paragraph demonstrates some confusion with respect to the limitation, which actually is a limitation in the work history data available at the time the work histories were collected in the early 1980s, rather than in the JEM. Many early workers did not have job assignments, and in many cases did not have department assignments (e.g., mine/mill/etc.). Note that this is a weakness of all the studies of Libby workers, irrespective of the decisions made as to exposure level assigned by the various JEMs because these early job assignments were not retained in existing records and thus could not be used by any research team to estimate exposure.

In the Sullivan [2007] paper, a single value was not assigned; the estimated value assigned was a weighted average of exposure in all unskilled job assignments (among workers with known jobs) in the relevant department (if available) and during the relevant calendar time period.

Page 5-46, line 9: delete the word "some" or explain it. Line 12, delete the word "same", and refer to the average as a "weighted average." Line 13: add to the end of the sentence "….and department (if available)." Lines 13-15: suggested edit: "The lack of information on specific job assignments for these workers ~~in the JEM~~ <u>may have</u> resulted in exposure misclassification, making duration the most precise exposure metric before 1968." Lines 23-24 should read "Sullivan (2007) ~~reabstracted work histories by~~ ~~extrapolating exposure estimates~~ estimated exposure for the additional jobs and calendar time period-specific combinations based on professional experience and review of exposure records from earlier studies of the Libby worker cohort."

Page 5-48, Table 5-9: when discussing uncertainty, EPA should acknowledge that the trade-off involved when limiting the analytic cohort to the subset hired 1960+ is that the IUR is developed based on only about 30% of the lung cancer deaths among these workers. The discussion should acknowledge that the number of lung cancer deaths (n=32 vs. 110) that each slope is based on

determines the measure of variability, and the width of the confidence interval surely has some impact on the CL value used in deriving the IUR. Can EPA estimate that impact, as it is another source of uncertainty? Can the impact of limiting the range of exposure (comparing table 5-7 to 5-9) be estimated?

Page 5-48 line 14: suggest "drilling, ore loading, river dock, and bagging plant…" because the first two are operations, while the last two are locations. Line 16: Note that plant operations continued until 1990, and workers were not engaged solely in shut down operations.

Page 5-48 lines 17-18 and page 5-96, taken together: the statement on lines 17-18 may result from a misunderstanding of the data. The work history data were collected by NIOSH in May 1982; as a result, May 1982 was used as the end-date of the last job in the work history data file because we do not know the job experience of the workers after May 1982. Those working in May 1982 may have been employed until 1993, or they may have left employment June 1, 1982. Thus, exposure was underestimated for those working after May 1982. It is not usual in occupational epidemiology studies to calculate exposure beyond the date that work history data are available. This uncertainty could be addressed in sensitivity analysis, and discussed under "uncertainties." Page 5-96 states "NIOSH records on work histories and job-specific exposure extended from the 1930s through May 1982. However, the vermiculite mining and milling operation continued on for several years, and some workers were retained through 1993 for plant close-out activities. However, none of the members of the post-1959 cohort (n = 880) were employed as of the 1982 employment records. Of the employees still working in 1982 (n = 167), all were hired prior to 1960." If it is accurate that all workers active in 1982 had been hired prior to 1960, consider the implications for estimation of lifetime risk from an analysis that excludes 167 workers with >=22 years employment—i.e., focuses on short-term workers. Would a valid and unbiased estimator be expected? This should be discussed in the uncertainties section.

Section 5.4.2.4, pages 5-48 to 5-49 reads "NIOSH staff and contractors abstracted demographic data and work history data from company personnel records, including W-2 federal tax forms. An individual's work history was determined from job change slips, which recorded new job assignment, date of change, and change in hourly pay rate (which differed by the job assignment). Work history records span the time period from September 1935 to May 1982. Dates of termination were unknown for 58 of 640 workers (9%), who left employment before September 1953. EPA adopted the assumption used by NIOSH (Sullivan, 2007) that these people worked for 384 days, based on the mean duration of employment among all workers with known termination dates before September 7 1953." Sullivan didn't use contractors. NIOSH recommends EPA verify whether Amandus used contractors. Change "personnel records" to "personnel and payroll records," as the work histories were from the payroll records. W-2 should be changed to W-4 tax forms. EPA did not use data on workers who terminated before 1953, so should delete statement about EPA adopting 384 day duration assumption.

Page 5-49, line 10: "…the maximum number of jobs changes was 32." Actually, the maximum number of job changes in any cohort member was something around 25, including periods of lay off. In cases where a worker's job assignment spanned more than one calendar time period in the JEM, a record was added to the work history data file to facilitate cumulative exposure calculation. Thus, there are records in the data file that do not correspond with an actual job assignment change.

Page 5-51 is very well-written. Is it a problem if the model selected does not have a biologic interpretation?

Page 5-51, lines 24-25 read "EPA calculated …. until they ceased to be employed in the Libby operations." Should add "or until the date NIOSH collected the work history data, if still employed in May 1982."

Page 5-57, line 34 reads "Sex and race were not used as covariates since all mesotheliomas were observed in men assumed to be white (Sullivan, 2007)." This is incorrect because women and non-white workers were included in the analysis. If the analytic cohort itself (not the deaths due to mesothelioma) were limited to white men, then sex and race would not be needed in the models.

Page 5-58 reads "Moreover, as described in Section 5.4.2.3, for 686 of 991 (69%) workers hired from 1935 to 1959, only the duration of employment was known, but not the job category, and thus the same exposure concentration had been assigned to 653 of these workers (Sullivan, 2007)." This phrasing should be changed because the concentration assigned to workers without job assignment should vary by department and time period (as described above).

NIOSH recommends revising Table 5-24 (page 5-90) to assure that the statistics presented are consistent between studies. Column 2 should include actual hire and end of work history data collection for each study, and the table should include vital status follow-up year. For example, the EPA analysis includes all workers hired 1960-May 1982, followed through 2006. Larson et al. includes workers hired from date x (check paper) to approximately 1993, and followed through 2006. The Sullivan, as well as Berman and Crump, analyses were based on white male workers hired September 1935 to May 1982, and known to be alive after 1959 (whether still employed or not), followed through 2001. Moolgavkar et al. may have used different criteria for their analysis. The analyses limited to white males should not be described as full cohort analyses because the full occupational cohorts include some women and non-white males.

The difference in the number of lung cancer cases listed for the Sullivan and Berman and Crump publications. The Berman and Crump analysis was based on an unpublished 10-year lagged SMR analysis done by Sullivan. Sullivan published a 15-year lagged analysis. Both analyses reflect the experience of the same sub-cohort, with 99 underlying-cause lung cancer deaths, yet Table 5-24 indicates that Berman and Crump had fewer lung cancer cases than Sullivan. A 10-year lagged analysis should not include fewer cases than a 15-year lagged analysis. This suggests that the 99 cases cited for Sullivan reflect total cases among white males, not accounting for the 15-year exposure lag. Both lines in the table should reflect the same measure.

Table 5-12 (page 5-68): "credible intervals" should be "confidence intervals"?

Table 5-15 (page 5-75) typo: All workers higher after 1959 (All workers hired after 1959?)

Page 5-90, lines 1-3 reads "The SRR analysis involves internal comparisons of lung cancer mortality rates in the lowest exposure category to the lung cancer mortality rates in the higher exposure categories." Perhaps it would be better to reverse this because mortality in each category of increasing exposure is compared to the experience of the lowest exposure group.

Page 5-90, lines 25-26 reads "Berman and Crump (2008) re-analyzed Sullivan (2007) data except they used lag of 10 years." Please note that this is incorrect. Berman and Crump did not use the NIOSH data, rather a table of 10-year lagged SMRs provided directly by Sullivan, but previously unpublished.

Page 5-90, line 27 reads "They fit IRIS IUR (1988) lung cancer model to aggregate data using extra multiplicative parameter α." Does this mean they applied a multiplicative model which includes an intercept (describing risk of lung cancer in those not exposed to Libby amphibole) to categorical SRR results provided by Sullivan, which assume by default that the relative risk in the lowest exposure group = 1.0, and they found that the model with the larger intercept provided a better fit? Or does it mean something else?

Page 5-91, line 26 reads "lung cancer (ICD-9 160-165) is much more expansive than other researchers' definitions." Two comments about this line: (1) ICD-9 codes 160-165 define respiratory cancer, not lung cancer. Since most respiratory cancers are lung cancers, this probably does not have too much impact on the slope; (2) the reason the McDonald et al. (2004) b estimates are much higher than those reported by other researchers probably has more to do with the fact that the McDonald cohort is limited to a subset of the most-highly exposed workers (408 white men hired before 1964, check the paper).

The comments regarding the content of Table 5-24 found above also apply generally to Table 5-25.

Page 5-92, lines 24-25 state "Duration of employment is the best metric for the full cohort, and it does not support dose-response estimation," yet Table 5-25 demonstrates almost no difference in either the slope or UCL absolute risk estimate per fiber/cc of exposure derived using Poisson analysis based on the full or partial cohort. How then can the statement be made that cumulative exposure is not an appropriate measure for risk estimation with the full cohort, but is for the sub-cohort? Isn't the difference in the IUR, rather, a function of the difference in the upper level of exposure achieved by the post 1959 hires, versus those who worked earlier when exposures were higher? That is, the IUR from the full cohort analysis assumes that the risk is associated with a higher level of exposure (mean 96.0, median 9.8 fibers/cc-years), while the IUR from the 1959+ hire sub-cohort analysis assumes that the risk results from exposure at a lower level (mean 19.2, median 3.4 fibers/cc).

Page 5-94, line 5: suggested edit: "…to consider ~~the discussion of~~ uncertainties…"

Page 5-95, line 6: suggested edit: "…the <u>low-dose</u> exposures…"

Page 5-95, lines 14-15: "…there were 19 (4%) with exposures to average occupational concentrations of less than 0.3 fibers/cc, including one out of 20 lung cancer deaths (5%) in these workers" is confusing and should be clarified.

Page 5-96, Lines 7-8 suggested edit "Almost all of these workers were assigned the same exposure concentration for all years without <u>department and</u> job category information." Actually, the concentration assignment for workers with unknown jobs was more complicated; see Sullivan [2007] which states that these workers were assigned exposure based on their department assignment and these estimates varied by calendar time. For each department (mining, milling, service, other, unknown) Sullivan (2007) assigned weighted-average exposure

for all unskilled jobs in that department (if known) during a calendar time period, as also explained on page 4-14 of this document. So, if most workers were assigned the same exposure concentration, it is because both their department and job assignment were not available, and they worked in the same time period. These workers would also have been assigned the same exposure concentration by the other studies of Libby workers, although it would have been a different concentration.

Page 5-110, line 37 to page 5-111, lines 1-2 state "This assessment showed that unit risk results from analysis of the lung cancer mortality in the full cohort (Sullivan, 2007; Larson et al., 2010a) compared to the sub-cohort hired after 1959 may have been attenuated as much as 2-6 times (see earlier section on statistical uncertainty)." First, Sullivan 2007 did not include a unit risk estimate. Second, if the lung cancer risk estimates are attenuated, why are the slope and CL estimates for mesothelioma based on the full NIOSH cohort (Moolgavkar 2010) the same as those based on the EPA sub-cohort (Table 5-225)? And isn't this the correct comparison, since both used Poisson regression?

Page 5-113, line 3: suggested edit: "Libby Amphibole asbestos, ~~a contaminant of~~ a component of vermiculite ore mined…"

Comments on Chapter 6 Major conclusions in the characterization of hazard and exposure response

Chapter 6 repeats content from Chapter 5 addressed above; thus, the same comments apply to the parallel text in chapter 6.

Page 6-1, lines 23-24: suggested edit: "Vermiculite ore mined near Libby, MT contained Libby Amphibole asbestos, which remained in the final vermiculite product shipped from the mine ~~was not mined for industrial or commercial use, but it was a contaminant of vermiculite mined near Libby, MT~~ (Section 2).

Page 6-2, line 15: replace "were contaminated with" with "contained".

Page 6-2, line 27: reconsider the verb tense used in "there was exposure potential" because there is still exposure potential.

Page 6-2, line 32: replace "asbestos fibers" with Libby Amphibole asbestos fibers".

Page 6-2, lines 33-35: suggested edit: "…for exposure ~~for~~ in homes that contain vermiculite attic insulation from Libby, MT, as residents and workers enter attics for various uses, repairs, and renovations, and ~~for using~~ handle firewood cut from the Libby, MT area"

Page 6-3, lines 17-18: suggested edit: "…than other natural mineral fibers, including serpentine asbestos (i.e., chrysotile) fibers."

Page 6-3, line 22: delete "which are".

Page 6-3, lines 24: replace "may" with "can".

Page 6-3, line 36: suggested edit: "Studies of non-cancer respiratory system ~~effects~~ ~~Studies of respiratory system effects~~ morbidity…"

Page 6-4, line 10: suggested edit: "~~anomalies~~ abnormalities in workers exposed to Libby Amphibole asbestos."

Page 6-7, line 1: "…when examining both workers with a minimum tenure…" is confusing and should be revised for clarity.

Page 6-7, lines 31-32: "…a total uncertainty factor of 100 (10 for interspecies variability and 10 for 32 database deficiencies): 0.076 fibers-yr/cc x 1/100 = 0.00076 fibers-yr/cc." What is the rationale for including the factor of 10 for interspecies variability, as the data was derived from a human study? This should be "intraspecies" variability, correct? (Perhaps "intra-individual variability" would be better in this context.)

Page 6-8, lines 34-36: "However, uncertainty in the prevalence of localized pleural thickening in each individual is considered minimal due to the use of a team of highly qualified chest radiologists evaluating the radiographic films and the use of consensus diagnosis." See previous comment on same sentence appearing on page 5-32, lines 23-26.

Page 6-18 reads "published re-analysis of categorical data of Sullivan (2007)." Please correct to reflect the fact that Berman and Crump utilized an unpublished analysis of 10-year lagged lung cancer SMR provided by Sullivan.

Table 6-2, page 6-18, and Table 6-3, page 6-19: the phrase "still employed post-1959" should be deleted; it is incorrect.

Table 6-3, page 6-19: the footnote a "Re-analysis of Sullivan" does not apply to the Berman and Crump estimates, see above.

Page 6-21, line 36: replace "do" with "does".

Page 6-22, line 6: replace "were" with "was".

Page 6-22, line 15: drop upper case lettering in "Phase Contrast Microscopy".

Comments on References

The reference list at the end of the document is seriously incomplete. It should include everything cited in the document.

Comments on Appendices

NIOSH suggests reorganizing the document to incorporate the relevant appendices into the main text, so that when the text is read, the information available in the appendices will be known.

Appendix C: no specific comments on the analytic methods or results. However, this appendix highlights a major problem with the risk assessment assumptions. Note that there is variation in fiber content within a mine, depending on depth and area being mined. Thus, samples from all batches of vermiculite used, for all mines and time periods 1957-2000, would be necessary to determine that all the fibers that might account for the asbestos-related disease observed at Marysville had originated in the Libby amphibole. Here, we are looking at no samples from the Enoree, and a few samples from South Africa and Louisa VA. These are not enough to rule out

fiber exposure from the several vermiculite sources used at Marysville (in addition to Libby vermiculite, which reportedly was never used after 1980). This appendix confirms that amphibole fibers have been found in Virginia Vermiculite and vermiculite from Palabora, and that tremolite has been found in vermiculite from Enoree, South Carolina.

Attribution of health effects observed in Marysville workers to the Libby amphibole is based on the assumption that other sources of vermiculite from other sources used at Marysville over the 44-year period spanning 1957-2000 contained no amphibole fibers. As Appendix C confirms, amphibole fibers have been observed in vermiculite from each of the other three sites known to have shipped vermiculite to Marysville. Further, the proportion of amphibole fiber in the ore body would have varied by mine over time, and by area and depth within the mine. No basis has been presented to support the assumption that asbestos-related disease observed in Marysville workers can be uniformly attributed to the Libby amphibole.

Appendix E: should describe the significance of these radiographic changes. What do they signify for long term health, given that they appear at older ages, and after a long latency? How quick would progression be, and what health consequences might it have? How important is this health effect?

This Appendix needs editing for clarity. Define acronyms and symbols the first time they are presented in the Appendix text and as a footnote to each table or figure. Add these abbreviation to the list of abbreviations and acronyms beginning on page xii: CHEEC, BMD, BMDL, BMR, CE, Plateau (or don't introduce the plateau model on page E-3 until it has been described), CHIDIST, etc.

Begin by describing what is covered in Appendix E and the derivation of the two data sets.

The inherent assumption that fibers from other sources at Marysville 1957-1962 and 1981-2000 could not explain radiographic abnormalities is problematic. Is it appropriate to attribute all observed disease to the Libby amphibole? This assumption limits confidence in the resulting RfC.

Table E-2: please define "P(CE)". Presumably it is not cumulative exposure. How is pleural thickening defined? An increase of how much? Compared with last radiograph? Compared with expected for age, race, sex, etc.? Is the CE on the left side of these models the same as the CE on the right side of the model? Define "a" in the models. As the differences in AIC listed in Table E-2 do not exceed those expected due to random error, why not use the simplest model? That is, the model used to assess confounding.

Figure E-1: Is the exposure variable logged—i.e., Ln(CHEEC)?

Page 3: the fit p-value cited in the text does not correspond with the Hosmer-Lemeshow GOF p-value listed in the table for the lag10 CE model.

Page 4: how do the two data sets discussed in Sections 1 and 2 differ? Is the analysis based on the experience of 252 former workers, 23% of whom developed disease? It would be helpful if the exact cohort analyzed were described in this Appendix, and if Appendix F were placed before Appendix E so the reader understands what calendar time period the exposure variable describes.

Page 5: How do the two data sets differ? Why is time since exposure important in the full data set and not in the data set described in Section 1 of this appendix? Is Section 1 analysis of the Lockey data and Section 2 analysis of the Rohs et al. data? When discussing the fact that time since first exposure is time of radiograph, rather than time of disease occurrence, consider that the outcome variable is prevalence, rather than incidence.

Page 6: describe how the cut-points between cumulative exposure categories in Figure E-1were selected. Statements in the partial paragraph at the top of page 6 may be correct, but are not supported here. For example, cite background literature , present correlations coefficients., demonstrate multicollinearity, examine the effect of age at x-ray minus age at hire, or present an analysis comparing models using the different variables.

Figure E-1, Panel A: great plot design and very informative figures. However, consider this interpretation: those with cumulative exposure >0.2 fiber/cc-years continue to experience increasing disease prevalence over time, even 45 years after 1st exposure—i.e., fibers remain in the lung and contribute to disease. At lower levels of exposure < 0.2 fibers/cc-years, prevalence of disease decreases after 25 years. What explains this? Are the people with lowest cumulative exposure not available for follow-up radiography? In describing the 2005 radiography (due to long latency, the radiography that is likely to demonstrate radiographic abnormality) Rohs states this is the case. Rohs et al. showed a clear relationship between age and prevalence of pleural changes, after control for cumulative exposure (Figure 1, Rohs 2008). Why isn't age included in models presented here?

Figure E-1, Panel B provides evidence that prevalence of disease increases with increasing time since first exposure regardless of cumulative exposure—i.e., that fibers remain in the lung for more than 20 years after exposure ceases. As all (or most) of these workers ceased exposure at the same point in calendar time, the TSFE variable is a measure of duration of exposure.

Page 8 states "fitting parameters are m, s, and a." Where are m, s, and a defined?

BMR should be defined before page 9.

What are the differences among the three data sets? Only two data sets appear to have been described to this point.

Table E-3: state that table values are expressed as f/cc-years. Why does Table E-3 include 434 subjects, when Rohs et al. 2008 state there were only 431 eligible study subjects (82 were deceased when follow-up radiographs were taken), and radiographs available only on 280? Also, note the difference in number of cases of pleural thickening, 61 in Table E-3, and 80 in the Rohs et al. 2008 paper. Explain the rationale.

Page E-14: note that 0.0042 fibers/cc years is listed in Table E-3 as the BMDL, while this page uses 0.0041. Explain what happened in 1972. The 0.0134 listed here differs from the 0.0136 in Table E-3. Clarify the statement "the reasonably good correlation in the calculated RfC values with the two different data sets provides….". Does this refer to the similarity between 0.7×10^{-05} and 0.1×10^{-04} discussed on page E-4? Or the 0.4×10^{-05} mentioned in the next line?

Page E-15: add that the PODs plotted are the BMDL from Table E-3. Last sentence. If EPA cannot postulate a biological reason for the plateau, isn't the plateau more likely to result from a

limitation in the data (or self-selection into the 2005 study group). In that case, is it appropriate to include the plateau in the model form? What does the plateau represent? A possible explanation for the plateau is differential ascertainment of disease by exposure group (resulting from self-selection of the 2005 study subjects). The plateau was observed at <0.4 fibers/cc-years cumulative exposure. It appears that the low exposure group includes the nonparticipants, but does not include any of their disease. 9.4% of those hired 1974+ had radiographic changes (n=10). If we assume that 9.4% of the 75 living nonparticipants hired after 1973 had pleural changes, then there would be an additional 7 cases. These workers would be in the lowest exposure group <2.13 fibers/cc-years (as the highest cumulative fiber exposure among those hired 1973+ was 2.13 f/cc-years). In addition, 13 workers with low cumulative exposure hired 1974+ were deceased, at least one of whom may have developed pleural plaques since the 1984 radiograph. How many workers with low cumulative exposure may have had pleural plaques in radiography 25 years after last exposure? Page 16: does Figure E-3 show that as time since first exposure increases (or in this case duration), the POD decreases?

It should be clearly stated early in this Appendix that the radiographs from both the 1984 and 2005 study were included in this analysis. Many people in the low exposure group didn't participate in the later study, so their 1984 radiographs were used. However, these were taken at a time when very few had yet to develop disease (based on the experience of those who participated in both radiographic studies). It seems reasonable to assume that this design underestimates the accurate prevalence of disease. By how much (we know that only 65% of eligible study subjects participated in the 2005 radiography? What assumptions about these non-participants were made in the new exposure characterization used in this analysis? Is it appropriate to develop the RfC based on data that is significantly incomplete, particularly in the group with low cumulative exposure in the range that might be observed in the community?

Appendix F: suggest switching the order of appendix E and F. It is not obvious when reading Appendix E that a new exposure assessment was done for Marysville for this document. After reviewing the exposure assessment, there were fewer questions about the modeling.

Appendix F documents new job exposure estimates developed for this survey, stating that fiber estimates for the period 1957-2000 were made for the 280 study subjects who participated in the 2004 radiographic survey. Note, however, that Appendix E documents analysis supporting RfC development that includes 413 workers (including the 151 workers who did not participate in the radiographic screening). What assumptions regarding fiber exposure are made for these 133 workers without new exposure estimates?

Note also that the Appendix F exposure assessment is for all fibers, not just for Libby amphibole fibers. The assumption is made that the Libby amphibole is responsible for all disease, yet the exposure assessment is for total fiber exposure. What part of disease is assumed to be attributable to fibers from other mines?

Appendix G: including the life table is helpful. Suggest placing lung cancer (1% excess risk) first, followed by mesothelioma (absolute risk).

Pages G-1 and G-7: NVSR 58(19) 2010 is cited; however, in the References it is listed as U.S. DHHS. Make tables consistent with the References.

More precise labeling of the columns might be helpful, to address these questions:

Column B: Wouldn't this be 684.5 x 10^{-5}/year? Rates are usually expressed per 100,000 rather than using scientific notation; it would be clearer if that approach could be used here.

Columns B and C: Column headings could be clearer, for example: "U.S. population age-specific all cause mortality rate per 100,000" "U.S. population age-specific lung cancer mortality rate per 100,000."

Column I: Where do these exposure values come from?

Columns K, L, M, and N refer to "exposed." Are these the study subjects, i.e., the cohort?

Explain why there are 1-year age intervals until age 30, and then 5-year intervals? Is this to calculate risk to children? If no reason, put it all on one page, with 5-year age intervals.

Are all these columns used in the calculation? If not, delete unnecessary columns. Are Column E and L the same? Column D and K are the same. Column F and M are the same. Columns H and N?

Suggest this column arrangement might be more logical, or something similar that would require less jumping around the table: A, B, D, F, E, C,G,H,I,K,J,M,L,N

Table G-3 footnote states that "occupational lifetime unit=0.0524." How is that number derived?

Table G-4, Column I: how does this account for 10-year half-life?

OMB Staff Working Comments on EPA's Libby Amphibole Asbestos draft Toxicological Review (page numbers refer to the draft dated May 2011) **and Draft Charge to External Reviewers**

June 15, 2011

General Science Comments:

- We recommend consideration of the following questions and additions to ensure that the final RfC of 1x 10^{-5} fibers/cc is realistic.
    - As EPA is proposing an RfC that is at or below background levels, we suggest a discussion of current levels of detection and analytical sensitivity to ensure that the RfC is realistic and implementable. In addition, EPA should clarify how the RfC, in fibers/cc relates to s/cc (structures/cc).
    - Page 2-23, states that ambient air in schools, in 2006/7 ranged from 0.0022 to 0.039 f/cc in the Libby community. If one assumes that the level was less in 2006/7 (when sampling was conducted) compared to the 1950s, wouldn't we expect most if not all of the population to show pleural thickening? Does EPA have information about the rates of pleural thickening in the Libby community, and if so, could EPA compare the predictions from the analysis with actual rates?
    - Page 2-27, notes that background air samples in homes were below 0.0016 f/cc when the air was not disturbed, and modeled to be 0.001 and 0.25 f/cc during renovations. Table 2-3 shows all area and personal samples to be orders of magnitude above the RfC. If the RfC is accurate, does this mean that most of the homeowners in the US (page 2-26 notes that 80% of the vermiculate used in US homes came from Libby) should be showing pleural thickening?
    - According to the HSDB, ambient air levels are generally less than 5 x 10^{-5} fibers/cc. In addition (see http://books.google.com/books?id=rR4ewu4IfmsC&pg=PA26&lpg=PA26&dq=asbestos+how+many+ng+to+a+fiber&source=bl&ots=Os8L5aPaqP&sig=eOrVAN6mtuwvRA_IflgvrsfIlAE&hl=en&ei=GxK_TdK5DM6ztweS-bnNBQ&sa=X&oi=book_result&ct=result&resnum=1&ved=0CEMQ6AEwAA#v=onepage&q&f=false) the table below shows that throughout the US, air in schools and US cities is above the proposed RfC. Again, this would seem to suggest that the we would see a large amount of pleural thickening. What do we know about the current rates in the US?

Table 2-1. Summary of asbestos exposure samples in different environments

Sample set	Sample No.	Measured concentration (ng/m³) Median	Measured concentration (ng/m³) 90th %ile	Equivalent concentration (fibers/cc)* Median	Equivalent concentration (fibers/cc)* 90th %ile
Air of 48 U.S. cities	187	1.6	6.8	0.00005	0.00023
Air in U.S. school rooms without asbestos	31	16.3	72.7	0.00054	0.00242
Air in Paris bldgs with asbestos surfaces	135	1.8	32.2	0.00006	0.00107
Air in U.S. bldgs with cementitious asbestos	28	7.9	19.1	0.00026	0.00064
Air in U.S. bldgs with friable asbestos	54	19.2	96.2	0.00064	0.00321

Source: Modified from Ref.17. *Based on conversion factor of 30μg/m³ = 1 fiber/cc.

- Page 4-30, line 22, notes that the exposures in group 1 (the non-exposed group) in Marysville Ohio studies was 0.049 fibers/cc, and the levels in the low-exposure groups were 1.2-1.5 fibers/cc before 1974. How do the levels of pleural thickening in these non-exposed and low-exposure groups compare to the levels EPA would expect considering that these exposures are orders of magnitude above the RfC?
- Page 4-34, table 4-10, shows that at the lowest exposure (0.12 fiber/cc) the number of workers was only 7%. If the RfC is correct, shouldn't a much greater percentage have shown changes?
- It would also be helpful to provide a clear discussion regarding US background rates of pleural thickening and how these may be impacted by age and or smoking. This comparison information would be helpful when EPA discusses the radiographic changes in the Libby cohort. It would be helpful for EPA to have a specific charge question on the background rate chosen for the RfC analysis.
- For the RfC analysis and for exposure reconstruction, EPA assumes 365 days of exposure per year for workers and 24hr/day exposure. Further discussion about why this was chosen (rather than a 40-hour work week with holidays and vacation) would be helpful. EPA may also want to consider a charge question relating to these assumptions.
- In discussing the RfC, perhaps greater discussion and weight could be given to potential confounders such as age and smoking. Further discussion in 5.2.1 would be helpful.
- Table 5-3 clearly shows a dose response for local thickening, but a similar relationship is not seen for the other changes (until the highest dose is reached). We also note that the lowest exposures here (0.061 fibers-yr/cc), where minimal effects are seen, is orders of magnitude above the RfC.

- The approach to deriving the RfC raises the following questions.
  - Cohorts:
    - Page 5-10 notes that exposure estimates were developed, and are shown in App F. Has this analysis by the Univ. of Cincinnati undergone independent

external peer review? Undergoing review in the context of this larger IRIS document will not be as rigorous as a separate review of the analysis. We suggest that EPA have a separate review and a separate charge (that will ensure that the analysis meets IQ standards) for the analysis. Charge questions should also include a clear question about the adjustment factors that were used.

- § EPA relies on Locky and Rohs, where Rohs is a followup of the Locky study. Both use the same cohort, however, EPA notes (page 5-8) that there was selection bias in that only 280 employees of the original cohort were evaluated in Rohs. Please ensure that this selection bias and its implications are discussed. Similarly would any bias be introduced by the way that the two cohorts were combined due to differences in the length of follow up?
- § EPA only presents RfC derivations for the Marysville cohort. It is not clear why EPA did not carry forward and present analysis using the Amandus and McDonald studies as well. While the studies may be less preferred, they may help to inform the reliability of the value derived from the Marysville Cohort. EPA states that they chose this cohort due to increased risk of "pleural and paranchymal effects". Please discuss how EPA came to this conclusion--e.g., did EPA run all the numbers for all the cohorts? If so, consider presenting.
- § EPA on page 5-18, treats Rohs and Locky as two separate cohorts and combines them. If one was follow-up of the other, how does EPA avoid double counting individuals (the cohort appears to be 434 workers)? In addition, is EPA creating bias by excluding those individuals negative in 1984 but positive in 2008 and keeping those individuals positive in 1984 and positive in 2008? While we think this is an oversight, if EPA continues with this approach we suggest a very clear and specific charge question about how the individuals were included and excluded. EPA should consider reanalysis of the POD estimates from what EPA determined to be the full cohort.

- o Endpoint:
  - § Page 5-12 notes that pleural thickening can be graded, but these data are not always provided (can they be presented?) It seems it would be helpful to examine the radiographs where such grading was provided to see how the severity is related to the effect). Is the RfC relating to minimal effects or severe effects? It would also be helpful to have discussion about the clinical implications of local pleural thickening vs diffuse vs paranchymal change.
  - § Page 5-15, notes that discrete pleural thickening was chosen due to its minimal adversity. What does this mean? Are there clinical effects? EPA states that this is considered an adverse effect; please explain why it is adverse as well as why it is not being considered a precursor. The current discussion is very general and it is unclear if EPA is referring to discrete or diffuse pleural thickening, which have very different dose-response relationships.
  - § On page 5-20 EPA references the available baseline information on such thickening. Did those who reported the results of the NHANES and other datasets consider these effects 'adverse.' Perhaps adding text to page 5-15

that uses these authors' characterization of this same endpoint would help the reader put this endpoint in perspective.

- Benchmark dose modeling
  - EPA discusses choosing the model with the lowest AIC from all models with AICs within 2 units of the lowest AIC. Please explain what is meant by 2 units, the rationale for this choice, and provide the lag for all the models so that it is clear what it means to choose the lowest AIC, .
  - If the AICs were within 2 units of each other, it is not clear why EPA is treating one as preferable. [we note that page 5-71 states that AIC values within 2 units may not always be meaningfully differentiated.] Should the similarity in measurements be interpreted within the context of the margin of error? Did EPA consider using an average of the derived BMDL values for all those that fit equally well. If it is a policy choice rather than a real difference in the interpretation of the numbers, EPA should clearly state this throughout the document and also let the risk managers know the range of options (for instance, let them know that had EPA chosen an equally well fitting model with a higher BMDL, the difference would have been X in the final RfC). In table 5-5, it looks like this would have led to a 4x difference in BMDL values.
  - When EPA discusses choice of models, in addition to discussing fit, it would be helpful to provide discussion of the biological plausibility of the different model choices (for both the main and alternative analyses)

- Uncertainty Factors:
  - It is not clear how EPA can have medium-high confidence in the principal study. It makes sense that using a human study with fairly low occupational exposures as the basis of its POD, would lead to fairly high confidence, but if this is the case, why are 2 orders of magnitude of uncertainty factors needed?
  - EPA applies a 10x uncertainty factor for inter-individual variability. Applying a full factor of ten here (where the extrapolation is from low level exposure in presumably health adults to even lower levels of exposure for the general population) seem incongruous with the amount of uncertainty that would be introduced in extrapolating from, for instance, rats to humans. We recommend reconsidering the application of a full 10 fold factor of uncertainty, if for consistency reasons alone. Regardless of the factor applied (e.g., even at a 2 or a 4), please discuss what other populations EPA expects to be more sensitive to this endpoint.
  - EPA applies a 10x uncertainty factor for database deficiencies. It is unclear to us why a full factor of 10 rather than a relatively low factor for this is appropriate given that EPA is basing the RfC on the most sensitive effect seen. What is the specific scientific rational to expect cardiovascular or immune effects at levels below the chosen point of departure? EPA should clarify what data support this should use a weight of evidence approach that looks at the full body of information and what is known about mode of action to inform whether or not a full 10x factor is needed using the POD of 0.0012

fibers/cc. EPA can still articulate the extent to which specific information is lacking and acknowledge the gaps, without applying a full factor of 10.

- § Page 5-31 line 31 notes the potential co-exposures in the Marysville facility but states that the fiber levels were very low in these areas; what did EPA do to address the possibility of confounding? EPA should discuss how low they were and if they were above or below the proposed RfC.

- The weight of evidence characterizations of effects could be better clarified. A few examples are provided in the bullets below.
  - For instance, page 4-14, line 3-6, EPA states that table 4-4 shows similar effects in terms of the increased risk for lung cancer. It is not clear how EPA is drawing this conclusion. In the Amandus study, the SMRs are very low and since confidence intervals are not reported, it is hard to know if there were any statistical differences. There don't appear to be any notable increases until exposures exceed 400 fibers/cc-year. In the McDonald study, the only statistical increase is above 113 fibers/cc-year, which is not consistent with Amandus where in the 100-399 fibers/cc-year range the SMR was 1.1, and no confidence interval was reported. In the Sullivan study, the SRR at the highest level (>100 fibers/cc-year) was not statistical significant, and the Larson study did show an elevated RR at > 44 fibers/cc-year. As these findings do not seem consistent across studies, it is unclear how EPA can state: "Increasing risks across categories of cumulative exposure and duration were observed….indicating a positive exposure-response relationship." It would be helpful if EPA clarified, throughout this section and elsewhere, exactly where there was statistical significance, where there was not, and where it was not determined.
  - Similarly 4.1.1.3.4 states that the studies provide "clear evidence of an increased risk.." and that an increase in risk is seen with increasing exposure. As it is unclear if EPA is referring to trends that were not statistically significant, or what studies and exposure metrics EPA is relying on, more clarity on what is driving this weight of evidence determination would be helpful. Line 35 also notes a plateau. As this was not discussed previously, more clarity on what data are showing this would provide helpful support for this concept. EPA cites Sullivan and Larson here but this is confusing. The mean durations of exposure were much longer in Sullivan compared to Larson (4yrs vs 0.8 yrs) however the SRR in the Sullivan study were never statistically significant. In Larson, only the highest dose was statistically significant making it unclear where the plateau concept is coming from.
  - 4.1.1.4.4, states that "the risk of mortality related asbestosis and other forms of non-malignant respiratory disease is elevated…with increasing risk seen with increasing exposures..". It is unclear what studies provide the support for these findings. For instance, in table 4-5 the Amandus study shows, when accounting for latency, a decrease in SMR for non-malignant respiratory diseases is seen as exposure increases. The McDonald study only shows statistically significant effects once 113 fibers/cc-yr is exceeded and the Larson study only shows an effect above300 fibers/cc-yr.
  - On page 4-70, EPA states that there is a 'convincing association'. Further clarification of what studies and doses/exposures are providing this information would be helpful as the individual tables were conflicting when one looked at the details.

- On page 4-15, EPA, adds a sentence discussing the possibility of confounding due to smoking. As it is well known that there are syngerstic effects seen among those who smoke and are exposed to asbestos, it would seem that EPA should have a clear discussion of what this research has shown. CDC/ATSDR fact sheets note that the risk to lung cancer greatly increases when there are exposures to both, yet the EPA document treats the relationship as more uncertain. It would be helpful for EPA to have a more complete discussion of what the data have shown, consistent with CDC/ATSDR and then further discuss the impacts of this on the studies EPA evaluated.
    - Discussion on page 4-15 seems to present a comparison of smoking rates at different points in time compared to what is known about some of the workers in the Amandus study. It is unclear how the analysis was conducted but Amandus states that confounding could have resulted in a 23% increase in the risk ratio. It is not clear how EPA takes this into account throughout the assessment.
    - EPA also states that there is a lack of information on smoking for some of the time periods and workers and (on page 4-16) there is "considerable uncertainty regarding the evidence for differences in smoking rates..". While this is true, based on what the scientific literature shows, there is also considerable uncertainty regarding whether the relative risks shown are due to asbestos alone or asbestos and smoking together. EPA should clearly state this and take this into account throughout the assessment.
    - A clear overarching discussion regarding the impact smoking may have on non-cancer lung effects (eg asbestosis and pleural thickening) as well as radiographic anomalies, would also be helpful.
    - Section 4.5, in the discussion of each critical endpoint, should include discussion of confounders such as smoking and aging.
    - While there is some minimal discussion in 4.7.6, there should probably be a separate discussion of the impact of smoking in the susceptible populations section. In addition, whereas EPA states (page 4-86, line 17) that "smoking might contribute to increases in lung cancer..", we believe the weight of evidence is much stronger than "might contribute" and "might also" (line 19). Please see CDC/ATSDR and NIH documents on this.
    - Section 5, in discussing the RfC, based on pleural effects, should discuss the impact of smoking and age on these endpoints in the general population.
    - Page 5-61, more clarity is needed regarding the extent to which EPA accounted for smoking in the lung cancer analysis. A specific charge question should be added addressing this known confounder.
    - Page 5-64 notes that smoking data were missing for 60% of the workers. Please clarify how EPA appropriate controlled for smoking when so much data were missing. For the sub-cohort analysis, how many workers had data on smoking?
    - Page 5-108, EPA only notes that it is "theoretically possible" that there is a positive synergy. This statement underestimates what is known. EPA notes that the derived IUR would be heath protective for smokers. While this may be true, one wonders if the IUR was derived to represent the combined risk of asbestos and smoking, not just asbestos exposure alone.

- When discussing the non-cancer lung effects, it would be helpful to use consistent terminology. We sometimes see the results of Lockey and Rohs referred to as "pleural changes", other times it is "pleural thickening" or "discrete pleural thickening" or "localized pleural thickening" of "diffuse pleural thickening". Clear definitions for each of these terms, and how they intersect are needed. When summarizing effects, EPA often gives percent/prevalence of workers that showed pleural changes. As not all these changes are equal (eg diffuse vs local) it would be helpful to describe what percent of workers showed each effect in more detail.

- Consistent with its Cancer Guidelines, EPA should conduct and present non-linear modeling for the cancer effects of asbestos. We suggest this analysis be added to the document before it is sent for external peer review.
    - There is sufficient information and significant biological support to find that asbestos, acting as a fiber, acts through a mode of action that is due to the presence of inflammation and oxidative stress. This is absolutely plausible and in vitro data support this, as EPA notes on page 4-55. While we can agree that a specific mechanism of action may be unknown, and data gaps regarding specific mechanisms exist, it is more than plausible that this is a likely mode of action. As per EPA cancer guidelines, we see no reason for the exclusion of a non-linear modeling approach as supported by this plausible mode of action, for which there is biological support.
    - The EPA cancer guidelines (2005) at page 1-8 state: "When there are alternative procedures having significant biological support, the Agency encourages assessments to be performed using these alternative procedures, if feasible, in order to shed light on the uncertainties in the assessment, recognizing that the Agency may decide to give greater weight to one set of procedures than another in a specific assessment or management decision." Page 1-9 states: "If critical analysis of agent-specific information is consistent with one or more biologically based models as well as with the default option, the alternative models and the default option are both carried through the assessment and characterized for the risk manager." Page 1-15 states: "The linear approach is used when: (1) there is an absence of sufficient information on modes of action or (2) the mode of action information indicates that the dose-response curve at low dose is or is expected to be linear. Where alternative approaches have significant biological support, and no scientific consensus favors a single approach, an assessment may present results using alternative approaches." Finally, page 3-23 states: "Nonlinear extrapolation having a significant biological support may be presented in addition to a linear approach when the available data and a weight of evidence evaluation support a nonlinear approach, but the data are not strong enough to ascertain the mode of action applying the Agency's mode of action framework. If the mode of action and other information can support chemical-specific modeling at low doses, it is preferable to default procedures."
    - Section 4.6.2 and 4.6.2., and elsewhere in Sections 5 and 6, should be revised to reflect that while the mechanism of action is unknown, there is a biologically plausible mode of action. As stated on page 4-73, we do not agree that the limitations of the available mechanistic data prevent EPA from making a finding that the mode of action cannot be established. The available limited studies are supportive and suggestive of a non-linear mode of action.

  - We note that external peer reviewers (including SAB, NAS and external panels), as well as interagency reviewers have concluded that in recent assessments such as dioxin, formaldehyde and chromium (see pre-meeting notes of external reviewers), EPA should have presented non-linear modeling. This is another case where EPA should conduct such modeling and carry it forward for the risk manager (as per the cancer guidelines).

- Page 5-56, line 1, EPA states that they accounted for uncertainty by choosing the metric which estimated the highest risk. This appears to be a policy decision which may be more appropriate for risk managers than for risk assessors. In any case, EPA should note that this is a policy choice and also carry forward for risk managers what the impact would have been if EPA accounted for uncertainty by choosing the lowest and median risk values. Risk managers should be seeing the full range of impacts. An uncertainty table which presents ranges around EPA decision points would be helpful.

- Concerns regarding the cancer modeling:
  - For the cancer modeling, should EPA be concerned that the best fitting models were those that showed no lag? Is this biologically plausible and if not, couldn't this point to some concerns with the models and or the data set?
  - For the cancer modeling, EPA used a sub-cohort that included workers hired after 1959. However, it seems that data on fiber concentrations did not improve until 1968. Did EPA consider a cohort that started in 1968? Can anything be said about the difference between the cohorts? From the tox review, it seems that better data were available after 1968, rather than 1959.
  - In Table 5-14, many of the AIC values are within 2 units. Has EPA considered using an average value of the slopes rather than the policy decision of choosing the lowest AIC? EPA should discuss the impact the other equally plausible and well fitting models would have had on the slope. Again, presentation of these ranges in an uncertainty table, or table of critical choices, would be helpful to external reviewers and risk managers.
  - Page 5-76, EPA states that there was no clear distinction between model fit in the cohorts, but table 5-16 does show very different AIC values, with much lower values in the cohort that excluded highly exposed workers. It would also be helpful to show the slopes in table 5-16.
  - Regarding the treatment of confounding as described on page 5-77, EPA should add a specific charge question for the external reviewers taking comment on the limited analysis that was conducted. Since there is such a known synergy, it would increase confidence in the assessment if EPA used multiple approaches to address the confounding issue and then compared them.
  - Page 5-87, line 5-14, we suggest revising to present all models with equal fit, biological plausibility and statistical plausibility.
  - Section 5.4.6.1, in general these paragraphs discuss how the EPA approach decreased the uncertainty, but is not quite as clear in the discussion of the extent and magnitude of the uncertainties before and after EPA accounts for them. For instance, page 5-95, line 22, states that some uncertainty remains; however the extent of this uncertainty and its impact is never discussed. Similarly at page 5-96, line 12 states that there are still uncertainties, but their magnitude is not clear.

- We recognize this is a very important assessment and the implications of a new RfC and IUR will be broad and far-reaching with potentially large regulatory implications. Therefore, in light of concerns and implications raised we suggest that EPA consider an NAS review. The review panel should include: multiple clinical pulmonologists, multiple biostatisticians, multiple exposure assessors, including experts in dose reconstruction, as well as toxicologists with expertise in the pulmonary system to ensure representation of a diversity of perspectives and encourage debate.

Editorial Comments (with Scientific Impacts):

- We noticed that many of the EPA citations were missing from chapter 7, the references. This should be checked before release. A few examples (but a complete check was not conducted)
  - Page 2-21, line 8, EPA 2008.
  - Page 2-23, line 7, EPA 2001a,b
  - Page 5-93, line 17, EPA OSWER
  - Page 5-94, line 1, EPA 1986b
  - Page 5-94, line 2, EPA 2005- (which one was used is not clear)

- Page xv, the Forward, draws attention to Section 6. As written, Section 6 appears to be simply a reiteration of other chapters without any synthesis or further elaboration. It may be helpful for EPA to think about ways to make this chapter more useful to IRIS users. EPA may also want to consider more explicit discussion regarding overall confidence in the cancer values. While many uncertainties are discussed, there is no final opinion provided regarding confidence.

- Page 1-4, line 24, when mentioning the IRIS IUR, please clarify if you are referring to the existing IUR or the IUR derived in the document. Similarly on line 28, please clarify that the current document does derive an RfC.

- Page 1-4, lines 24-30, it would be helpful if EPA provided citations for each of these sentences. How does EPA know that 80% of the world's vermiculite, between 1923-1990, was produced at Libby. Similarly a citation is needed on page 2-26, at line 34.

- Page 2-21, line 8, is this document the draft OSWER document that was negatively reviewed by the SAB? If so, can a better citation, to a final peer reviewed document be provided to discuss the TEM technique that is recommended?

- Page 3-5, Table 3-1, is derived from a version of Casarett & Doull that is 25 years old. Has the science evolved since then and can more be said about retention, clearance, dissolution and translocation?

- Page 3-10, line 6-10, please provide a citation for this statement.

- Page 3-11, and also in Section 3.2 in general, it would be useful to provide some discussion regarding how and when clearance mechanisms are overwhelmed. It seems that this is likely a non-linear process and if more could be said about what it takes to overwhelm the natural clearance mechanisms this would be useful and relevant to the assessment.

- Page 4-2, line 10-12, it would be helpful to provide the status and expected completion dates for the 17 health consultations that are not available yet. Is it possible that these could help inform the toxicity values being derived?

- Page 4-2, line 15, and elsewhere throughout the document, EPA also draws attention to and discusses findings for Tremolite asbestos (see for example section 4.2). As EPA states that this is only 6% of the Libby mix, it is unclear why EPA brings this up. Are there other components of the Libby mix that are greater than 6% that should also be discussed, or is Tremolite the main component? More clarity throughout the document regarding the discussion of Tremolite would be helpful.

- Page 4-4, line 11. Please clarify who the McGill and NIOSH researchers were. The document seems to jump between authors and institutions.

- Page 4-6, line 27-29. Can EPA clarify why an alternative procedure was needed and used by McDonald to estimate the mean of the log-normal distribution? What impact did this have on the mean compared to using a more typical approach to estimating the mean?

- Page 4-16, line 6-9, here and elsewhere throughout section 4.1, please always provide confidence intervals when presenting risk numbers.

- Page 4-16, line 13-16, please clarify if this analysis was conducted by Larson or EPA. If conducted by EPA, please clarify where these data can be found.

- Page 4-16, section 4.1.1.3.2, it would be helpful to provide the mesothelioma data in a table. Please also discuss and present the confidence intervals relating to the McDonald RR values.

- Page 4-18, table 4-5, the Amandus study appears to show a decrease in SMR for nonmalignant respiratory disease with cumulative exposure when a latency period is considered. Where in the text does EPA discuss the implications of this?

- Page 4-34, it is unclear where Table 4-10 is discussed.

- Page 4-35, Table 4-11 shows a significant association between prevalence of radiographic changes and age. It is not clear that this association is discussed in the text. Should this be treated as a confounder?

- Page 4-36 discusses co-exposures in the Rohs and Lockey study. However the text does not discuss formaldehyde or urea which were previously mentioned (page 4-30) as being in the vermiculate blend. The uncertainty provided by these co-exposures, as well the others mentioned, should be discussed. A clear charge question about the potential impact of these co-exposures, would be helpful.

- Page 4-48, line 21-22, please clarify the route of exposure in this sentence.

- Page 4-52, line 22, mentions Blake, 2008. We did not see where the findings of this study were discussed. It looks like this is an *in vitro* rodent study.

- Page 4-53, line 11-17, sentence is unclear. On line 17 please also provide the confidence intervals for the RR values.

- Page 4-60, line 3, states: "These results suggest that Libby Amphibole asbestos may act through similar mechanisms as other forms of asbestos..", however, it is unclear that EPA has discussed the mechanisms of other forms of asbestos.

- Page 4-69, section 4.5.5.1 would benefit from a discussion regarding at what level typical clearance mechanisms are overwhelmed and chronic inflammation is seen.

- Page 4-69, line 22, please describe the route of exposure for these animal studies as this is relevant to the effects seen.

- Page 4-71, line 19, EPA presents the RR values as showing a plateau. As the finding for the lowest dose was not statistically significant, EPA should mention this and consider it when discussing this 'plateau'. Whenever a RR value is presented, please present the confidence intervals.

- Page 4-77, section 4.7.1.1, it would be helpful to say more about the relevance of the route of exposure in the studies showing transplacental transfer and the impact this may or may not have on findings.

- Page 4-80, line 30-32, please provide confidence intervals for these SMR values.

- Page 4-87, line 6-9, perhaps smoking should be mentioned here as well.

- Page 5-7, "Logistic regression analysis was used to examine the relationship between cumulative Libby Amphibole asbestos exposure and radiographic abnormalities, controlling for age and smoking." Can more details be provided since these are such important confounders?

- Page 5-7, discusses how Lockey 1980, did pair-matching by age. Please discuss how smoking was controlled for. Did the Rohs follow-up do similar matching?

- Page 5-15, 2nd paragraph, last sentence, please clarify that EPA has made this determination.

- Page 5-27, more clarity is needed on how Table 5-6 should be used by risk assessors and risk managers.

- Page 5-28, line 1 states that there were no repeat observations for workers. This is not consistent with page 5-18.

- Page 5-29, it is very difficult to follow the discussion of the alternative analyses. Tables should be provided to present the data in a clearer manner.

- Page 5-62, line 30-35, the impacts of the lack of proportionality are unclear.

- Page 5-69, how was confounding controlled for in table 5-13? It is also unclear what EPA means by 'decay' and which models showed decay and which did not.

- Page 5-72, line 15-18, where are these derivations presented?

- Page 5-75, table 5-15, it would be helpful to show the slopes in the table.

- Page 5-79, line 28, considering the age of the cohort, is 16 yrs of age an appropriate starting point?

- Page 5-81, line 25, please confirm that the Kopylev study has been peer reviewed.

- Page 5-82, line 5, it would be helpful to clarify what it means to use the Selikoff and Seidman approach. Is this analysis in an appendix? Please also clarify what the baseline values were.

- Page 5-107, line 28, it is unclear how confounding is decreased and the extent of the confounding which could still remain is not clear.

- Page 5-110, line 15-18, we could not find this sentence or concept in the cancer guidelines. Please use a direct quote from the cancer guidelines or explain the basis for this interpretation.

- Page 5-111, line 17-23, is this bullet discussed earlier in the tox review?

Comments on the Draft Charge:

[Note: some suggestions for charge questions are provided in comments in the above sections. Many of those comments have not been reiterated here, but should be considered as equally important.]

- Throughout the charge, please replace "appropriate" with a more robust standard that will ensure that the document meets and exceeds standards set in the Information Quality Guidelines. These guidelines suggest that information must be objective and based on the best available science. While the IQ utility standard requires information to be appropriate for its intended use, since IRIS files have many uses, EPA should ensure that the highest standards are met and EPA should treat this as a highly influential scientific assessment.

- To ensure that reviewers are aware of the implications of their review, we recommend that paragraph 3 of the charge note that, as per findings in the tox review, 80% of the vermiculate used in US homes came from Libby, and thus exposures are broad and widespread. This will also help to frame the issue of whether we are seeing results in the general population consistent with the final values EPA proposes.

- EPA should add a charge question regarding the impact smoking may have had as a confounder in the studies evaluated, particularly for lung cancer (as well as for the RfC). In addition, explicit questions regarding whether the methodologies used to adjust for this confounding are sufficient should also be added (for instance, is the bias-adjustment factor used by Larson et al, sufficient). Peer reviewers should be asked to comment directly on the impact of smoking as a potential confounder.

- As noted above, we suggest that EPA revise the document to present non-linear cancer modeling, as well as linear, as there are plausible biological modes of action that would support this. We also suggest an explicit charge question be added to take comment on a preferred approach, based on the scientific evidence. This will also impact question B2.

- General Questions 2: It is unclear how reviewers will be able to tell if additional studies would have a significant impact on the conclusions. Suggest reframing this to simply ask about relevant studies and then EPA can conduct further evaluation to determine if the studies will have a significant impact.

- In A2, EPA calls 'localized pleural thickening' a critical effect. Please clarify for reviewers whether or not this is an adverse effect, a precursor, or something else. Suggest also taking comment on EPAs determination of it as being an adverse effect.

- A3: as per previous comments, EPA should have a separate and distinct peer review on this exposure reconstruction. This charge should address specific issues including: adjustments, treatment of confounders, use of the subcohort, strength of data, and exposure time periods (24hr, 365 days/yr).

- A4: please add an explicit question about confounders—including co-exposures.

- A7: please ask questions about whether the weight of evidence (including what is known about effects seen, mode of action, and data gaps) support the use of a 10x UF for database uncertainties. We note that this application does not seem consistent with past practices. Please also ask a similar question about human variability as well.

- A8: please specifically ask reviewers to comment on whether the uncertainties and limitations are presented in an objective (in both presentation and substance) and accessible manner. Please also ask if the role of these uncertainties and limitations have been objectively and transparently synthesized into the weight of the evidence to derive the RfC.

- Please add a question asking reviewers about how they would interpret the proposed RfC in the context of known background levels.

- B3: Please add a specific question taking comment on EPAs treatment of smoking and other confounders.

- B8: please specifically ask reviewers to comment on whether the uncertainties and limitations are presented in an objective (in both presentation and substance) and accessible manner. Please also ask if the role of these uncertainties and limitations have been objectively and transparently synthesized into the weight of the evidence to derive the IUR.