

Compilation of Revised Individual Comments from Panel Members

(as of February 29, 2012)

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Dr. John R. Balmes

Section 4.5- Synthesis of Non-Cancer Effects and Section 4.7- Susceptible Populations (General charge questions 1 and 2)

1. Is the Toxicological Review logical, clear, and concise? Has EPA clearly, and in sufficient detail, presented and synthesized the scientific evidence for health hazards from Libby Amphibole asbestos?

The scientific evidence for non-cancer effects of Libby Amphibole asbestos is reasonably well presented in Section 4.5. Subsection 4.5.5 indicates that “there is currently insufficient evidence to establish the non-cancer mode of action for Libby Amphibole asbestos.” While this statement may be true in an absolute sense, a great deal is known about the mechanisms of injury, inflammation, and fibrosis due to asbestos. This subsection undervalues this knowledge by focusing on the evidence available that is specific to Libby Amphibole asbestos. There is no reason to suspect that the mechanisms in question are different for Libby Amphibole asbestos as compared to other asbestos fibers.

The scientific evidence presented in Section 4.7 is well summarized in Subsection 4.7.7. Little is actually known about potentially susceptibility due to age, sex, race-ethnicity, and health status. Based on what is known about other types of asbestos, smoking is likely to be a major factor regarding lung cancer risk. The subsections of 4.7 preceding 4.7.7 present the evidence in a manner that tends to obscure rather than clarify what is known.

2. Please identify any additional peer-reviewed studies from the primary literature that should be considered in the assessment of noncancer and cancer health effects of Libby Amphibole asbestos.

The most recent Larson et al. paper in the *Journal of Occupational and Environmental Medicine* (2012) regarding non-cancer endpoints in the Libby cohort and the two papers from the Minnesota population exposed to Libby Amphibole asbestos (Alexander et al., *Environ Health Perspect* 2012 and Adgate et al., *J Expo Sci Environ Epidemiol*, 2011) should be considered. In addition, the endpoint selected for the RfC calculation, localized pleural thickening (LPT) could be better justified by

inclusion of relevant literature on the association of LPT with decreased lung function and cancer risk.

Sections 5.2 and 5.3-Inhalation Reference Concentration (RfC) and Uncertainties
Uncertainty Factors (charge question III.A.6)

III.A.6. Please comment on the rationale for the selection of the uncertainty factors (UFs) applied to the POD for the derivation of the RfC. Are the UFs appropriate based on *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002; Section 4.4.5) and clearly described? If changes to the selected UFs are proposed, please identify and provide scientific support. Specifically, please comment on the rationale for the selection of the database uncertainty factor (UF_D) of 10 applied in the derivation of the RfC. The database uncertainty factor accounts for the lack of data on effects other than in the respiratory system, including other effects observed in community and laboratory animal studies (cardiovascular disease and autoimmune effects) that have not been well-studied (See Section 5.2.3 of the Toxicological Review); and lack of health data assessed at later time points. Is the rationale for the UF_D appropriate and clearly described? Please provide the rationale if a change in the UF_D is proposed.

The EPA's choice of uncertainty factors is reasonable based on standard risk assessment practice. However, the application of two uncertainty factors of 10, one for intra-species variability and one for database uncertainty makes the calculated RfC quite, and perhaps biologically implausibly, low. Effects on the cardiovascular system and autoimmunity are not likely to occur at very low exposures. I would favor the use of a more conservative UF_D for database uncertainty such as 3.

Section 6.1- Hazard Potential
(General charge question 1)

In general, this section is clearly written, with the appropriate level of detail, and well synthesized. That said, the sub-sections on mode of action and susceptibility suffer from a focus on data specific to Libby Amphibole asbestos and neglect the relevant body of knowledge on asbestos in general. There is little evidence to suggest that the mode of action of Libby Amphibole asbestos is different from that of

These Revised comments are from individual members of the SAB Libby Amphibole Asbestos Panel and do not represent consensus SAB advice or EPA policy. DO NOT CITE OR QUOTE.

other amphiboles or that smokers would not have increased susceptibility to the lung carcinogenic effect of Libby Amphibole asbestos.

Dr. James C. Bonner

General Charge Questions: (Relevant Section 4.5 – synthesis of non-cancer effects and section 4.7 – susceptible populations)

1. Is the Toxicological Review logical, clear, and concise? Has EPA clearly, and in sufficient detail, presented and synthesized the scientific evidence for health hazards from Libby Amphibole asbestos?

Comments:

- a) Section 4, pg 4-1: The review mentions the different types of minerals present in Libby amphibole (LA) and it is uncertain how the various components relate to adverse health effects, although it is made clear that tremolite is a highly carcinogenic and pro-fibrogenic amphibole. LA contains ~6% tremolite and there is clear evidence from human and animal studies that tremolite causes adverse health effects in humans and experimental animals. However, since Libby Amphibole asbestos also contains winchite (84%) and richterite (~11%), it would be prudent to determine whether these mineral forms contribute to the adverse health effects of Libby amphibole or whether there are interactive effects of winchite or richterite that modify the toxicity of tremolite. This issue is particularly important to highlight since it is well-known that tremolite is highly toxic, profibrogenic, and causes mesothelioma. However, the contribution of winchite or richterite to adverse health effects is apparently unknown.
- b) Section 4.1, pg 4-2: Since several studies have shown that tremolite in community soil is associated with increased pleural and peritoneal malignant mesothelioma, it would be helpful to comment on the relative amount of tremolite present in the Libby, MT community compared to other communities that have high incidence of asbestosis, non-cancer pleural disease (e.g., localized pleural thickening LPT) and/or mesothelioma. Examples include community exposure to amphiboles in Turkey and Greece. This issue is important to emphasize since there is concern that community exposures (non-occupational) in Libby, MT contribute to adverse health effects, and these individuals likely include children who may be at increased risk for asbestosis or mesothelioma. Because of the long latency period for the development of either of these diseases, clinical symptoms for children exposed to Libby amphibole may not occur until adulthood. Also, from studies conducted in sites other than Libby, MT where community exposures occurred from amphibole-contaminated soil, it would be helpful to determine from the literature whether there is reason to believe that significant exposures occurred in children.
- c) Section 4.1.1.3.4, pg 4-20: In the summary of cancer mortality risk in the Libby vermiculite mining operation workers it is stated that studies provide evidence of an increase risk of lung cancer mortality and of mesothelioma mortality among the workers in the Libby vermiculite mining and processing

operations, but it would be helpful to be more specific. What was the increased risk among these workers? A numeric (i.e., quantitative) range of the relative risk based on the epidemiologic studies cited would be more informative.

- d) Section 4.1.1.4.3., pg 4-27, Cardiovascular-related mortality: This section states that the combined category of cardiovascular-related mortality resulted in modestly increased risks, but it would be helpful to clarify whether this was specifically related to occupational exposures. The last sentence of this section should also clarify that "...the observed association between exposure and cardiovascular disease-related mortality..." should specify what type of exposure; i.e., "...occupational Libby amphibole exposure...?"
2. Please identify any additional peer-reviewed studies from the primary literature that should be considered in the assessment of noncancer and cancer health effects of Libby Amphibole asbestos.

Comments:

- a) A recent peer-reviewed article by Marchand *et al* [2012 Toxicology Letters 208: 168-173] reports that mesothelial cell autoantibodies detected in the serum of individuals exposed to Libby amphibole are associated with pleural abnormalities such as localized pleural thickening (LPT), the predominant non-cancer abnormality in the asbestos-exposed population of Libby. This recent finding is potentially important since it relates the discovery of a possible biomarker that could be used to identify those at risk for the development of pleural disease.

Specific Charge Questions:

1. Charge Question II.A.3. (Sections 4.2, 4.3, 4.4 – Non-cancer health effects; Animal and Mechanistic Studies). The database of laboratory animal and mechanistic studies of Libby Amphibole asbestos is summarized in the draft assessment (see section 4.2 and 4.3, details in Appendix D) to inform the mechanisms of the biological response to Libby Amphibole asbestos and support the epidemiology studies used for derivation of the RfC. Please comment on whether the laboratory animal and mechanistic information presented is used appropriately in the draft assessment.

Comments:

- a) In general, mode of action (MOA) data are lacking in the document. While there is little MOA data available in peer-reviewed publications relating directly to LA, it is very likely that the cellular and molecular mechanisms and modes of action for LA are similar to other types of asbestos (e.g., crocidolite) that cause similar pathologies in the lung and/or pleura. For example, it is well-known that several types of asbestos (crocidolite, tremolite, chrysotile) all act through similar mechanism to induce cellular stress involving the generation of reactive oxygen species (ROS) and subsequent activation of

intracellular signaling cascades that result in cell death or the production of inflammatory and/or pro-fibrogenic cytokines and growth factors by lung epithelial cells, macrophages, fibroblasts, and mesothelial cells. A great deal of this literature has been reviewed so it is not necessary to add a large number of new references. Rather, it would suffice to cite a few review articles related to MOA. Suggested reviews are:

Mossman BT, Lounsbury KM, Reddy SP. Oxidants and signaling by mitogen-activated protein kinases in lung epithelium. Am J Respir Cell Mol Biol. 2006, 34(6):666-9.

Robledo R, Mossman B. Cellular and molecular mechanisms of asbestos-induced fibrosis. J Cell Physiol. 1999 Aug;180(2):158-66.

Kamp DW, Weitzman SA. The molecular basis of asbestos induced lung injury. Thorax. 1999 Jul;54(7):638-52.

Brody AR, Liu JY, Brass D, Corti M. Analyzing the genes and peptide growth factors expressed in lung cells in vivo consequent to asbestos exposure and in vitro. Environ Health Perspect. 1997 Sep;105 Suppl 5:1165-71

- b) There are several recent references that should be discussed related to animal models and noncancer endpoints.
- First, a recent study by Cyphert et al [2012 J Toxicol Environ Health A 75(3): 183-200] exposed rats to Libby Amphibole (LA) by intratracheal instillation (IT) and compared to well-characterized amosite asbestos. The study is of potential importance because of the comparison to amosite (a relatively toxic form of asbestos) and because the study was long term (2 yrs in rats). The authors found that a single IT dose of LA was sufficient to cause fibrosis (i.e., asbestosis) but not carcinogenesis. The data also showed that LA was less potent than amosite on a mass basis.
- Second, another recent study by Shannahan et al [2012 Environ Health Perspect 120: 85-91] examined pulmonary biomarkers and lung pathology in health rats (Wistar) as well as spontaneously hypertensive rats (SH) and SH heart failure (SHHF) rats instilled with Libby Amphibole (LA). They found that all rat strains developed lung fibrosis (i.e., asbestosis). Only SHHF rats developed atypical hyperplastic lesions, likely originating from the bronchial epithelium, at 3 months after exposure to LA. This study is potentially important in understanding the effect of LA on individuals with pre-existing cardiovascular disease.
- Finally, a study by Fukagawa et al., [Environ. Health Perspect. 116: 1218, 2008] shows that inhalation of chrysotile asbestos fibers caused a 3-fold increase in atherosclerotic lesions in susceptible (ApoE-deficient) transgenic mice compared to the same mice that received air only or titanium dioxide particles. While not tremolite, this study suggests that adverse effects on the

cardiovascular system are possible with other types of asbestos in mice and humans.

- c) Section 4.2.2 Inhalation, page 4-49: The lack of any inhalation data in rats or mice is an important issue since the deposition of particles and fibers cannot be adequately addressed using intratracheal instillation of a bolus of fibers delivered in aqueous suspension. For example, the development of pleural lesions may be quite different when comparing fibrogenic or carcinogenic fibers or particles by inhalation versus instillation. While inhalation studies have been done with tremolite (e.g., Berstein et al 2005), the Libby Amphibole (LA) samples are only ~6% tremolite and therefore the relative potency of inhaled LA should be compared to that of tremolite. This could add new information for refining the RfC for LA. Finally, the section on inhalation studies (pages 4-53, 4-54) could be improved by clarifying which rodent models developed fibrosis and mesothelioma (or both), and more detail on exposure conditions and experimental endpoints.
- d) 4.4 Mechanistic Data and other studies in support of the mode of action, page 4-62: A shortcoming that contributes to our lack of understanding of the mode of action (MOA) of Libby Amphibole is a lack of mechanistic data. Section 4.4.1. page 4-63 mentions increases in Th1 and Th2 cytokines but these are not specific to the effects of LA or other types of asbestos, but rather generalized mediators of non-allergic or allergic inflammatory responses. Likewise, pro-inflammatory cytokines (e.g., IL-8), enzymes (e.g., COX-2) and oxidative stress markers (e.g., heme oxygenase) are biomarkers of a wide variety of cellular stress and inflammation that will probably not shed much light on the mechanisms of LA-induced disease. Instead, it would be valuable for future research on LA mode of action to focus on biomarkers that are more clearly and specifically related to non-cancer endpoints (i.e., asbestosis) or cancer endpoints (i.e., mesothelioma). Examples of potentially valuable endpoints of asbestosis are members of the transforming growth factor (TGF-beta) family and the platelet-derived growth factor (PDGF) family members, which have been specifically associated with fibrogenic outcomes in humans and experimental animals (Mossman et al., 2011). Other potential biomarkers of asbestosis are chemokines (e.g., CCL2, osteopontin). Potentially valuable biomarkers of mesothelioma are mediators such as mesothelin and arrestin. The overall development of a more logical plan and approach for elucidating MOA should be a top priority. Moreover, the identification of more appropriate biomarkers to predict human disease, and especially which subpopulation(s) are at greatest risk, should have high priority.
2. Charge Question III.A.6. (Uncertainty factors – Exposure-Response Assessment; Inhalation Reference Concentration (RfC). Please comment on the rationale for the selection of the uncertainty factors (RfC) applied to the POD for the derivation of the RfC. Are the UFs appropriate based on *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002; Section 4.4.5) and clearly described? If changes to the selected UFs are proposed, please identify and provide scientific support. Specifically, please comment on the

rationale for the selection of the database uncertainty factor (UF_D) of 10 applied in the derivation of the RfC. The database uncertainty factor accounts for the lack of data on effects other than in the respiratory system, including other effects observed in community and laboratory animal studies (cardiovascular disease and autoimmune disease) that have not been well-studied (See Section 5.2.3 of the Toxicological Review); and lack of health data assessed at later time points. Is the rationale for the UF_D appropriate and clearly described? Please provide the rationale if a change in the UF_D is proposed.

Comments: The rationale for the data base uncertainty factor (UF_D) is appropriate and, for the most part, clearly described. The Inhalation Reference Concentration (RfC) appears appropriate and takes into account uncertainty factors such as susceptibility in populations and lack of information on effects of LA on organ systems other than the respiratory system. The strongest evidence for a structural abnormality in individuals exposed to LA is localized pleural thickening (LPT), which has been associated with reduced lung function and LPT is a risk factor for other asbestos-related outcomes such as asbestosis (interstitial lung fibrosis). The RfC is further supported and strengthened by animal data showing LA causes non-cancer effects in rodents (pulmonary interstitial fibrosis). However, there are some weaknesses that should be clarified. First, the justification of using LPT as an endpoint linked to adverse effect and human health hazard should be made stronger in the document. Also, there is insufficient information on mode of action (MOA) for LA and since much is known about the MOA for other types of amphiboles (see suggested review articles listed above under comment “a” for Charge Question II.A.3. Also, the RfC is based on data from a single study and this is a weakness. Furthermore, discussion of smoking issues in the text of the document is not adequate and smoking is a risk factor for asbestos-related lung and pleural disease. A discussion of early life exposures should be strengthened. This issue is addressed somewhat in the susceptibility section but could be strengthened by discussing early life exposures related to other types of asbestos. This discussion could also include animals studies on age-specific effects to other amphiboles. In general, the RfC could be strengthened with external validation by comparing LA to other amphibole-exposed cohorts for there are exposure data and other LA-exposed cohorts.

Dr. Jeff Everitt

General Charge Questions:

- 3. Is the Toxicological Review logical, clear, and concise? Has EPA clearly, and in sufficient detail, presented and synthesized the scientific evidence for health hazards from Libby Amphibole asbestos?**

Preliminary comments:

In general yes the Review is logical, clear and concise and appropriately presented and referenced relative to health hazards of Libby amphibole.

- a) One area of the review that could be enhanced would be quantitative comparison of the environmental exposures that have taken place in other geographic regions of the world (ie. Anatolia region of Turkey, Greece etc.) with the Libby, Montana community with regard to airborne tremolite. This comparison should be with respect to numbers and size of fibers and comparison of health effects. Not sure to what extent there are comparable exposure comparisons that can be made.
- b) Libby amphibole is primarily winchite a form of asbestos that has no associated animal data. It would be useful to examine how winchite might act to augment or diminish the health hazards of tremolite.

- 4. Please identify any additional peer-reviewed studies from the primary literature that should be considered in the assessment of noncancer and cancer health effects of Libby Amphibole asbestos.**

Preliminary comments:

- (a) Although not involving Libby amphibole there was a recent study by Bernstein and colleagues [Inhalation Toxicology 23(7):372-391, 2011] that nicely demonstrated pleural translocation in rats using non-invasive means following airborne amosite asbestos exposure. This study examined animals up to one year following a short 1 week exposure to amphibole and characterized the size of fibers that were present in parietal pleura. Non-cancer inflammatory pleural changes were demonstrated associated with fiber translocation.
- (b) An article by Marchand *et al* [2012 Toxicology Letters 208: 168-173] reports that mesothelial cell autoantibodies were detected in the serum of individuals exposed to Libby amphibole are associated with pleural abnormalities. This paper is potentially important in the quest for biomarkers of non-cancer pleural disease.

Specific Charge Questions:

- 3. The database of laboratory animal and mechanistic studies of Libby Amphibole asbestos is summarized in the draft assessment (see Section 4.2 and 4.3, details in**

Appendix D) to inform the mechanisms of the biological response to Libby Amphibole asbestos and support the epidemiology studies used for derivation of the RfC. Please comment on whether the laboratory animal and mechanistic information presented is used appropriately in the draft assessment.

I believe that the laboratory animal and mechanistic information is presented and used appropriately in the draft assessment. The animal data supports the human health outcomes associated with Libby Amphibole exposure in epidemiology studies. Unfortunately there is a paucity of good information relative to Libby Amphibole exposure and no well-conducted inhalation studies leading one to depend on a limited number of less than optimal tremolite inhalation studies and a variety of other animal and mechanistic experiments.

The literature review up through July, 2011 is complete but there have been several recently published studies with Libby amphibole since the draft document was put together. These include:

Long-term study by Cyphert et al [2012 J Toxicol Environ Health A 75(3): 183-200] that exposed rats to Libby Amphibole (LA) by intratracheal instillation (IT) and compared to well-characterized amosite asbestos. The study showed that a single IT dose of LA was sufficient to cause fibrosis. The data also showed that LA was less potent than amosite on a mass basis.

A study by Shannahan et al [2012 Environ Health Perspect 120: 85-91] examined pulmonary biomarkers and lung pathology in healthy Wistar as well as spontaneously hypertensive rats (SH) and SH heart failure (SHHF) rats instilled with Libby Amphibole (LA). They found that all rat strains developed lung fibrosis but only SHHF rats developed atypical proliferative epithelial lesions 3 months after exposure to Libby Amphibole.

Neither of these studies contributes significantly in providing critical information that would allow a different interpretation or contribute to an MOA determination.

1. Under EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005; www.epa.gov/iris/backgrd.html), the draft IRIS assessment characterizes Libby Amphibole asbestos as "carcinogenic to humans" by the inhalation route of exposure. Please comment on whether the cancer weight of evidence characterization is scientifically supported and clearly described.

My preliminary assessment prior to group discussions is that the draft IRIS assessment characterization of Libby Amphibole as "carcinogenic to humans" by the inhalation route of exposure is well supported by the weight of evidence and is scientifically supported and clearly described.

2 Due to the limitations of the data available, the draft assessment concludes that there is insufficient information to identify the mode of carcinogenic action of Libby Amphibole asbestos. Please comment on whether this determination is appropriate and clearly described. Note that in the absence of information to establish a mode of action, a linear low dose extrapolation is recommended by the *Guidelines for Carcinogen Risk Assessment* (U.S., EPA, 2005; Section 3.3).

I am in support of the description in Section 4.6.2 and agree that there is absence of information to establish an MOA for Libby Amphibole.

5. The database of laboratory animal and mechanistic studies of Libby Amphibole asbestos is summarized in this draft assessment (see Section 4.2 and 4.3, details in Appendix D) to inform the mechanisms of the biological response to Libby Amphibole asbestos and support the epidemiology studies used for derivation of the IUR. Please comment on the use of laboratory animal and mechanistic information in the draft assessment.

My preliminary assessment is that the database of laboratory animal and mechanistic studies pertaining to Libby Amphibole is complete relative to July, 2011. There are several additional mechanistic studies (role of iron, pre-existing cardiovascular disease etc.) that have been published in the peer reviewed literature since but these do not alter my evaluation that there isn't mechanistic information to establish a mode of action.

Dr. George Guthrie

Chapter 2 provides a discussion of the mineralogical and geological aspects of Libby amphibole. In general, the panel felt that the section provided an important foundation for understanding the nature of Libby amphibole asbestos (LAA) as related to evaluation of potential exposures. There are places where the section can be improved relative to clarity and accuracy, and these are detailed below.

One aspect recognized by the panel is the gap between the mineralogical detail embodied in the definition of mineral species and the detail available relative to specific exposures. Specifically, mineral species define a very specific structure (e.g., amphibole) and a specific composition or range of compositions (e.g., winchite or tremolite). Given that these factors affect a mineral's physical and chemical behavior, they may in principle be factors to consider for risk. However, the panel recognizes that this level of detail is not typically available for toxicity studies to allow its application to the evaluation of LAA per se. The observed unique aspects of amphibole asbestos, in general, however, support the evaluation of LAA by comparison with other amphibole studies based on particle morphology and amphibole designation. Nevertheless, the panel encourages a rigorous and accurate description of LAA in Chapter 2, perhaps while noting the potential ambiguities in the use of mineral-species names in other studies.

Specific comments follow:

- The discussion of mineralogy of Libby Amphibole asbestos is generally clear, concise, and accurate. Discussions of mineralogy and morphology are good, with appropriate discrimination between methods/definitions that are applied to field samples versus terms/definitions that are applied to environmental samples delineated (lines 4 and 5 of page 2-10).
- Section 2.1 is generally sufficient for providing a background relative to historical aspects of the operations.
- Section 2.2 needs significant modification. This section should lay a foundation for understanding the nature of Libby amphibole (e.g., mineralogical characteristics such as composition and morphology), information on how the material may vary spatially and temporally (with respect to mining operations), and other factors that may impact exposures. The section does contain much relevant information. However, there are parts of the section that are incorrect and misleading; general suggestions to address these issues include:
 - *Adopt a tight and consistent use of terminology associated with particle morphology.* The section mixes a number of terms that address particle morphology, and these are critically important in assessing potential exposures and subsequent impacts. (As an example, “fibers (e.g., acicular...” implies fibrous and acicular are the same, when in conventional usage they are different. See, for example, Veblen and Wyllie, 1993.) A tight use of terms that are defined up front should be followed, recognizing that a lax use of terms may nevertheless exist in the literature cited. A partial attempt is provided in section 2.2.1.2, but it could be expanded and carefully vetted with respect to accepted terminology. The three most important types to lay out clearly are

fibrous, acicular, prismatic, and asbestiform. If the report's intent is to note differences in these terms, they should be discussed; if the conclusion is that there are poorly defined distinctions, that could be discussed too. One specific example of inaccurate usage is: prismatic, which by definition is "prism" shaped (meaning parallel sides; it is incorrectly used in multiple places).

- *Double-check all mineral formulae.* There are numerous incorrect compositions in the report; although some of these may be typos (which, of course, should be fixed), some may be incorrectly reported. An example of one incorrect formula is that attributed to vermiculite (which is listed incorrectly as:
 $[(\text{Mg,Fe,A})_3(\text{Al,Si})_2\text{O}_{10}(\text{OH})_2 \cdot 4\text{H}_2\text{O}]$).
- *Double check that all mineral-species definitions are accepted mineralogical standards.* Mineral species are fundamental terms that describe a material with a specific structure and a specific composition or ranges of compositions; both factors are primary determinants of a material's properties. Indeed, at the heart of this report is the definition of likely exposures to (and risks from) inhaled particles based on the use of mineral species names. The problems in this category are probably most rampant in section 2.2.1.1, which details amphibole mineralogy (central to the report). For example, anthophyllite is not a Li-amphibole.
- The panel appreciated the discussions that highlighted the complexity and variability of LAA in the context of compositional solid solutions, emphasizing that even the use of mineral-species names for LAA may mislead readers to believe that LAA is represented by a few discrete materials as opposed to a mixture of materials with varying composition.
- Figure 2-4 (d) caption—Chrysotile formula should be $\text{Mg}_3\text{Si}_2\text{O}_5(\text{OH})_4$; vermiculite formula should be $(\text{Mg,Fe,Al})_3(\text{Al,Si})_4\text{O}_{10}(\text{OH})_2 \cdot 4\text{H}_2\text{O}$. The vermiculite structure should also indicate the presence of interlayer cations, not currently represented in the formula above.
- Overall, the mineralogy section could benefit from some technical editing. It presents some irrelevant material (e.g., section 2.2.1, which is a general description of silicate mineral hierarchy), omits some critical information (e.g., section 2.2.1.1 does not provide the mineralogical definitions of key minerals like winchite or richterite), and presents some erroneous and irrelevant (e.g., some of the vermiculite-mineralogy descriptions in section 2.2.2).
- Top of page 2-7, the identification of the amphibole groups presented here is a bit different from the scheme in Leake et al (1997). Generally, the groupings are based on B site composition.
- In the context of the information on the LAA, the report is good. One specific observation that could be added is one reported by Sanchez et al. (2008), namely that they observed no correlation between morphology (fibrous vs. prismatic) and major-/minor-element chemistry. In other words, this is consistent with the implication that the large set of compositional data from Meeker et al. (2003) shown in the report reflects the range of compositions associated with inhaled-fiber exposures.
- Figure 2-12 shows morphology data (CDFs) for particles as reported by U.S. EPA (2010). It might be useful to compare these with other morphology data that are cited in

report (e.g., Amandus et al. (1987)), which show a different distribution. Have exposures evolved with respect to particle morphology?

- Discussion on page 2-10 glosses over a serious shortcoming of PCM: it's inability to detect fibers narrower than $\sim 0.25 \mu\text{m}$. These thin fibers are the most biologically potent according to the Stanton-Pott hypothesis. The fact that only a third of the TEM-visible Libby fibers were PCM-visible is buried in McDonald *et al.* 1986a. Furthermore, Text Box 2-2 does not adequately contrast the capability of EM versus PCM. EM's capability to yield elemental composition via EDS provides information to identify different asbestos types. PCM's, in contrast, can't even determine if the fiber is mineral. Furthermore, the SAED capability of TEM allows determination of crystalline structure, e.g., amphibole versus serpentine. Finally, Box 2-2 incorrectly states that *SEM produces three-dimensional (3-D) images*. Rather, SEM produces 2-D images that reveal surface structure of particles.
- The text box on comparison of PCM and TEM needs expansion as background. The panel recognizes, however, that most of the evaluation will be based on data derived from PCM, due to the nature of the published work.
- PCM section on page 2-10 is a bit unclear regarding identification of particle morphology. PCM can differentiate fiber from non-fiber (which to me is morphology) but can't identify composition (elemental or mineralogical).
- Electron microscopy section on page 2-11 could be clarified. SEM and TEM provide higher magnification to allow better particle morphological analysis. Electron diffraction allows mineralogical assessment. Energy dispersive X-ray analysis allows elemental composition determination, which can corroborate the mineralogical determination. X-ray diffraction (XRD) mentioned in this section is useful for bulk sample mineralogy measurements.
- Page 2-12. Composition of vermiculite should be as above.
- Table 2-1. Composition of vermiculite should be as above. Mohs hardness is about 2 (looks like a typo in the table).
- Page 2-18. Seems the particle size distribution of the ore samples will depend in part on how energetic the sample prep was. Might be good to point that out here, and emphasize in Appendix C.
- Appendix C could provide more detail on how the work was done.

Mr. John Harris

In general, I'm in agreement with the study performed by EPA Region 8, Appendix C, "Characterization of Amphibole Fibers From Ore Originating from Libby, MT; Louisa County, VA; and Palabora Republic of South Africa", pp. C-1 through C-1 and Appendix A, "Raw Data : LA Structure Data from the Libby 2 Databases and the Libby OU3 Database, pp. B-8 through B-17

There are some limitations to the methods used in this study. The use of the FBAS technique to measure airborne levels of LA by TEM is a useful tool to measure exposure data from the manufacturing processes at the Libby mine site but it is a new technique to EPA and is still under study by the agency. Certainly, the glove box method referenced in this method is not well standardized and could create a high degree of variation. Both techniques don't have sufficient characterization, in my opinion, to compare to activity based sampling (i.e., personal sampling) of exposures at the vermiculite plant in Libby. The best method of measuring worker exposure would be historical air filters reanalyzed by TEM. However, these are not available, so I agree that the next best approach is FBAS. In my experience with FBAS samples, this method performs very well with soil samples such that structure dimensions and structure counts are quite accurate.

I also agree with the use of the ISO 10312 method to define the asbestos structures more accurately than other TEM methods, such as AHERA. However, there are deficiencies in the ISO method that affect actual fiber length and aspect. The estimation of fiber dimensions by the ISO method leads to variations in the true fiber length and aspect, in my opinion. This is especially true with complex structure arrangements, such as clusters and matrices. Therefore, it was good to see that most counts were fibers and bundles, which have very little variation, unless they included those bound to matrices. The AHERA method doesn't provide accurate measurement of substructures in complex arrangements such as matrices and clusters. If there were special counting rules used with AHERA samples to improve measurements of complex structures, it should be noted.

Regarding mineralogy, EPA did not calculate iron oxides as recommended in the Leake method for its definition of Libby amphibole in this study, which would cause a much higher amount of variation in mineralogical naming convention. True, the Leake method is an estimation of the state of iron present. However, it's better than not attempting it at all. Though EPA referenced the Meeker Rainy Creek paper, Meeker did provide an established iron oxidation state value from earlier Mössbauer spectroscopy data from the area for his calculations. His data was probably the most definitive since it did attempt to use an established iron oxidation state value as well as microprobe for quantitative measurements.

The data presented by EPA is the best that can be currently obtained for risk exposure data from the vermiculite studies included in this report. Going forward, there should be better opportunities to provide more definitive data for exposure risk assessments.

Dr. Tom Hei

Animal and Mechanistic Studies

Libby amphibole asbestos is a complex mixture of amphibole fibers including winchite (84%), richterite (11%), tremolite (6%) and trace amounts of magnesioriebeckite, edenite and magnesio-arfvedsonite. The adverse health effects of the Libby Amphibole asbestos are likely to derive primarily from the tremolite contaminant of the mineral mixture. Animal studies utilizing various strains of mice and rats as well as hamsters have been used to ascertain the potential fibrogenic and carcinogenic potential of the Libby amphibole fibers. While inhalation is regarded as the most physiologically relevant mean of fiber exposure in animals, there is NO published study with this route of fiber administration in animals. Intratracheal instillation of Libby amphibole fibers in short term studies with mice and rats resulted in inflammatory changes in the airways consistent with those earlier changes seen in tremolite exposed animals.

In vitro assay systems utilizing both primary and established human and mammalian cells have been used to provide mechanistic insights on the potential mode of action of Libby Amphibole asbestos. These limited *in vitro* studies have demonstrated the importance of fiber-cell interaction, the ability of Libby Amphibole fibers to induce reactive radical species, inflammatory gene expression and micronucleus, a marker of genomic instability. Unfortunately, with the exception of the later, most of these endpoints are non-specific and can be demonstrated with any particles including glass fibers in short term assays. Critical genotoxicity studies including mutagenesis and chromosomal aberration studies have not been reported/ examined with Libby Amphibole fibers.

In general, the Toxicological Review is clearly written, well balanced and, for the most part, concise. Given the limited data base available in the literature on both animal and mechanistic base studies on the Libby Amphibole fibers, the Review is considered comprehensive and up-to-date.

A few recent additions to the published literature as follow:

Shannahan, J.H. *et al.* Transcriptional activation of inflammasome components by Libby amphibole and the role of iron. *Inhalation Toxicology* **24**:60-69, 2012. PMID: 22168577

Antao, V.C. *et al.* Libby vermiculite exposure and risk of developing asbestos-related lung and pleural diseases. *Curr. Opin. Pulmonary Med.* **18**:161-167, 2012. PMID: 22139761.

Weight- of- Evidence Evaluation of Carcinogenicity and Mode of Action

In environmental toxicology, human epidemiological data supersede animal and other laboratory studies in the identification of human carcinogen/ toxicant. In the Libby Amphibole studies, while concrete laboratory studies in unequivocal support of the carcinogenicity of the fiber mix is lacking, there is overwhelming epidemiological data in support of the notion that Libby Amphibole fiber is closely linked to cancer incidence in humans under both occupational and domestic settings. In contrast, the only solid evidence that the Libby Amphibole fiber is carcinogenic to animals is in hamsters injected intraperitoneally with a single, 25 mg dose of the fiber mix. While tissue inflammation has been demonstrated in the lungs of both mice and rats exposed to Libby Amphibole fibers by Intratracheal instillation, these short term studies failed to demonstrate any cancer induction. Additional supporting evidence for the carcinogenic potential of Libby Amphibole fibers has been derived from studies with tremolite fibers. While this provide circumstantial, supporting evidence of its carcinogenic potential in light of its ~6% tremolite by composition, the limited data base cannot provide a well defined mode of action in both lung cancer and mesothelioma induction.

In general, the Toxicological Review is clearly written, balanced in scope and concise. The various uncertainties are well considered. However, the laboratory-based weight of evidence for the carcinogenic potential of Libby Amphibole fiber is weak. Given the limited data base available in the literature, the Review summary on mode of action of Libby Amphibole fiber is justified. An area of improvement in the report includes a discussion on known determinants of fiber toxicity and the difference between Libby Amphiboles from other known amphiboles. Furthermore, the section on fiber exposure should begin a brief description on the relevance of different routes of fiber exposure relative to human experience.

An addition to the published literature pertaining to this chapter is listed below:

Antao, V.C. *et al.* Libby vermiculite exposure and risk of developing asbestos-related lung and pleural diseases. *Curr. Opin. Pulmonary Med.* **18**:161-167, 2012. PMID: 22139761.

Dr. Agnes B. Kane

General Charge Questions

Comments on 1. Introduction

p. 1-3 line 2: Stomach cancer is listed as associated with asbestos exposure; this statement is incorrect. The IARC Monograph vol. 100C states: “Asbestos causes mesothelioma and cancer of the lung, larynx, and ovary.” Positive associations were noted for gastrointestinal cancer and asbestos exposure; however, the Working Group was divided on the evidence supporting a causal association with colon cancer. The meta-analysis conducted by the IOM in 2006 showed a suggestive relationship between asbestos exposure and cancers of the pharynx, stomach, and colorectum.

p. 1-4 lines 15-17: Although workers exposed to vermiculite with no significant amphibole contamination do not show adverse health effects, it is not clear whether the mixture of vermiculite plus Libby amphibole fibers are related to the health effects observed in Libby, MT.

Comments on 2. Libby Amphibole Asbestos: Geology, Use and Exposure Potential

p. 2-2 line 7 and p. 2-12 line 26: It is stated that vermiculite ore is expanded at 150°C; however, Bandli and Gunter, 2006 state that expansion occurs at 1100°C.

p. 2-6 Figure 2-4d. Chrysotile is listed as an example of a sheet silicate; however, it also occurs in fibrous form.

p. 2-12: A section regarding durability of vermiculite should be added or included in Table 2-1.

p. 2-21 line 24: A map and total population of the Libby community should be included.

pp. 2-22 and 2-23: The text switches from s/cc and f/cc and this is confusing. These data should be presented as a table with the units clearly defined. Nonoccupational exposure levels are commonly expressed as f/1; for example, in Goldberg and Luce, 2009. This may be less confusing than 5.1×10^{-4} s/cc, for example, on line 11, p. 2-23. On lines 29-30, exposure pathways for residents living near other expansion plants were mentioned; are there any air sampling data available in these communities?

Chemical-Specific Charge Questions

3. Fiber Toxicokinetics

p. 3-7 and p. 3-8: There are several references to fiber burdens in the lungs and pleura; however, there are many technical limitations and caveats in interpretation of these data as discussed in detail in Broaddus et al. (2011) and in Roggli, 1990, 1992; Roggli and Sharma, 2004; Dodson and Atkinson, 2006. The statement regarding systemic

translocation of asbestos fibers on p. 3-8 lines 12-18 is very definitive, but it should be qualified by the technical limitations involved in quantitation of tissue fiber burdens. On p. 3-7, lines 12-13, there are additional measurements of pleural fiber burdens that should be included (see review by Broaddus et al., 2011).

pp. 3-10, lines 28-31: The term “overload” should be described more precisely.

p. 3-11, lines 1-2: The role of inflammasome activation following “frustrated phagocytosis” should be included. Inflammasome activation also occurs in response to other crystalline materials, including quartz. Is quartz present in vermiculite mined in Libby, MT?

p.3-11, line 3: It is unclear whether all inhalation studies in rodents have been conducted under overload conditions.

p. 3-11, line 6: “Encapsulation” is misleading; the title of this paragraph should be “Formation of asbestos bodies”. It is incorrect that most are formed on amosite fibers; other minerals including silicates can also form ferruginous bodies (Churg and Green, Pathology of Occupational Lung Disease).

p.3-11, line 28: It is not clear that fiber translocation is hindered by fibrosis; no reference is given.

p.3-12: See comments above regarding difficulties in tissue fiber burden analysis. The studies on transplacental transfer of asbestos fibers are not widely accepted due to technical concerns.

3.3 Summary

p. 3-15, lines 8 and 9: This sentence on location of deposition and clearance is confusing.

4. Hazard Identification of Libby Amphibole Asbestos

p. 4-2: This paragraph describing health impacts of nonoccupational exposure to asbestos fibers is very important; however, it is incomplete. A recent review of this topic was published by Goldberg and Luce, 2009. A table should be included in this section summarizing the magnitudes and health risks associated with these exposures. The region of Casale Monferrato in Italy is most relevant to the exposure in Libby, MT and the epidemiology studies describing occupational, household, and environmental exposures related to this asbestos-cement plant should be described.

p.4-42: A paragraph is included describing other exposures at the Marysville, Ohio plant; however, no other exposures in Libby, MT were discussed. Saffiotti has reviewed all chemicals associated with development of malignant mesothelioma in rodent studies (chapter 4 in Pass et al., Malignant Mesothelioma); are related chemicals present in the Libby Community?

p. 4-54, lines 30-31: The specific markers used to evaluate changes in homeostasis, etc. should be included.

p. 4-56, line 28: Tremolite is one of the asbestos fibers in Libby amphibole, but this statement is confusing.

4.5 Pleural Effects

This section describes the radiologic changes associated with pleural plaques and diffuse pleural thickening; however, it does not describe bloody pleural effusions and the severity of the pleural diseases associated with exposure to Libby amphibole as discussed in Broaddus et al., 2011. The intensity of the pleural inflammatory response associated with this exposure appears to be greater than in other asbestos-exposed worker cohorts (e.g. Wittenoom, Australia) and may be linked with associated autoimmune diseases discussed in section 4.5.3.

4.5.5. Mode-of-Action Information (Noncancer)

p. 4-76, lines 22 and 26: The Pietruska et al., (2010) paper described genotoxicity of Libby amphibole, not oxidative stress, surface iron, or inflammatory markers.

p 4-77, lines 15-16: The link between fibrosis and proliferation is not clear. Line 17: The association between cytotoxicity and cell proliferation in noncancer health effects is not clear. The cited papers do suggest a link between inflammation and pulmonary fibrosis.

4.7 Susceptible Populations

p. 4-83, lines 9-11: The cited studies do not provide any evidence for effects of transplacental transfer of asbestos fibers on fetal development.

4.7.4 Influence of Genetic Polymorphisms on Susceptibility

This discussion is incomplete and confusing. Epidemiologic studies on genetic susceptibility to lung cancer and malignant mesothelioma associated with asbestos exposure should be included in this discussion: Neri et al., 2008; Weiner and Neragi-Miandoab, 2009; Below et al., 2011; Testa et al., 2011. The experimental studies in cultured cells and short term exposures in mice are not relevant to this discussion on genetic susceptibility.

p. 4-87, lines 13-25: A recent review of molecular alterations in malignant mesothelioma and genetic susceptibility was published in an IARC Monograph, vol. 100C. This paragraph is incomplete and confusing because it cites experimental data but omits molecular alterations in human malignant mesotheliomas. This document should make the distinction between acquired molecular alterations in malignant mesothelioma and inherited, germ-line mutations that may increase susceptibility to the development of malignant mesothelioma.

References

Broadus, V.C.; Everitt, J.I.; Black, B.; Kane, A.B. (2011) Non-neoplastic and neoplastic pleural endpoints following fiber exposure. *J Toxicol Environ Health, Part B* 14:153-178.

Goldberg, M.; Luce, D. (2009) The health impact of nonoccupational exposure to asbestos: what do we know? *Eur J Cancer Prev* 18:489-503.

Testa, J.R.; Cheung, M.; Pei, J.; Below, J.E.; Tan, Y.; Sementino, E.; Cox, N.J.; Dogan, A.U.; Pass, H.I., Trusa, S.; Hesdroffer, M.; Nasu, M.; Powers, A.; Rivera, Z.; Comertpay, S.; Tanji, M.; Gaudino, G.; Yang, H.; Carbone, M. (2011) Germline BAP1 mutations predispose to malignant mesothelioma. *Nature Genetics* 43:1022-1025.

Weiner, S.J.; Neragi-Miandoab, S. (2009) Pathogenesis of malignant pleural mesothelioma and the role of environmental and genetic factors. *J Cancer Res Clin Oncol* 135:15-27.

Below, J.E.; Cox, N.J.; Fukagawa, N.K.; Hirvonen, A.; Testa, J.R. (2011) Factors that impact susceptibility to fiber-induced health effects. *J Toxicol Environ Health, Part B* 14:246-266.

Neri, M.; Ugolini, D.; Dianzani, I.; Gemignani, F.; Landi, S.; Cesario, A.; Magnani, C.; Mutti, L.; Puntoni, R.; Bonassi, S. (2008) Genetic susceptibility to malignant pleural mesothelioma and other asbestos-associated diseases. *Mutation Research* 659:126-136.

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 100: A Review of Human Carcinogens. Part C: Arsenic, Metals, Fibres, and Dusts, Lyon, France, 2011.

Asbestos Selected Cancers, Committee on Asbestos: Selected Health Effects; Board on Population Health and Public Health Practices; Institute of Medicine of the National Academies, The National Academies Press, 2006.

Dr. David Kriebel

General Charge Questions:

1. Is the Toxicological Review logical, clear, and concise? Has EPA clearly, and in sufficient detail, presented and synthesized the scientific evidence for health hazards from Libby Amphibole asbestos?

While the toxicologic review is generally well-written, it fails to make clear the relevance of the extensive literature on the health effects of asbestos fibers generally, and other amphibole fibers specifically. Without explicit evidence to the contrary, I assume that the mechanisms of toxicity and quantitative risk relations are similar for Libby Amphibole asbestos and other asbestos fibers. The document suffers from a failure to make this point clearly. It also does not compare the final proposed IUR and RfC with those for other types of asbestos.

2. Please identify any additional peer-reviewed studies from the primary literature that should be considered in the assessment of noncancer and cancer health effects of Libby Amphibole asbestos.

Zeka A, Gore R, Kriebel D. The two-stage clonal expansion model in occupational cancer epidemiology: results from three cohort studies. Occupational and Environmental Medicine 2011; 68:618-24.

II. Hazard Identification of Libby Amphibole Asbestos

A. Noncancer Health Effects:

1. An occupational cohort of workers in a Marysville, OH facility exposed to Libby Amphibole asbestos (Lockey et al., 1984; Rohs et al., 2008) was selected as the basis for the derivation of the reference concentration (RfC). Please comment on whether the selection of this study population is scientifically supported (**yes**) and clearly described (**yes**). If a different study population is recommended as the basis for the RfC, please identify this study and provide scientific support for this choice (**No**).
2. Radiographic evidence of localized pleural thickening in humans was concluded by EPA to be an adverse effect and was selected as the critical effect for the derivation of the RfC. Pleural thickening is associated with restrictive lung function,

breathlessness during exercise and, for some individuals, chronic chest pain. Please comment on whether the selection of this critical effect and its characterization is scientifically supported and clearly described. If a different health endpoint is recommended as the critical effect for deriving the RfC, please identify this effect and provide scientific support for this choice.

Comment on the potential relevance of a broader inclusion criterion for types of radiographic outcomes to consider. While in the chosen study, LPT is appropriate, this does not necessarily mean that other radiographic changes are not also relevant endpoints in general.

III. Exposure-Response Assessment

A. Inhalation Reference Concentration (RfC):

4. EPA has evaluated potential confounders and covariates where data are available. Specifically, EPA has explored the influence of age, body mass index, smoking status, time since first exposure, gender, and alternative exposure metrics on model fit and evaluated their association with the modeled health outcomes (see Section 5.3). Are these analyses clearly described and appropriately conducted?

Time since first exposure is really better thought of as a component of the exposure metric and the choice of exposure response model. I suggest investigating the alternative summary exposure metrics used in the cancer analysis that add time weights to cumulative exposure.

Are the results of these analyses appropriately considered in the RfC derivation?

(yes)

Additionally, there is a possibility of exposure-dependent censoring in participant selection for the update of the Marysville cohort (Rohs et al., 2008) but no evidence of selection bias. Does the panel have any specific recommendations for evaluating and, if appropriate, quantitatively addressing exposure-dependent censoring in these analyses?

I do not suggest any additional analyses directed at this issue.

6. Please comment on the rationale for the selection of the uncertainty factors (UFs) applied to the POD for the derivation of the RfC. Are the UFs appropriate based on *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002; Section 4.4.5) **(yes)** and clearly described? **(yes)** If changes to the selected UFs are proposed, please identify and provide scientific support. Specifically, please comment on the rationale for the selection of the database uncertainty factor (UF_D) of 10 applied in the derivation of the RfC. The database uncertainty factor accounts for the lack of data on effects other than in the respiratory system, including other effects observed in community and laboratory animal studies (cardiovascular disease and autoimmune effects) that have not been well-studied (See Section 5.2.3 of the Toxicological Review); and lack of health data assessed at later time points. Is the rationale for the UF_D appropriate and clearly described? Please provide the rationale if a change in the UF_D is proposed.

Database uncertainty factor of 3 is not appropriate. There remains considerable uncertainty in the quality of the data and a factor of 10 is more appropriate.

This is an example of a place where experience with other amphibole fibers should have been included. Ignoring this literature leaves the impression that Libby amphibole fibers are assumed to be different, while the appropriate assumption is that they are the same unless specific evidence suggests otherwise. No such evidence has been convincingly presented.

7. Please comment on whether the document adequately describes the uncertainties and limitations in the methodology used to derive the RfC and whether this information is presented in a transparent manner.

See comment immediately above on other types of amphibole fibers.

B. Inhalation Unit Risk (IUR):

1. Exposure-response modeling was conducted separately for lung cancer and mesothelioma mortality. The POD estimates for these endpoints are based upon analysis of the subcohort of workers first exposed after 1959 when the exposure data were judged to be better characterized. The exposure-response modeling included consideration of a variety of exposure metrics that varied with time and incorporated different lag and decay parameters. Based on the results of the exposure-response modeling, a lifetable analysis was used to determine the PODs

for each type of cancer for the various exposure metrics. Have the exposure-response modeling and determination of the PODs from lifetable analysis been appropriately conducted **(Yes)** and clearly described? **(Yes)** If a different approach to exposure-response analysis is recommended as the basis for the estimating the IUR, please identify the recommended methods and provide a rationale for this choice.

For lung cancer: it would be appropriate to compare the results of the final model against a two stage clonal expansion model (TSCE). Such a fit would allow a strong justification for an age-dependency of the IUR. I recommend Richardson's application of the TSCE rather than Moolgavkar's (see reference below).

2. Smoking is a strong independent risk factor for lung cancer and may be an important confounder of the lung cancer mortality analysis. Data on individual smoking habits and history were largely missing and could not be used to control for potential confounding in regression analyses. However, EPA used three approaches to evaluate the confounding issue, including restriction of the cohort and two analytic evaluations of the potential for confounding by smoking (see Section 5.4.3.6.5). Please comment on whether the methods and analyses are clearly presented and scientifically justified. If additional analyses are recommended, please identify the methods and scientific rationale.

The discussion of the results of the Richardson method should make it clear that the direction of the association between exposure and COPD was negative – suggesting that if proper control for confounding by smoking was possible, it might actually strengthen the asbestos – lung cancer association.

4. Please comment on the adjustment for mesothelioma mortality underascertainment. Is this adjustment scientifically supported and clearly described? If another adjustment approach is recommended as the basis for the IUR, please identify that approach and provide the scientific rationale.

I don't think the method was explained clearly in the document. A summary of where the adjustment factors come from should be included, so the reader doesn't need to refer to the original journal article.

Additional specific comments:

p. 4-20, section 4.1.1.3.4. Evidence of carcinogenicity from other studies of amphibole asbestos should be cited here. Similarly in section 4.1.1.4. Noncancer Effects, the literature from other studies of workers exposed to amphiboles should be included.

p. 4-27, line 20. I don't understand the sentence: "Because Larson et al. (2010b) analyzed multiple causes of death, the observed association between exposure and cardiovascular disease-related mortality may reflect, at least in part, a consequence of an underlying respiratory disease."

p. 4-71, line 25. In section 4.5.1.1. Pulmonary Fibrosis (Asbestosis), evidence from other studies of amphiboles should have been included.

p. 4-80, 4.6.2. Mode-of-Action Information. A great deal is known about the mode of action of asbestos fibers generally and amphiboles specifically, which should be assumed to be relevant to Libby asbestos. The mathematical modeling of mesothelioma and lung cancer patterns that has been done for other asbestos exposures shows clearly that cumulative exposure is not the best exposure metric. The duration of exposure is a stronger predictor than the intensity. This is reasonable for an early stage carcinogen, which asbestos appears to be. See work from the 1980s of Peto, Moolgavkar and others. Also the recent Zeka paper I cited on the first page.

p.5-31, section 5.2.3.3.1. Statistical model evaluation and selection. Explain here why BMI considered a relevant covariate. Line 20. "initial modeling was done using a standard logistic regression model, as is commonly applied in 20 analysis of epidemiological data." This is a poor justification. In fact, modern methods for analysis of cross-sectional data avoid the logistic model because the odds ratio over-estimates the prevalence ratio, which is the correct measure of association. See Spiegelman 2005 and Barros 2003 papers referenced below.

p. 5-53. Section 5.4.2. Choice of Study/Data—with Rationale and Justification. This makes clear that the analysis applies only to Libby asbestos. But it provides no justification for this choice.

p. 5-69, line 19. "The RTW exposure metric in this current assessment is sometimes called the cumulative burden, or the area under the curve". This is confusing. The area under the curve (AUC) is often used to refer to the simple cumulative exposure. Here it is the AUC for the "cumulative cumulative exposure" or something like that. I would not describe the RTW as an AUC.

p. 5-72, line 22. Rothman's discussion of comparing latencies is out of date. Time windows rather than lagging is a more widely accepted approach now. See page 321 in Checkoway's occupational epidemiology textbook, 2nd edition, 2004.

p. 5-49, sections 5.3.7 and 5.3.8. I recommend that a table be included summarizing the results of the various sensitivity analyses and how they change the POD.

p. 5-35, section 5.2.4 Application of Uncertainty Factors. I recommend that this section be integrated with section 5.3 on Sources of Uncertainty. The latter, which are thoughtfully described and fairly comprehensive, should be linked to the decisions about specific uncertainty factors being applied in section 5.2.4. As it is now, the justifications for the 100-fold UF are cryptic and pro forma and not very convincing. The two 10-fold factors, intraspecies and database, should be justified including the specific issues laid out in section 5.3. Also please explain briefly how these 2 factors are described in the EPA standard methods so that the non-expert can understand them.

References.

Spiegelman D. Am J Epi 2005; 162(3): 199-200. DOI: 10.1093/aje/kwi188

Barros AJD. BMC Medical Research Methodology 2003; 3:21.

Richardson DB. Multistage Modeling of Leukemia in Benzene Workers: A Simple Approach to

Fitting the 2-Stage Clonal Expansion Model. Am J Epi 2008;

DOI:10.1093/aje/kwn284.

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Dr. Mort Lippmann

Content

- 1) Responses to General Charge Questions**
- 2) Generic Comments** [that go beyond the Charge Questions]
- 3) Specific Text Comments**

Responses to General Charge Questions (My responses in bold-faced type)

1. Is the Toxicological Review logical (**Yes**), clear (**Mostly**), and concise? (**NO**). Has EPA clearly, and in sufficient detail presented (**Too much detail, much of it extraneous, as for chrysotile asbestos**), and synthesized the scientific evidence for health hazards from Libby Amphibole asbestos? (**Yes, but only in Chapter 6.**)

2. Please identify any additional peer-reviewed studies from the primary literature that should be considered in the assessment of noncancer and cancer health effects of Libby Amphibole asbestos.

Recent relevant papers:

- 1) Shannahan JH, Nyska A, Cesta M, Schladweiler MCJ, Vallant BD, Ward WO, Ghio AJ, Gavett SH, Kodavanti U. Subchronic pulmonary pathology, iron overload, and transcriptional activity after Libby amphibole exposure in rat models of cardiovascular disease. *Environ Health Perspect* on-line (2012).
- 2) Alexander BH, Raleigh KK, Johnson J, Mandel JH, Adgate JL, Ramachandran G, Messing RB, Eshenaur T, Williams A. Radiographic evidence of nonoccupational asbestos exposure from processing Libby vermiculite in Minneapolis, Minnesota. *Environ Health Perspect*, on-line (2012).

Chemical-Specific Charge Questions:

I. Background

A. Mineralogy and Toxicokinetics

1. In order to inform the hazard identification and dose response of Libby Amphibole asbestos, background material is included in the document briefly describing the mineralogy and toxicokinetics of asbestos and related mineral fibers (Section 2 and 3):
 - a. Please comment on whether the presentation of the available data on the mineralogy of Libby Amphibole asbestos is clear, concise and accurate. (**Yes**)
 - b. In the absence of toxicokinetic information specific to Libby Amphibole asbestos, the draft assessment contains a general summary description of fiber toxicokinetics. Please comment on whether this overview of general fiber

toxicokinetics is clear (**No**), concise (**No, especially when it fails to distinguish between chrysotile and amphibole fibers**) and accurate (**No, in too many places, as noted in my specific comments that follow**).

II. Hazard Identification of Libby Amphibole Asbestos

A. Noncancer Health Effects:

1. An occupational cohort of workers in a Marysville, OH facility exposed to Libby Amphibole asbestos (Lockey et al., 1984; Rohs et al., 2008) was selected as the basis for the derivation of the reference concentration (RfC). Please comment on whether the selection of this study population is scientifically supported (**Yes**) and clearly described (**Yes**). If a different study population is recommended (**No**) as the basis for the RfC, please identify this study and provide scientific support for this choice.
2. Radiographic evidence of localized pleural thickening in humans was concluded by EPA to be an adverse effect and was selected as the critical effect for the derivation of the RfC. Pleural thickening is associated with restrictive lung function, breathlessness during exercise and, for some individuals, chronic chest pain. Please comment on whether the selection of this critical effect and its characterization is scientifically supported (**Yes**) and clearly described (**Yes**). If a different health endpoint is recommended (**No**) as the critical effect for deriving the RfC, please identify this effect and provide scientific support for this choice.
3. The database of laboratory animal and mechanistic studies of Libby Amphibole asbestos is summarized in the draft assessment (see Section 4.2 and 4.3, details in Appendix D) to inform the mechanisms of the biological response to Libby Amphibole asbestos and support the epidemiology studies used for derivation of the RfC. Please comment on whether the laboratory animal and mechanistic information presented is used appropriately in the draft assessment. (**Yes**)

B. Carcinogenicity:

1. Under EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005; www.epa.gov/iris/backgrd.html), the draft IRIS assessment characterizes Libby Amphibole asbestos as "carcinogenic to humans" by the inhalation route of exposure. Please comment on whether the cancer weight of evidence characterization is scientifically supported (**Yes**) and clearly described (**Yes**).

2. Due to the limitations of the data available, the draft assessment concludes that there is insufficient information to identify the mode of carcinogenic action of Libby Amphibole asbestos. Please comment on whether this determination is appropriate (**Yes**) and clearly described (**Yes**). Note that in the absence of information to establish a mode of action, a linear low dose extrapolation is recommended by the *Guidelines for Carcinogen Risk Assessment* (U.S., EPA, 2005; Section 3.3). If it is judged that a mode of action can be established for Libby Amphibole asbestos, please identify the mode of action and its scientific support (i.e., studies that support the key events, and specific data available to inform the shape of the exposure-response curve at low doses).

3. An occupational cohort of workers from Libby, MT exposed to Libby Amphibole asbestos (i.e., the Libby worker cohort) was selected as the basis for the derivation of the inhalation unit risk (IUR). Please comment on whether the selection of this study population is scientifically supported (**Yes**) and clearly described (**Yes**). If a different study population is recommended as the basis for the IUR, please identify this study and provide scientific support for this choice.

4. Mortality from lung tumors and mesothelioma in the Libby worker cohort was selected to serve as the basis for the derivation of the IUR. Please comment on whether this selection is scientifically supported (**Yes**) and clearly described (**Yes**). If a different health endpoint is recommended for deriving the IUR, please identify this endpoint and provide scientific support for this choice.

5. The database of laboratory animal and mechanistic studies of Libby Amphibole asbestos is summarized in this draft assessment (see Section 4.2 and 4.3, details in Appendix D) to inform the mechanisms of the biological response to Libby Amphibole asbestos and support the epidemiology studies used for derivation of the IUR. Please comment on the use of laboratory animal and mechanistic information in the draft assessment.

Response: The text treatment is too simplistic and fails to provide a holistic framework based on a more comprehensive integration of available knowledge. It is now widely accepted that the toxicity and carcinogenicity of mineral and synthetic vitreous fibers is governed fiber dimensions, *in vivo* durability, and dose, and that all long amphibole fibers are very durable *in vivo*. Thus, the differences in biological potency among the various amphibole fiber types are due primarily to their differences in dimensional distributions, especially in their fiber length

distributions. The text of Sections 4.2 and 4.3, and the Tables cited therein are deficient in not citing all that is known about the dimensions of the administered fibers. Thus, the paucity of data on the potency of Libby amphibole fibers should not be an excuse to make a judgment call when there is a large body of data on other amphibole fibers.

III. Exposure-Response Assessment

A. Inhalation Reference Concentration (RfC):

1. Exposures to Libby Amphibole asbestos for workers in the Marysville, OH facility were reconstructed based on industrial hygiene data collected in the facility from 1972 to 1994. Exposures from 1957 to 1971 were estimated based on extrapolation from the available industrial hygiene data. The information used for the exposure reconstruction was based on employee interviews, court and company records, and the expert judgment of the researchers. Is the methodology used for the exposure reconstruction reported in Appendix F and the subsequent development of exposure estimates used in the analyses scientifically supported and clearly described?

Response: Yes, the methodology and the uncertainties associated with the reliance on imperfect exposure indices and expert judgment were both well described, clearly acknowledged, and appropriate. It raises the question as to why the authors of the document refrained from making comparable expert judgments on the toxicity of Libby amphibole fibers.

2. Exposure-response modeling was conducted using the incidence of localized pleural thickening in workers and cumulative exposure to estimate the point of departure (POD) for derivation of the RfC. EPA's estimate of the POD is based upon a Michaelis-Menten model applied to the subcohort of workers examined in 2002-2005 and first exposed to Libby Amphibole asbestos in 1972 (when measurements of fiber levels in the workplace began) or later with cumulative exposure as the explanatory variable. Is the selection of the model scientifically justified (**Yes**) and clearly described (**Yes**)? Has the modeling and the choice of a benchmark response (BMR) for the POD of 10% extra risk of localized pleural thickening been clearly described (**Yes**) and appropriately conducted according to EPA's *Draft Benchmark Dose Technical Guidance* (U.S. EPA, 2000b) (**Yes**) ?

3. EPA's assessment also provides the results of alternative modeling approaches to derive a POD for localized pleural thickening. This modeling used the full Marysville worker data set with exposures from 1957 and later and a Cumulative Normal Michaelis-Menten model that incorporates both cumulative exposure and time from first exposure as explanatory variables. Please comment on whether EPA's rationale for presenting these alternative approaches is scientifically justified (**Yes**) and clearly described (**Yes**). Please identify and provide the rationale if a different approach for identifying the most appropriate population within the cohort of Marysville workers is recommended as the basis for estimating a POD.

4. EPA has evaluated potential confounders and covariates where data are available. Specifically, EPA has explored the influence of age, body mass index, smoking status, time since first exposure, gender, and alternative exposure metrics on model fit and evaluated their association with the modeled health outcomes (see Section 5.3). Are these analyses clearly described (**Yes**) and appropriately conducted? (**Yes**). Are the results of these analyses appropriately considered in the RfC derivation? (**Yes**). Additionally, there is a possibility of exposure-dependent censoring in participant selection for the update of the Marysville cohort (Rohs et al., 2008) but no evidence of selection bias. Does the panel have any specific recommendations for evaluating and, if appropriate, quantitatively addressing exposure-dependent censoring in these analyses?

5. The modeled POD estimate is based on cumulative exposure estimates for the worker cohort examined. For the derivation of the RfC, this cumulative exposure is prorated over the period of environmental exposure (lifetime or shorter duration chronic exposure when appropriate). The RfC is provided in units of continuous air concentration. Is the basis of this conversion clearly explained (**Yes**) and scientifically justified? (**Yes**).

6. Please comment on the rationale for the selection of the uncertainty factors (UFs) applied to the POD for the derivation of the RfC. Are the UFs appropriate based on *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002; Section 4.4.5) (**Yes**) and clearly described? (**Yes**). If changes to the selected UFs are proposed, please identify and provide scientific support. Specifically, please comment on the rationale for the selection of the database uncertainty factor (UF_D) of 10 applied in the derivation of the RfC. (**This seems to be too high**). The database uncertainty factor accounts for the lack of data on effects other than in the respiratory system, including other effects observed in community and laboratory animal studies (cardiovascular

disease and autoimmune effects) that have not been well-studied (See Section 5.2.3 of the Toxicological Review); and lack of health data assessed at later time points. Is the rationale for the UF_D appropriate and clearly described? Please provide the rationale if a change in the UF_D is proposed. **(Note: Reliance should be placed on past experience for other types of amphibole fibers).**

7. Please comment on whether the document adequately describes the uncertainties and limitations in the methodology used to derive the RfC (**Yes**) and whether this information is presented in a transparent manner (**Yes**).

B. Inhalation Unit Risk (IUR):

1. Exposure-response modeling was conducted separately for lung cancer and mesothelioma mortality. The POD estimates for these endpoints are based upon analysis of the subcohort of workers first exposed after 1959 when the exposure data were judged to be better characterized. The exposure-response modeling included consideration of a variety of exposure metrics that varied with time and incorporated different lag and decay parameters. Based on the results of the exposure-response modeling, a lifetable analysis was used to determine the PODs for each type of cancer for the various exposure metrics. Have the exposure-response modeling and determination of the PODs from lifetable analysis been appropriately conducted (**Yes**) and clearly described? (**Yes**). If a different approach to exposure-response analysis is recommended as the basis for the estimating the IUR, please identify the recommended methods and provide a rationale for this choice.

2. Smoking is a strong independent risk factor for lung cancer and may be an important confounder of the lung cancer mortality analysis. Data on individual smoking habits and history were largely missing and could not be used to control for potential confounding in regression analyses. However, EPA used three approaches to evaluate the confounding issue, including restriction of the cohort and two analytic evaluations of the potential for confounding by smoking (see Section 5.4.3.6.5). Please comment on whether the methods and analyses are clearly presented (**Yes**) and scientifically justified (**Yes**). If additional analyses are recommended, please identify the methods and scientific rationale.

3. In order to derive an IUR which represents the combined risk of mortality from lung cancer or mesothelioma, a cancer-specific unit risk for each tumor type was calculated

according to the *Guidelines for Carcinogen Risk Assessment* (U.S., EPA, 2005; Sections 3.2 and 3.3) by linear extrapolation from the corresponding POD (i.e., the lower 95% confidence limit on the exposure associated with 1% extra risk of lung cancer or 1% absolute risk of mesothelioma mortality). The IUR was then determined as a combined upper bound risk estimate for mortality considering both cancers. Has this approach been appropriately conducted (**Yes**) and clearly described? (**Yes**).

4. Please comment on the adjustment for mesothelioma mortality underascertainment. Is this adjustment scientifically supported (**Yes**) and clearly described? (**Yes**). If another adjustment approach is recommended as the basis for the IUR, please identify that approach and provide the scientific rationale.

5. Please comment on whether the document adequately describes the uncertainties and limitations in the methodology used to derive the IUR (**Yes**) and whether this information is presented in a transparent manner (**Yes**).

Generic Comments [that go beyond the Charge Questions]

- 1) In view of the fact that the focus of the document is on Libby amphibole fibers, it would be better to shorten and simplify the text by limiting the literature reviews and discussions to those dealing with the various kinds of amphibole asbestos fibers. Chrysotile asbestos fibers, which are not a significant complication in exposures to Libby vermiculate, are very different from amphibole fibers in terms of their: a) airborne concentration measurement errors and uncertainties; b) much lower biopersistence; c) clearance and translocation pathways and rates; and risks. One rationale for the exclusion of the literature on risks associated with exposures to chrysotile from this document is that most of the risks have been due more to amphibole fibers within the chrysotile ores than to the much more numerous chrysotile fibers that dominate the measured airborne fiber concentrations.
- 2) More clearly present and acknowledge that the risks per unit of airborne fiber count concentration, which are quantified in terms of: a) inhalation unit risk (IUR); and b) reference concentration (RfC). The IUR is a best estimate, while the RfC is a conservative upper bound estimate that incorporates multiple 10-fold safety factors. Advocating that EPA and others rely on an RfC for amphibole fibers makes them come to ridiculous risk management decisions when the calculated RfCs turn out to be orders of magnitude below measurable background levels. This conundrum needs to be discussed in the document, and some realistic guidance should be provided on risk communication.
- 3) There are many mis-statements and omissions of knowledge on fiber deposition and dosimetry in the document that, fortunately, are not included in the well-crafted Section 6 on “Major Conclusions in the Characterization of Hazaed and

Exposure Response”. The authors of the earlier Sections, in cleaning up the text, should draw on some more authoritative and comprehensive reviews in the literature (e.g., Lippmann 2009; Mossman et al. 2011).

Specific Text Comments:

page line Comment

- 1-3 1, 2 IRIS IUR – It is important to emphasize that excess cases are based on central tendency – not upper bound estimates.
- 3-5 19, 32 impaction is not materially affected by fiber length.
- 3-6 1 replace “sedimentation and impaction” with “interception”. Cite work by Sussman et al. (1991a,b) that demonstrates that interception of fibers is demonstrably in excess when fiber lengths are >10 μm .
- 3-6 24-36 there is a need to cite the work of Brody and colleagues (Brody et al. 1981, Brody and Roe 1983, and Warheit and Hartsky 1990) on fiber deposition in the alveolar region.
- 3-8 20 Change: “minutes or hours” to “hours or a few days”.
- 3-8 22 particles depositing in the alveolar region can reach the tracheobronchial tree in 2 ways; 1) on surface fluids drawn onto the mucociliary escalator by surface tension, and 2) by passing through lymphatic channels which empty onto the escalator at bronchial bifurcations.
- 3-9 18 insert “short” before “fibers”.
- 3-10, Section 3.2.1.1.5 Remove nearly all of the discussion of chrysotile in the discussion of translocation. The Libby asbestos fibers are essentially all amphibole fibers, and there is very little commonality among serpentine and amphibole fibers in terms of translocation or long-term retention.
- 4-49 10 Instead of starting this discussion with “No inhalation...”, start with the inhalation study of Davis et al. (1985) with fibrous tremolite, which is very similar to “Libby amphibole”, as opposed to the Gouveneur tremolite cited on line 23 as not being fibrous. Also, what about the tremolite inhalation study of Bernstein et al. (2003,2005) that is cited in Table 4-16 on page 4-53?
- Section 4.2 The results of the various studies cited in this section are almost all very difficult to interpret with respect to the toxic effects that were, or were not, reported, since no information was provided on the key dosimetric factors of fiber dimensions.
- 4-69 23 What does “there are limited data” mean? Is this a positive or negative statement?
- 4-70 19 What is being said here?
- 4-78 4,5 The statement that: “the mode of action of Libby amphibole asbestos cannot be established” is too easy a cop-out. The weight of the evidence cited in this document supports the toxic equivalence of Libby amphibole fibers with tremolite fibers in particular, and with all amphibole fibers more generally, and this should be stated here!
- 4-78 26 change “cannot be established” to “will not, for some unstated reason, be established here”.
- 4-79 15 change “from” to “related to”.
- 4-88 28 is it 2008, or 2007 as in the reference list?

REFERENCES CITED:

Brody AR, Hill LH, Adkins B Jr, O'Connor RW (1981) Chrysotile asbestos inhalation in rats: deposition pattern and reaction of alveolar epithelium and pulmonary macrophages. *Am. Rev. Respir. Dis.* 123:670-679.

Brody AR, Roe MW (1983) Deposition pattern of inorganic particles at the alveolar level in the lungs of rats and mice. *Am. Rev. Respir. Dis.* 128:724-729.

Lippmann, M. Asbestos and other mineral fibers. In: M. Lippmann, Ed., *Environmental Toxicants: Human Exposures and Their Health Effects*, 3rd Ed., John Wiley, New York, NY, 2009, pp. 395-458.

Mossman, B.T, Lippmann, M, Hesterberg, T.W., Kelsey, K.T., Barchowsky, A., Bonner, J.C.. Pulmonary endpoints (lung carcinomas and asbestosis) following inhalation exposure to asbestos. *J Toxicol Environ Health, Critical Reviews, Part B* 14:76-121 (2011).

Sussman RG, Cohen BS, Lippmann M (1991a) Asbestos fiber deposition in a human tracheobronchial cast. I. *Exp. Inhal. Toxicol.* 3:145-160.

Sussman RG, Cohen BS, Lippmann M (1991b) Asbestos fiber deposition in a human tracheobronchial cast. II. Empirical model. *Inhal. Toxicol.* 3:161-179.

Warheit DB, Hartsky MA (1990) Species comparisons of alveolar deposition patterns of inhaled particles. *Exp. Lung Res.* 16:83-99.

Dr. John S. Neuberger

General Charge Questions:

1. Is the Toxicological Review logical, clear, and concise? Has EPA clearly, and in sufficient detail, presented and synthesized the scientific evidence for health hazards from Libby Amphibole asbestos?

The August 2011 document is extensive and represents an exhaustive amount of work. Its clarity could be improved in spots and it is not as concise as it could be. It is redundant and repetitive in several sections and could benefit from having a summary at the conclusion of all of the six major chapters. The additional review, received after I had marked up the first version, might contain some of these suggestions.

The review would also benefit from greater usage of graphs and figures to highlight conclusions. A figure describing the two major occupational groups studied, including their time-lines of exposure, would be very helpful.

Some of the material included appears to be excessive and should be greatly reduced. We already know that asbestos is hazardous, thus the focus of the report should be more on the dose/response aspects. For example, is intrapleural injection and ingestion for animals all that important when we have historical and relatively recent data on humans? There are large areas of analysis (e.g., nine community studies in 4.1.4) and two case reports (4.1.5) that appear to offer nothing new, given a lack of detailed exposure information and a lack of a population, respectively. Discussions that appear to offer little or no new insights into the toxicology of asbestos should be more briefly summarized. These sections could be left out from or greatly reduced unless there is some novel mechanistic information provided.

The focus should be on inhalation and, for cancer endpoints, the resultant lung cancer and mesothelioma in humans. This would include the slope of the dose response curve for these two conditions. Some more health (mortality) endpoint data from the Libby workers would be useful as background information (e.g., Tables 5-6 and 5-8). These tables are partially mislabeled since they also include data on mortality from lung cancer and mesothelioma.

A table comparing these results with the results from the earlier 1988 EPA report on asbestos would be helpful. Chapter 6 would be a good place for this. The data herein seem to suggest that the slope for asbestos is lower herein than the earlier slope (0.17 versus 0.23 excess cancers per 1 fiber per cc). If this interpretation is correct, then some explanation would be needed as to why this could be the case. It was my impression that Tremolite and other asbestos fibers found at Libby were on the whole among the most toxic subsets of asbestos.

2. Please identify any additional peer-reviewed studies from the primary literature that should be considered in the assessment of noncancer and cancer health effects of Libby Amphibole asbestos.

No additional references identified at this time.

Chemical-Specific Charge Questions:

B. Carcinogenicity:

1. Under EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005; www.epa.gov/iris/backgrd.html), the draft IRIS assessment characterizes Libby Amphibole asbestos as "carcinogenic to humans" by the inhalation route of exposure. Please comment on whether the cancer weight of evidence characterization is scientifically supported and clearly described.

The weight of evidence for carcinogenicity is scientifically supported and clearly described. There is repetitiveness throughout this draft, however, that should either be reduced or eliminated.

2. Due to the limitations of the data available, the draft assessment concludes that there is insufficient information to identify the mode of carcinogenic action of Libby Amphibole asbestos. Please comment on whether this determination is appropriate and clearly described. Note that in the absence of information to establish a mode of action, a linear low dose extrapolation is recommended by the *Guidelines for Carcinogen Risk Assessment* (U.S., EPA, 2005; Section 3.3). If it is judged that a mode of action can be established for Libby Amphibole asbestos, please identify the mode of action and its scientific support (i.e., studies that support the key events, and specific data available to inform the shape of the exposure-response curve at low doses).

Several modes of action are described, but none are with great certainty. These include inflammation, reactive oxygen species, direct genotoxicity, cytotoxicity, and cellular proliferation due to attempted injury repair. It's likely that multiple modes of action are involved and a linear low dose extrapolation seems warranted.

5. The database of laboratory animal and mechanistic studies of Libby Amphibole asbestos is summarized in this draft assessment (see Section 4.2 and 4.3, details in Appendix D) to inform the mechanisms of the biological response to Libby Amphibole asbestos and support the epidemiology studies used for derivation of the IUR. Please comment on the use of laboratory animal and mechanistic information in the draft assessment.

This section does support the biological plausibility of asbestos. However, this section seems overly complex. Laboratory animal data should be focused on the respiratory mode of exposure. Ingestion data in animals may be helpful due to the fact that some asbestos fibers may be swallowed after clearance from the respiratory tract. Information

on implantation and injection in animals does not seem that useful. The section should be organized in such a way that the most relevant information from animal studies (i.e., respiratory studies) comes first and the less relevant come later.

III. Exposure-Response Assessment

A. Inhalation Reference Concentration (RfC):

4. EPA has evaluated potential confounders and covariates where data are available. Specifically, EPA has explored the influence of age, body mass index, smoking status, time since first exposure, gender, and alternative exposure metrics on model fit and evaluated their association with the modeled health outcomes (see Section 5.3). Are these analyses clearly described and appropriately conducted? Are the results of these analyses appropriately considered in the RfC derivation? Additionally, there is a possibility of exposure-dependent censoring in participant selection for the update of the Marysville cohort (Rohs et al., 2008) but no evidence of selection bias. Does the panel have any specific recommendations for evaluating and, if appropriate, quantitatively addressing exposure-dependent censoring in these analyses?

The influences of body mass index, time since first exposure, background rate of LPT, model function, and smoking are described. There is no discussion of gender, except in places where the number of females is listed as too few to analyze in any detail. Gender is believed, however, to be included in the overall statistical model.

Smoking is included in the follow-up study by Rohs et al. However, the ever/never categorization of smoking in this follow-up is much less informative than the pack-year analysis of smoking used in the earlier study by Lockey et al.

As exposure levels were undoubtedly higher in the past, more current measurements of lower level exposures could overstate the risk per unit of exposure. Since exposure measures are lacking prior to 1972, it would be of interest to compare health effects both pre and post 1972. Appendix F indicates that from 1980 forward Libby asbestos was not used at the Marysville facility.

II. Hazard Identification of Libby Amphibole Asbestos

B. Carcinogenicity:

3. An occupational cohort of workers from Libby, MT exposed to Libby Amphibole asbestos (i.e., the Libby worker cohort) was selected as the basis for the derivation of the inhalation unit risk (IUR). Please comment on whether the selection of this study population is scientifically supported and clearly described. If a different study population is recommended as the basis for the IUR, please identify this study and provide scientific support for this choice.

The selection of the Libby cohort is scientifically supported and clearly described. This cohort has been thoroughly studied previously, had detailed work histories available, had elevated asbestos exposure, had a wide range of measurements of asbestos exposure, was large, and had cancer mortality data available.

Use of the sub-cohort post 1959 seems reasonable due to the lack of exposure information in many of the earlier workers. 706 out of 991 workers hired before 1960 had all department and job assignments listed as unknown. Thus, it would seem highly problematic to include these workers in the model. However, that leaves 285 workers with at least some information. Possibly some additional analysis could be done on that group. However, of the 991 workers, 811 had at least one job with an unknown job assignment.

It would be informative to calculate an overall Standardized Mortality Ratio (SMR) for the two cohorts for lung cancer. Comparison should be made to both Montana and U.S. data. The later cohort also had lower levels of exposure to asbestos, which would be closer to the lower levels found in the environment.

4. Mortality from lung tumors and mesothelioma in the Libby worker cohort was selected to serve as the basis for the derivation of the IUR. Please comment on whether this selection is scientifically supported and clearly described. If a different health endpoint is recommended for deriving the IUR, please identify this endpoint and provide scientific support for this choice.

Use of the endpoints lung cancer and mesothelioma are entirely appropriate. It would, however, have been useful to know the other major categories of mortality in this cohort. This could include the numbers of COPD, cardiovascular, colorectal cancer, and other cancer deaths. The report mentions laryngeal (n = 2) and ovarian (n = 0) cancer deaths in the text. Reference to Tables 5-6 and 5-8.

III. Exposure-Response Assessment

B. Inhalation Unit Risk (IUR):

2. Smoking is a strong independent risk factor for lung cancer and may be an important confounder of the lung cancer mortality analysis. Data on individual smoking habits and history were largely missing and could not be used to control for potential confounding in regression analyses. However, EPA used three approaches to evaluate the confounding issue, including restriction of the cohort and two analytic evaluations of the potential for confounding by smoking (see Section 5.4.3.6.5). Please comment on whether the methods and analyses are clearly presented and scientifically justified. If additional analyses are recommended, please identify the methods and scientific rationale.

This section is scientifically supported. I would also include cardiovascular disease mortality (n = ?). How many COPD deaths were there? Some COPD deaths may have been related to asbestos exposure independent of smoking.

4. Please comment on the adjustment for mesothelioma mortality underascertainment. Is this adjustment scientifically supported and clearly described? If another adjustment approach is recommended as the basis for the IUR, please identify that approach and provide the scientific rationale.

The mesothelioma undercount is adjusted for the entire lifespan (70 ÷ 54) and for the undercount in death certificates. Both of these approaches seem quite logical and are well described.

6.1

An excellent summary. There is no residential data for the slope of the dose/response curve due to the lack of exposure information.

Early-life Exposure

Early-life exposure examples are provided in the text and indicate potential for mesothelioma from asbestos exposure in general. It seems likely that exposure to Libby Amphibole Asbestos among Libby, Montana residents would increase the risk for that disease, and possibly lung cancer. Perhaps the Peto model can be utilized to estimate the resultant risks.

Long-term Research Needs

It would be informative and very important for NIOSH and ATSDR to continue monitoring mortality among Libby workers and Libby City (multiple geographic boundaries) residents, respectively, to determine the number of new lung cancers, mesotheliomas, and non-malignant pulmonary diseases (i.e., asbestosis) in these two populations.

The last occupational ascertainment was through 2006; an additional five years of data should now be available. In addition to a dose-response evaluation, an overall SMR should be calculated for lung cancer in this population by comparison to both the Montana and U.S. populations.

The previous ATSDR community SMR mortality survey was from 1979-1998. It should now be extended through 2011 and should include an analysis specific for community, non-occupationally exposed, individuals. Early-life exposure to Libby Amphibole Asbestos could possibly be obtained from surrogate interview information from the community population. Smoking, occupational, and residential histories should be obtained for the lung cancer, mesothelioma, and non-malignant respiratory disease (i.e., asbestosis) categories. Data concerning previous Libby residents who had moved away

(and died in other states) would need to be obtained by means of a special effort of ATSDR.

A community cross-sectional respiratory health screening was conducted in Libby by ATSDR in 2000 and 2001. A non-malignant respiratory health update since then would be useful. The appropriate smoking, occupational, and residential histories should be included.

None of the above suggestions for additional research should be taken to suggest a delay in the current clean-up activities of EPA at Libby. However, if new information is obtained, a revision of the EPA document pertinent to Libby, Montana Amphibole Asbestos exposure could be considered.

Dr. Lee S. Newman

General Charge Questions:

1. *Is the Toxicological Review logical, clear and concise? Has EPA clearly, and in sufficient detail, presented and synthesized the scientific evidence for health hazards from Libby Amphibole asbestos?*

Comment:

Yes.

2. *Please identify any additional peer-reviewed studies from the primary literature that should be considered in the assessment of noncancer and cancer health effects of Libby Amphibole asbestos.*

Comment:

Two peer-reviewed studies have been published that should be taken into consideration by the EPA:

Alexander, B., Raleigh, K., Johnson, J., Mandel, J., Adgate, J., Ramachandran, G., Messing, R., Eshenaur, T., and Williams, A. Radiographic Evidence of Nonoccupational Asbestos Exposure from Processing Libby Vermiculite in Minneapolis, Minnesota. *Environmental Health Perspectives*, 120 (1), 2012, 44-49.

Adgate, J., Sook, J., Cho, J., Alexander, B., Ramachandran, G., Raleigh, K., Johnson, J., Messing, R., Williams, A., Kelly, J., and Pratt, G. Modeling Community Asbestos Exposure near a Vermiculite Processing Facility: Impact of Human Activities on Cumulative Exposure. *Journal of Exposure Science and Environmental Epidemiology*, 21, 2011, 529-535

Chemical-Specific Charge Questions:

II. Hazard Identification of Libby Amphibole Asbestos

A. Noncancer Health Effects:

1. An occupational cohort of workers in a Marysville, OH facility exposed to Libby Amphibole asbestos (Lockey et al., 1984; Rohs et al., 2008) was selected as the basis for the derivation of the reference concentration (RfC). Please comment on whether the selection of this study population is scientifically supported and clearly described. If a different study population is recommended as the basis for the RfC, please identify this study and provide scientific support for this choice.

Comments:

Overall, the Marysville, OH worker cohort provides sufficient basis for the derivation of the RfC, despite some limitations. As noted in the draft Review, there is uncertainty in the exposure data prior to 1973, leading to potential underestimation of exposures. Along with the cohort's potential biases, it is important that the RfC account for this uncertainty, and also for the fact that the cohort is not representative of the general population (All-adult, 94% male, and Caucasian.) Nevertheless, the data are robust in that they include individual measurements on smoking, BMI, sex, age, and hire date.

Exposures in this cohort ranged from 0.01 to 19.03 fibers/cc-years and were lower than in those of the Libby worker cohort which ranged from 0 to >400 fibers/cc-years. The size of the cohort was reduced over time by 31%. Participation bias is thus important to consider, which could lead to an underestimation of risk. Those who did participate in the study were likely to be healthier and nonsmoking. A degree of misclassification of exposure is also still probable, (Rohs et al., 2008).

I recommend that the EPA consider inclusion of the Minneapolis Exfoliation Community cohort in the calculation of the RfC. The results for the Minneapolis Exfoliation Community cohort study suggest that the effects of exposure to Libby asbestos may occur at levels lower than indicated in the Marysville cohort. Therefore, it is imperative that this additional community cohort be considered for derivation of the RfC, which should be based on the lowest observable adverse effect level (LOAEL). This cohort consisted of 461 non-workers, including women and children, and is therefore more representative of the general population than the Marysville worker cohort. Pleural anomalies were observed at exposures to lower concentrations of Libby amphibole asbestos. Exposures, which ranged from 0.096 to 5.76 fibers/cc-years, were modeled at the low end of the exposures for the Marysville worker cohort; development of pleural abnormalities was the measured

outcome. Possible disadvantages are that there is uncertainty in the modeled ambient air concentration (which accounts for the bulk of the exposure concentrations). However, the studies do provide individual level modeled exposures. The authors provide no information on race and ethnicity, which would be helpful if it is available. BMI information was not provided.

Alexander, B., Raleigh, K., Johnson, J., Mandel, J., Adgate, J., Ramachandran, G., Messing, R., Eshenaur, T., and Williams, A. Radiographic Evidence of Nonoccupational Asbestos Exposure from Processing Libby Vermiculite in Minneapolis, Minnesota. *Environmental Health Perspectives*, 120 (1), 2012, 44-49.

Adgate, J., Sook, J., Cho, J., Alexander, B., Ramachandran, G., Raleigh, K., Johnson, J., Messing, R., Williams, A., Kelly, J., and Pratt, G. Modeling Community Asbestos Exposure near a Vermiculite Processing Facility: Impact of Human Activities on Cumulative Exposure. *Journal of Exposure Science and Environmental Epidemiology*, 21, 2011, 529-535

2. Radiographic evidence of localized pleural thickening in humans was concluded by EPA to be an adverse effect and was selected as the critical effect for the derivation of the RfC. Pleural thickening is associated with restrictive lung function, breathlessness during exercise and, for some individuals, chronic chest pain. Please comment on whether the selection of this critical effect and its characterization is scientifically supported and clearly described. If a different health endpoint is recommended as the critical effect for deriving the RfC, please identify this effect and provide scientific support for this choice.

The selection of radiographic evidence of localized pleural thickening in humans is the appropriate critical effect for the derivation of the RfC. This is well supported by the lines of evidence presented in section 4.1.1.4.2. The section is clearly described. Additionally, the data in the Larson 2010 paper helps reinforce the point that pleural changes would be more suitable than presence of small opacity profusion score, given that the time from hire to date of radiographic appearance of pleural changes precedes that of small opacities.

While there are other health endpoints that might have been considered candidates for the critical effect for deriving the RfC, none is superior to localized pleural

thickening. Ones that I considered included diffuse pleural thickening and small opacity profusion. Localized pleural thickening has the appropriate specificity and is not confounded by cigarette smoking.

B. Carcinogenicity:

3. An occupational cohort of workers from Libby, MT exposed to Libby Amphibole asbestos (i.e., the Libby worker cohort) was selected as the basis for the derivation of the inhalation unit risk (IUR). Please comment on whether the selection of this study population is scientifically supported and clearly described. If a different study population is recommended as the basis for the IUR, please identify this study and provide scientific support for this choice.

Comments:

The Libby worker cohort is the most appropriate study population available for the derivation of the inhalation unit risk (IUR). The selection is scientifically supported by the size of the cohort, confirmation of cancer outcomes by thorough review of death certificates, sufficient follow up (lag) time for the presentation of lung cancer, the use of a well documented and well defined job exposure matrix supported by measured asbestos concentrations and which covers a two order range of magnitude (0 to 400 fiber/cc-year). Libby amphibole asbestos is the only possible source of the asbestos measured in the air samples (i.e. no other sources of asbestos at the mine and associated facilities).

It should be noted, however, that this study population may not be representative of the larger population, in that most of its members are white males, exposed as adults, and contains more cigarette smokers than the larger population. If an appropriate study population that includes a larger proportion of women, other races, and those exposed as children becomes available, the derivation of the IUR should be revisited. Additionally, it is noted that the endpoints are based on cancer mortality on death certificates. This may lead to an undercounting.

The section is clearly written.

4. Mortality from lung tumors and mesothelioma in the Libby worker cohort was selected to serve as the basis for the derivation of the IUR. Please comment on whether this selection is scientifically supported and clearly described. If a different health endpoint is recommended for deriving the IUR, please identify this endpoint and provide scientific support for this choice.

Mortality from mesothelioma as the basis for derivation of the IUR is scientifically supported and clearly described. Mesothelioma is specific to asbestos, eliminating the potential for confounding.

While lung cancer in this cohort is appropriate for the derivation of the IUR, it may be less desirable. Confounding or effect modification from other exposures associated with lung cancer, such as cigarette smoking and radon exposure, cannot be fully addressed with this cohort. Given the potential effect modification or confounding, the EPA should consider an alternative model that uses mesothelioma mortality alone to derive the IUR, recognizing significant limitations, including the relatively small number of mesothelioma events. I would like to see this discussed at the meeting.

Both outcomes (lung cancer and mesothelioma) may be under represented in the study population. Although the five year survival rate for both is low (Lung cancer = 14%, mesothelioma < 10%), determining the cancer outcome from mortality rather than incidence may have resulted in an undercount of both cancer outcomes. The discussion would benefit from more detail on how this may impact the derived IUR. In addition, the mesothelioma outcome may be underrepresented because the cohort has been followed for 25-46 years and lag times from exposure to detectable disease onset range from 15 to > 60 year. Mesothelioma also may have been underreported on death certificates. Under represented outcomes could lead to an underestimated IUR. While there is sufficient information for derivation of the IUR, revisiting derivation of the IUR after additional follow up is warranted.

There may be an association between asbestos inhalation exposure and ovarian cancer – this cohort is mostly male and no ovarian cancer deaths have been observed in the female mortality data that is available.

Specific comments on Section 1

Page 1-2: Lines 3-4: The RfC is described in the preceding paragraph and does not need to be listed here.

Page 1-5: Lines 3-8: It is confusing to include the discussion for general asbestos here. Suggest moving up to Section 1.1.1.

Specific comments on Section 2

Page 2-20: Line 12 through 24: Need to clarify that the amphibole fibers identified in Marysville have the same characterization as those in Libby. How much of the asbestos in Marysville was from other places, such as South Carolina. How significant is the lack of information on the South Carolina ore?

Specific comments on Section 4

Page 4-4, Line 3-4: What were the years of operation for each of the 2 processing plants?

Page 4-6, Line 5: What was the time-interval for collection of samples after 1974 – 8 hours?

Page 4-6, Lines 10-12: Suggest clarifying the year when further standardization of the PCM method began. When did 25 μm width become the limit of resolution?

Table 4-2: a footnote needs to be added to explain the units of measurement of the MESA/MSHA and company records.

Page 4-9: Lines 9 through 16: What samples were the TEM and EDS performed on? What percentage of samples was this done on, how many samples? Were the samples collected from various operations?

Page 4-9: Line 23: Need to specify asbestos fiber.

Page 4-10: Line 10 through 12. These two sentences need to be rewritten. They do not make sense.

Table 4-3: Table should specify the years samples were collected and method used to characterize dimensions. The percents in the fiber length column add up to 101%.

Table 4-4: It is called out that the Amandus and Wheeler study did not include women, even though the description specifies “men”. For the McDonald studies there is no mention of whether women were included and the description specifies “men”.

Figure 4-1: Cannot see the Phase 1 Sites on this Figure. Suggest redoing figure so it is legible on Black and White copy.

Specific Comments Section 6:

Page 6-8 Lines 29 through 31 and Page 6-9 Lines 1-13: It follows from the first two sentences that asbestos should be considered as carcinogenic by other routes until there is adequate testing showing otherwise. This is because there is inadequate testing for the oral and dermal routes and mesothelioma is not considered a port-of-entry cancer. However, the conclusion of the paragraph concludes Libby asbestos is considered carcinogenic to humans by the inhalation route. It should also be stated that Libby asbestos is considered carcinogenic to humans by other routes.

Page 6-10: Lines 1-9: Is LPT considered to be a LOAEL? If so, need to state.

These Revised comments are from individual members of the SAB Libby Amphibole Asbestos Panel and do not represent consensus SAB advice or EPA policy. DO NOT CITE OR QUOTE.

Page 6-14: Lines 29 through 31 and Page 6-15 Lines 1-15: Would these effects have a lower LOAEL than LPT?

Page 6-26: Line 25: There may not be adequate years of follow-up for mesothelioma in this cohort.

Dr. Michael L. Pennell

General Charge Questions:

1. Is the Toxicological Review logical, clear, and concise? Has EPA clearly, and in sufficient detail, presented and synthesized the scientific evidence for health hazards from Libby Amphibole asbestos?

Overall, the review is logical, clear, and reasonably concise. However, in reviewing the material necessary for my assigned charge questions I have identified some aspects of their analysis that require more explanation and defense.

2. Please identify any additional peer-reviewed studies from the primary literature that should be considered in the assessment of noncancer and cancer health effects of Libby Amphibole asbestos.

Adgate et al. 2011, Journal of Exposure Science and Environmental Epidemiology;
Larson et al. 2012 Journal of Occupational and Environmental Medicine; Alexander et al. 2012 Environmental Health Perspectives; Lillis et al. 1991 American Journal of Industrial Medicine

III. Exposure-Response Assessment

A. Inhalation Reference Concentration (RfC):

2. Exposure-response modeling was conducted using the incidence of localized pleural thickening in workers and cumulative exposure to estimate the point of departure (POD) for derivation of the RfC. EPA's estimate of the POD is based upon a Michaelis-Menten model applied to the sub-cohort of workers examined in 2002-2005 and first exposed to Libby Amphibole asbestos in 1972 (when measurements of fiber levels in the workplace began) or later with cumulative exposure as the explanatory variable. Is the selection of the model scientifically justified and clearly described? Has the modeling and the choice of a benchmark response (BMR) for the POD of 10% extra risk of localized pleural thickening been clearly described and appropriately conducted according to EPA's *Draft Benchmark Dose Technical Guidance* (U.S. EPA, 2000b)?

The EPA clearly described their methods for model selection. They fit a series of quantal response models, retained models with adequate fit according to the Hosmer Lemeshow test (presumably based on $p > 0.1$, but this should be stated). Then, among the retained models, they selected the model with the lowest AIC. From a statistical standpoint, this methodology is scientifically justified. It does, however, deviate slightly from the decision tree for selection of the POD in the EPA's *Draft Benchmark Dose Technical Guidance* (p. 36-37); the decision tree states that the POD from the model with the

smallest AIC should be selected if, among models that adequately fit the data, the BMDLs are all within a factor of three. It appears as if the authors are calling all models within 2 AIC units of the smallest AIC as those that provide adequate fit. However, this criterion is not among those listed within the EPA's BMD document, which indicates that models with adequate fit have $p > 0.1$ from a goodness of fit test and pass a visual inspection of goodness of fit, particularly in the region of the BMR. No mention of fit within the region of the BMR is mentioned. Also, even within the set of models the authors deemed to have similar fit (all within 2 AIC units), the BMCLs are not within a factor of 3; the largest value (0.1352 from Michaelis-Menton model with lag 5 exposure) was 3.1 times that of the smallest value (0.0441 from the log-probit model with lag 15 exposure). Thus if the authors were to strictly follow the draft technical guidelines, the most conservative (smallest) BMCL should be used as the POD which comes from the log-probit model with lag 15 exposure, i.e., not the model they chose.

Biological plausibility of the selected model was not discussed; since model selection was based purely on comparison of fit statistics, I assume that there wasn't enough information to distinguish one model from another in this respect. Regardless, this issue should be addressed in this section of the IRIS document.

The authors chose 10% Extra Risk (ER) as the BMR, which is the default choice for quantal responses. In the EPA's *Draft Benchmark Dose Technical Guidance*, it is mentioned that a BMR of 1% ER is typically used for human quantal response data as epidemiologic data often have greater sensitivities than bioassay data. The authors should explain what features of the data set, test chemical, or outcome variable led them to choose a BMR which is considerably greater than the norm for epidemiologic data.

3. EPA's assessment also provides the results of alternative modeling approaches to derive a POD for localized pleural thickening. This modeling used the full Marysville worker data set with exposures from 1957 and later and a Cumulative Normal Michaelis-Menten model that incorporates both cumulative exposure and time from first exposure as explanatory variables. Please comment on whether EPA's rationale for presenting these alternative approaches is scientifically justified and clearly described. Please identify and provide the rationale if a different approach for identifying the most appropriate population within the cohort of Marysville workers is recommended as the basis for estimating a POD.

The rationale for the complete cohort analyses is scientifically justified and clearly described; it is important to compare the results from the sub-cohort to analyses of the complete cohort as it uses all of the available data. They may also want to mention that

comparisons of the full and sub-cohort analyses allow them to assess potential biases caused by non-random selection of cases for the analysis.

However, I am not sold on their rationale for incorporating time since first exposure (T) into the analyses. It seems the conceptual argument for including this variable is that it is a surrogate measure of intensity as those with larger T would have been more likely to be exposed during the early part of the study when exposure levels were at their highest.

While this seems reasonable, I wonder if there is a better measure available. For instance, date of first exposure would capture whether or not people were exposed during these early time periods and an interaction between date and T would capture differences in exposure duration over the early parts of the study. The problem with using T alone is that it doesn't account for exposure duration over the early period of the study. For instance, T could equal 20 for two people but one person could have been first exposed in 1960 and the other could have been first exposed in 1980.

I understand their arguments for using the cumulative normal Michaelis-Menten model; the plots presented in the appendix (which by the way should be referred to in the main text to help build their arguments) suggest that the plateau of the Michaelis-Menten model varies with T. However, the authors should perform a sensitivity analysis on how T is incorporated in to the model; for instance, how different is the BMCL when T is included as an independent linear predictor alongside exposure.

5. The modeled POD estimate is based on cumulative exposure estimates for the worker cohort examined. For the derivation of the RfC, this cumulative exposure is prorated over the period of environmental exposure (lifetime or shorter duration chronic exposure when appropriate). The RfC is provided in units of continuous air concentration. Is the basis of this conversion clearly explained and scientifically justified?

The conversion of the cumulative exposure POD to one based on continuous lifetime exposure (i.e., original POD/60) is explained clearly as is the sensitivity analysis. Given the current set of analyses, I believe their selected conversion method is justifiable given that it results in the most conservative POD. However, the second sensitivity analysis should be revised; when fitting a model relating LPT incidence to each individual's cumulative exposure divided by their exposure duration, the dichotomous Hill model should be used instead of the Michaelis-Menten model because the Michaelis-Menten model assumes a slope of one and one would not expect the slope of the rescaled exposure to be the same as the slope of the cumulative exposure.

B. Inhalation Unit Risk (IUR):

1. Exposure-response modeling was conducted separately for lung cancer and mesothelioma mortality. The POD estimates for these endpoints are based upon analysis of the sub-cohort of workers first exposed after 1959 when the exposure data were judged to be better characterized. The exposure-response modeling included consideration of a variety of exposure metrics that varied with time and incorporated different lag and decay parameters. Based on the results of the exposure-response modeling, a lifetable analysis was used to determine the PODs for each type of cancer for the various exposure metrics. Have the exposure-response modeling and determination of the PODs from lifetable analysis been appropriately conducted and clearly described? If a different approach to exposure-response analysis is recommended as the basis for the estimating the IUR, please identify the recommended methods and provide a rationale for this choice.

The explanation and justification of the methods used for modeling the relationship between exposure mesothelioma mortality could be improved. The authors indicate that Poisson regression was used, but their arguments for using this model are not convincing. A parametric survival model (e.g., Weibull) could have also been used to obtain estimates of absolute risk. Why weren't they considered? The Peto model was disregarded due to a much smaller AIC than the Poisson model. While this suggests better global fit of the Poisson model, how do the fits of the Peto and Poisson models compare in the region of the BMR? Some plots comparing the fit of the two models to the data would be useful in this respect.

All analyses using Poisson regression must assess the possibility of over-dispersion and there is no mention of whether or not this assumption was examined. Another smaller issue: they should include the mathematical form of the regression function.

For the most part, the use of Cox regression in the modeling of lung cancer mortality was clearly explained and justified. I was confused, however, why a Bayesian analysis was not conducted as was done for the Poisson regression model for mesothelioma risk. One correction (p. 5-79): the assumption of independent censoring for the Cox models refers to causes of death unrelated to risk of lung cancer conditional upon exposure.

The risk calculations in the life tables look correct but some items require explanation. First, what method was used to estimate the hazard function for the exposed population? Was it based on a nonparametric estimate of the baseline hazard from the sub-cohort? Given that the SEER data were used to calculate the background incidence of lung cancer, it would be more appropriate to use those data to estimate the baseline hazard and then use the regression coefficient obtained from the Cox model applied to the sub-cohort data to obtain the hazard of the exposed group. I first assumed that is what the EPA did,

but realized that they didn't when I divided the exposed hazard rate (Column J in Table G-3) by the unexposed rate (Column G) and saw that the hazards weren't proportional. Also, the rationale for scaling the unit risks by 70/54 to encompass the entire lifespan was clearly explained in Appendix G but not in the main text.

2. Smoking is a strong independent risk factor for lung cancer and may be an important confounder of the lung cancer mortality analysis. Data on individual smoking habits and history were largely missing and could not be used to control for potential confounding in regression analyses. However, EPA used three approaches to evaluate the confounding issue, including restriction of the cohort and two analytic evaluations of the potential for confounding by smoking (see Section 5.4.3.6.5). Please comment on whether the methods and analyses are clearly presented and scientifically justified. If additional analyses are recommended, please identify the methods and scientific rationale.

The EPA used two different approaches to indirectly evaluate the potential for confounding by smoking: 1. restricting the analysis to a subcohort whose smoking habits should be fairly uniform and 2. a method proposed by Richardson (2010) where a significant relationship between exposure and COPD would suggest a relationship with smoking (performed using two different exposure metrics—I assume that is where the three different methods mentioned in the charge question is coming from). Their analyses are clearly explained and supported by the literature. However, I don't entirely agree with their conclusions from the Richardson method. The p-values for the two additional Cox models were around 0.1 which is close to marginal significance. Thus, based on p-values alone, I don't find the evidence against confounding by smoking to be very compelling. However, the fact that the coefficients for exposure in the COPD Cox models were negative is strong evidence against positive confounding; smoking is positively related to COPD risk and thus if positive confounding is occurring then we would also expect the relationship between asbestos exposure and COPD risk to be positive. It is possible, however, that negative confounding is occurring in which case the risk of lung cancer associated with asbestos exposure would be understated. Finally, the EPA should provide the number of COPD cases in the sub-cohort.

3. In order to derive an IUR which represents the combined risk of mortality from lung cancer or mesothelioma, a cancer-specific unit risk for each tumor type was calculated according to the *Guidelines for Carcinogen Risk Assessment* (U.S., EPA, 2005; Sections 3.2 and 3.3) by linear extrapolation from the corresponding POD (i.e., the lower 95% confidence limit on the exposure associated with 1% extra risk of lung cancer or 1% absolute risk of mesothelioma mortality). The IUR was then determined as a combined upper bound risk estimate for mortality considering both cancers. Has this approach been appropriately conducted and clearly described?

The approach has been clearly described but it concerns me. The method they used assumes independence of the mesothelioma and lung cancer IURs, which is not a good assumption given that the two were estimated from the same sub-cohort. Violation of the independence assumption could result in either an inflated or deflated upper bound on the combined IUR depending on the sign of the correlation between the two cancer-specific IURs. A better approach would be to jointly model the two outcomes using a Bayesian approach in which dependency could be introduced through a shared random effect in the regression models or a correlated prior for the exposure effects in each model. At the very least, this very restrictive assumption must be mentioned and the potential consequences of a violation of this assumption must be discussed.

5. Please comment on whether the document adequately describes the uncertainties and limitations in the methodology used to derive the IUR and whether this information is presented in a transparent manner.

Most of the uncertainties are clearly and adequately described. The discussions of a few uncertainties require some more details or revisions:

- 1.) **Model form:** I found this discussion inadequate because there are many competing models that could have been used instead of the Poisson and Cox models which could have provided very different estimates of risk (e.g., parametric survival models, accelerated failure time models, additive models). Also, as I mentioned earlier, the description of independent censoring is incorrect; the Cox model assumes that the event and censoring processes are independent conditional upon the covariates in the model; i.e., conditional upon exposure. Thus, if the only link between the two processes is the exposure variable, which is unlikely, the assumption is valid.
- 2.) **Confounding:** The statement on p. 5-127, lines 4-5 that since the proportional hazards assumption is satisfied in the sub-cohort, “there is no evidence of confounding by smoking...” is too strong because it is based on some strong assumptions including the assumption that the decline in smoking prevalence observed in the general U.S. population also occurred in the Libby cohort. This statement should be deleted.
- 3.) **Uncertainty in combining risks for composite IUR:** In addition to normality, this method assumed independence of the measures which I find highly suspect.

Finally, I found the summary statement on p. 5-131 lines 21-23 confusing.

Dr. Julian Peto

My main criticism of this EPA draft review is the choice of models for predicting the effects of lifetime asbestos exposure. The central aim of the report is to estimate the effects of lifetime exposure for mesothelioma, lung cancer and localised pleural thickening (LPT) by choosing and fitting an appropriate model for each disease. Risk assessment models should be chosen primarily by comparing their predictions against reality (i.e. relevant epidemiological evidence), particularly the effects on the incidence rate of temporal variables, including duration of exposure, time since starting exposure, and age. The models adopted for LPT and mesothelioma fail to predict the long-term continuing increase in risk that is observed for these diseases even after exposure has ceased.

The incidence rate of LPT

It is well-known that LPT continues to develop for many years after asbestos exposure has ceased. In contrast, the fitted Michaelis-Menten model predicts that within 10 years of stopping asbestos exposure the prevalence reaches a plateau. The analysis of the prevalence of pleural thickening as a function of cumulative exposure with a lag of 10 years cannot be correct if pleural thickening continues to appear more than 10 years after exposure has ceased, as the lagged cumulative dose would remain constant while the prevalence continues to rise. The analyses based on this model are therefore wrong, and should be removed from the report. In sections 5-2-3 and 5-2-4 the Michaelis-Menten model is selected and fitted, including the uncertainty factor analysis and calculation of the RfC. The fact that the prevalence of LPT continues to increase with increasing time since first exposure is then belatedly acknowledged in section 5.2.5. Section 5-3-3 justifies this contradiction by the following statement: “Note that the likelihood that prevalence of localized pleural thickening may further increase beyond 30 years after first exposure is a principal rationale cited for the selection of a database UF of 10 in this current assessment”. It is not reasonable to fit a model that is clearly wrong and attempt to allow for the error in the uncertainty analysis. The model must be discarded.

In section 5.2.5 the effect of time since first exposure is incorporated into this model by multiplying the predicted risk by the cumulative normal distribution function. The justification for this (Appendix E section E3-2) is that “the plateau term based on the cumulative normal function was chosen because of its ease of use and familiarity”. Fig E-4 shows that the original model underestimates the lifetime risk by a factor of 30 compared with the predictions of the cumulative normal model. The latter is consistent with the data (appendix E, fig E-3), but so are other models discussed and discarded in section E3-2 such as the Weibull, which would predict an even higher lifetime risk. The fitted normal distribution implies that the rate of increase of prevalence (i.e. the incidence rate) peaks at 43 years after first exposure (the parameter m in table E-6) and then declines. The Weibull model would predict a continuing increase in the incidence rate in old age. A more appropriate sensitivity analysis would focus on this model-dependent

uncertainty in the extrapolation to predict the effects of lifetime exposure, which is the primary aim of the risk assessment.

The mesothelioma incidence rate

The lifetime mesothelioma risk is much higher when asbestos exposure occurs at an early age, because the incidence rate continues to increase sharply (roughly as the cube of time since first exposure) even after exposure has ceased. This is apparent in national mesothelioma death-rates within each birth cohort. At age 80, long after exposure has ceased, the rate is about 100 times greater than at age 40 and is still increasing. In contrast, the predicted mesothelioma rates in Tables G1 and G2 (Appendix G), which are supposed to show the effects of exposure beginning at age 16 and continuing into old age, are virtually constant from age 40 to age 80. As for LPT, the crucial assumptions implicit in the model should be identified and examined in relation to other epidemiological data. The effect of exposure from birth to age 70 rather than from age 16 to 70 (54 years) is then calculated by simply multiplying these predicted lifetime risks by 70/54. A factor of about 3 would be more appropriate. These models are inferior to the epidemiologically and biologically more plausible model for mesothelioma that the EPA adopted more than 20 years ago in its “Airborne asbestos health assessment update” (EPA 1986). It is not clear how this has affected the predicted lifetime risk from environmental exposure to Libby amphibole asbestos. The review underestimates the relative effect of early exposure, but the effect of exposure later in life is exaggerated.

Modelling incidence rather than prevalence

Models for chronic diseases should be formulated in terms of the incidence rate, which reflects the subject’s current physical state, rather than the prevalence rate, which has no intuitive meaning beyond being the cumulative risk implied by the complex lifelong variation in the incidence rate implied by the model. The prevalence has to be analysed for LPT, because the incidence rate cannot be observed without repeated monitoring, but the formula for prevalence should be calculated from an underlying model for the incidence rate. This would have avoided several unnecessary errors. No reasonable incidence model could predict constant prevalence (i.e. a zero incidence rate) 10 years after stopping exposure for any asbestos-related disease, or an LPT prevalence that increases as the square or cube of latency (appendix E), and will therefore eventually reach 100%. That would require an infinite incidence rate.

The effect of duration of exposure

A strong assumption implied by the all the models that were considered is that the effects of level of exposure (fibres/cc) and duration of exposure can be modelled jointly as a function of the cumulative dose. This should have been examined in the epidemiological data by analysing the relationship between duration of exposure and incidence rate for each disease. It may be approximately true for LPT and lung cancer, but it cannot be assumed for mesothelioma. The adoption of this assumption is a consequence of

inappropriate application of the EPA's "Guidelines for carcinogen risk assessment" (EPA 2005), which states "Unless there is evidence to the contrary in a particular case, the cumulative dose received over a lifetime, expressed as average daily exposure prorated over a lifetime, is recommended as an appropriate measure of exposure to a carcinogen. That is, the assumption is made that a high dose of a carcinogen received over a short period of time is equivalent to a corresponding low dose spread over a lifetime." This may be a reasonable approximation for some carcinogens, but it is certainly inconsistent with the epidemiology of lung cancer caused by smoking or by radon exposure, where doubling the duration of exposure causes a much greater risk than doubling the rate of exposure (cigarettes per day, or radon concentration). More importantly in this context, it is inconsistent with the epidemiology of mesothelioma, where exposure in middle age causes a much smaller lifetime risk than early exposure.

Lung cancer

The weaknesses in the lung cancer modeling are the assumption of proportional hazards despite the evidence against it, and the use of current lung cancer rates instead of projected rates within birth-cohorts. Neither is easily dealt with, as changes in the relative risk with age seen in different cohorts of asbestos workers are affected by various factors and artefacts, particularly differences in smoking history, and future national rates will depend on assumptions about future changes in smoking. An analysis of the uncertainties in the predictions should epidemiological evidence on lung cancer patterns in other cohorts of workers exposed to amphibole asbestos.

In summary, I would have preferred a shorter document presenting predictions based on the models previously adopted by the EPA and many other agencies worldwide for asbestos risk assessment, and comparing those predictions against the epidemiological evidence from other published studies. The prevalence of pleural changes due to prolonged environmental exposure in the ATSDR cohort (Weill et al 2011) is particularly relevant. These data, together with a reasonable estimate of their average exposure in fibre/cc since the 1970s, could provide a particularly reliable estimate of lifetime risk per fibre/cc. It would also be helpful to see mesothelioma mortality rates and lung cancer SMRs in the Libby cohort and LPT prevalence in the Marysville cohort, tabulated by time since first exposure, duration of exposure and period of first exposure.

Dr. Carrie Redlich

Section 4.5 Synthesis of Non-Cancer Effects

1. Is the Toxicological Review logical, clear, and concise? Has EPA clearly, and in sufficient detail, presented and synthesized the scientific evidence for health hazards from Libby Amphibole asbestos?

Overall, Yes.

However, it could be more concise and several points could use clarification. The section seems quite detailed in certain parts for a “Synthesis”. The section should focus more on the specific issues most relevant to the EPA’s risk assessment, which for non-cancer effects is localized pleural plaques, and the justification for that endpoint. The review of the relevant literature should more explicitly provide justification or support for decisions related to estimating the RfC for Libby asbestos, in particular the use of localized pleural thickening / plaques (LPT) as the adverse health effect to estimate an RfC.

The document should more thoroughly review the epidemiology / clinical literature relating to outcomes associated with localized pleural plaques, especially lung function. The literature is complicated by several factors, including combining localized and diffuse pleural thickening in some papers. However, overall, this literature (but not all studies) supports an association between LPT and reduced lung function (usually FVC). While issues are addressed in various places, the synthesis section should also address more thoroughly areas of debate (or misunderstanding), such as: misclassification of fat vs. plaque, smoking and plaques (little association), and “clinically” vs. “public health” relevant changes in lung function.

While addressed in other sections, the role of smoking in different asbestos-related diseases and other nonmalignant respiratory diseases (e.g. COPD) is of sufficient importance (and misunderstanding) that it should be discussed in the summary, especially in relationship to LPT, the non cancer adverse health effect most relevant to this EPA document. LPT is not associated with smoking (nor asbestosis to a great degree, but lung function FEV1 is). This is important to note in the synthesis section, especially as this section notes that Libby workers have a markedly increased risk of death from COPD, which implies Libby workers smoked more and/or Libby asbestos exposure increases risk for COPD.

Given the extensive literature on non-Libby forms of asbestos, in summarizing the non-cancer health outcomes and possible mechanisms it would be helpful for the report to state more clearly whether any of the findings / studies suggest any major differences between Libby amphibole (which contains tremolite) and other amphibole forms of asbestos, in terms of toxicity and modes of action. While there likely are differences in the degree of toxicity. Are the cellular and molecular changes seen in response to Libby asbestos (e.g. cytotoxicity, increased ROS) substantively different than what has been reported with other types of amphibole asbestos? If the answer is no, then it would be helpful to frame the summary discussion with that in mind, and also shorten some sections. The statement “*there is currently insufficient evidence to establish the non-cancer mode of action of Libby asbestos*” could alternately be worded “*studies to-date indicate that “Libby” asbestos likely acts through modes of action similar to that of other amphiboles*”. (or similar wording).

Minor: The statement “*These diseases are consistent with asbestos toxicity*” does not clarify what diseases “these” refers to and is overly broad. (page 4-73)

2. Please identify any additional peer-reviewed studies from the primary literature that should be considered in the assessment of noncancer and cancer health effects of Libby Amphibole asbestos.

The literature review is quite thorough. As noted above, the literature related to LPT and lung function should be more thoroughly reviewed. Whether or not smoking and /or obesity are likely to impact on these findings should be included in this discussion.

Two recent articles related to non-occupational exposure in Minneapolis, Minnesota should be included, given the concerns regarding non-occupational sources of Libby asbestos and risks of exposure.

- 1) Alexander et al. EHP 2012. Radiographic evidence of nonoccupational asbestos exposure from processing Libby vermiculite
- 2) Adgate et al. Modeling community asbestos exposure... J Exposure Sc and Envir Epi 2011.
- 3) It (obviously) would be helpful to include Dr. Lockey's submitted publications, if possible.

Section 4.7 Susceptible Populations

1. Is the Toxicological Review logical, clear, and concise? Has EPA clearly, and in sufficient detail, presented and synthesized the scientific evidence for health hazards from Libby Amphibole asbestos?

This section cites a wide range of animal and human studies that may provide information regarding the health effects of asbestos in susceptible populations (e.g. age, gender, race). While quite thorough, this section could be better organized and more succinctly summarized.

Since most clinical / epidemiological asbestos studies are based on white male occupational cohorts, the data regarding susceptible populations such as children and women, and any type of asbestos, let alone Libby asbestos, is limited.

The section should especially focus on childhood asbestos exposure, the asbestos susceptibility issue most relevant to this EPA document, and probably the topic where there is at least some (albeit limited) data.

2. Please identify any additional peer-reviewed studies from the primary literature that should be considered in the assessment of noncancer and cancer health effects of Libby Amphibole asbestos.

None aware of related to susceptibility, as far as Libby asbestos.

While studies (? most) of non-Libby community / environmental exposures are mentioned, this literature, including worldwide community / environmental asbestos exposures, should be more thoroughly reviewed, as it addresses a major concern with Libby asbestos.

Section 5.4 Cancer Exposure Assessment

Selection of Principal Study; and Endpoint Selection

Questions II.B3 and II.B4

3. An occupational cohort of workers from Libby, MT exposed to Libby Amphibole asbestos (i.e., the Libby worker cohort) was selected as the basis for the derivation of the inhalation unit risk (IUR). Please comment on whether the selection of this study population is scientifically supported and clearly described. If a different study population is recommended as the basis for the IUR, please identify this study and provide scientific support for this choice.

Yes. The Libby worker cohort is scientifically supported to use for cancer endpoints. Any cohort has limitations, but this cohort appears to be the best available cohort for cancer endpoints. Limitations of this cohort include limited smoking information. Also outcomes are based on death certificates, which could undercount cancer endpoints, especially mesothelioma. The EPA analysis attempts to take into account these factors.

Issues related to using the full cohort were discussed at the meeting.

4. Mortality from lung tumors and mesothelioma in the Libby worker cohort was selected to serve as the basis for the derivation of the IUR. Please comment on whether this selection is scientifically supported and clearly described. If a different health endpoint is recommended for deriving the IUR, please identify this endpoint and provide scientific support for this choice.

The use of lung cancer and mesothelioma in the Libby cohort is scientifically supported and clearly described. Issues with using death certificates are addressed. The issue of smoking, while taken into account by the EPA in the risk assessment, should be summarized with greater clarity.

Miscellaneous General Comments

If not already included, it would be helpful to have a clearer comparison of the Libby asbestos findings with other asbestos cancer and non-cancer risk assessments / reviews, although there is no Rfc previously estimated for asbestos. Have non-US agencies /groups attempted similar quantitative risk assessments? The EPA has probably already included what has been done previously that is relevant, but this could be summarized more clearly.

An overall summary Table or Figure describing the major cohorts (Libby workers, community, Marysville plant), and the studies / exposure info associated with each would be helpful, if not present somewhere already.

Dr. A.G. Salmon

General Charge Questions:

1. *Is the Toxicological Review logical, clear, and concise? Has EPA clearly, and in sufficient detail, presented and synthesized the scientific evidence for health hazards from Libby Amphibole asbestos?*

Response:

In general, the document is well written and, given the technical nature of the content, clearly and straightforwardly written. The logical structure of the underlying problem and the steps of the risk assessment are well expressed and the document layout reflects this. It is hard to use the term “concise” of a document of this size and inevitable complexity, but there are no major problems of redundancy or unnecessary material.

In particular, the weight of evidence analysis for the carcinogenicity evaluation (Section 4.6.1) is thoroughly and convincingly presented in regard to the identification of Libby asbestos as a human carcinogen by the inhalation route, based on human evidence with supporting evidence of carcinogenicity in animals and other supporting toxicity and mechanistic data. Discussion of the situation for other routes of exposure is obviously more difficult given the lack of any clear evidence of carcinogenicity by other routes (e.g. oral, dermal), in spite of the default expectation that carcinogens acting at sites remote from the point of entry would be active via multiple routes of exposure. I think I have correctly understood that the Agency’s position is that there is no evidence to support a determination by the oral route, so their position is agnostic. However this could be a little more clearly stated, to distinguish between this choice and a determination that exposure by the oral route is regarded as non-carcinogenic.

The mode of action evaluation in Section 4.6.2 is by contrast, less satisfying simply because the evidence for a clear mode of action is lacking. The review of available evidence is relatively brief considering the large number of studies which have been reported over the years on possible modes of carcinogenic action for asbestiform minerals, many of which could be regarded as having relevance to Libby asbestos in particular. However, given that in spite of the extensive literature on the topic there are no firm conclusions for any types of asbestos the discussion presented here is probably sufficient.

There is an underlying problem with the discussion in section 4.6.2.2 which considers the applicability of the age-dependent adjustment factors. I understand that this is based on a policy decision enshrined in the carcinogen assessment supplemental guidance (EPA 2005b), but the outcome here illustrates the problems with this policy. As a general principle, policy choices lacking a clear basis in scientific data should be made so as to protect public health, whereas this decision clearly leaves open the possibility that the adjustment factors might be applicable but chooses the less health-protective option, not to apply them. This arbitrary choice is even more egregious given that the decision to apply the factors according to the policy depends on the identification of a “mutagenic mode of action”, and the Agency has so far been unable to provide a defensible definition

of what they mean by this phrase. Even less rational is the appearance of this brief and arbitrary segment of the analysis before the discussion (in section 4.7.1) of the possible influence of lifestage on susceptibility to both cancer and non-cancer effects of asbestiform minerals. While this section, perhaps unsurprisingly, does not reach clear conclusions or find specific data on Libby asbestos, it does identify some documented issues which may shed some light on the question of susceptibility of infants and children. Evidence is presented of possible greater lung deposition in infants and children: this question has been raised in various previous discussions of early-in-life sensitivity. Reference is made to the well-known long “latency” of amphibole carcinogenesis, especially mesothelioma, which results in a strong dependence of cancer incidence on time since exposure: this of itself may be a reason to take a more precautionary approach to exposures at younger ages. While published evidence about early life susceptibility is not extensive or definitive, this issue nevertheless deserves discussion in the context of risk assessment for asbestos exposures to infants and children. Consideration of actual data should always take precedence over generic policy decisions.

The major conclusions presented in Section 6.3 reflect accurately and clearly the analyses presented in the earlier sections. They thus suffer from the defects noted in my review of those sections (especially the inadequate treatment of possible early-in-life susceptibility), but are otherwise well written and helpful in providing a clear summary and basis for application of the risk assessment’s conclusions.

2. *Please identify any additional peer-reviewed studies from the primary literature that should be considered in the assessment of noncancer and cancer health effects of Libby Amphibole asbestos.*

Response:

I have not myself identified any additional primary references. It does appear that there are some very recent publications of which the Agency is now aware that are worth considering in the assessment of non-cancer health effects^{1,2}

Chemical-Specific Charge Questions:

I. Background

A. Mineralogy and Toxicokinetics

1. *In order to inform the hazard identification and dose response of Libby Amphibole asbestos, background material is included in the document briefly describing the*

¹ Alexander, BH; Raleigh, KK; Johnson, J; Mandel, JH; Adgate, JL; Ramachandran, G; Messing, RB; Eshenaur, T; Williams, A. (2012). Radiographic evidence of nonoccupational asbestos exposure from processing Libby vermiculite in Minneapolis, Minnesota. *Environ Health Perspect* 120: 44-49

² Adgate, JL; Cho, SJ; Alexander, BH; Ramachandran, G; Raleigh, KK; Johnson, J; Messing, RB; Williams, AL; Kelly, J; Pratt, GC. (2011). Modeling community asbestos exposure near a vermiculite processing facility: Impact of human activities on cumulative exposure. *J Expo Sci Environ Epidemiol* 21: 529-535.

mineralogy and toxicokinetics of asbestos and related mineral fibers (Section 2 and 3):

a. Please comment on whether the presentation of the available data on the mineralogy of Libby Amphibole asbestos is clear, concise and accurate.

Response:

Although the mineralogy is not within my personal area of expertise, I do want to say that I thought this section was very clear and well-written, and the description of the various amphibole minerals as solid solution series covering a continuous range of compositions is very helpful. This will prove useful in countering some arguments which have been made in the past seeking to arbitrarily limit conclusions about the chemistry, physics and biological activity of various related minerals.

b. In the absence of toxicokinetic information specific to Libby Amphibole asbestos, the draft assessment contains a general summary description of fiber toxicokinetics. Please comment on whether this overview of general fiber toxicokinetics is clear, concise and accurate.

Response:

The summary provided is clear, concise and, to the extent that I can determine, accurate. Obviously with this topic one is not going to see the kind of detail that is available with, for instance, the PBPK models which are popular for volatile organic chemicals and can be used to modify and improve the quantitative risk assessment. But the delineation of available deposition models is useful, and both this discussion and the presentation of data on fiber transport between tissues are helpful in supporting consideration of mechanisms underlying the tissue and route specificity of asbestos health effects. Durability of fibers is also a topic of importance as noted in the later analyses of cancer and non-cancer effects.

II. Hazard Identification of Libby Amphibole Asbestos

A. Noncancer Health Effects:

1. An occupational cohort of workers in a Marysville, OH facility exposed to Libby Amphibole asbestos (Lockey et al., 1984; Rohs et al., 2008) was selected as the basis for the derivation of the reference concentration (RfC). Please comment on whether the selection of this study population is scientifically supported and clearly described. If a different study population is recommended as the basis for the RfC, please identify this study and provide scientific support for this choice.

Response:

The selection of this study as the basis for the RfC is explained on the basis of the completeness of epidemiological data, the thoroughness of the report, and the advantage of measuring lower overall levels of exposure and less severe effects than in other exposed cohorts. It also appears likely that coexposures from local non-occupational sources and take-home contamination by workers are lower for this cohort than for others such as those based in Libby. On these bases the selection of this study appears to be a good choice as the primary basis for the RfC. Although it may not be as good a basis for the primary determination (since *inter alia* community exposures are

necessarily harder to determine accurately), the studies at the Western Minerals/W.R. Grace (WM/WRG) facility in Minneapolis, Minnesota examined by Adgate et al. (2011) and Alexander et al. (2012) (citations given above) may be worth evaluating as the basis for a comparison value, which if compatible with the findings at Marysville would increase confidence in the overall number.

2. *Radiographic evidence of localized pleural thickening in humans was concluded by EPA to be an adverse effect and was selected as the critical effect for the derivation of the RfC. Pleural thickening is associated with restrictive lung function, breathlessness during exercise and, for some individuals, chronic chest pain. Please comment on whether the selection of this critical effect and its characterization is scientifically supported and clearly described. If a different health endpoint is recommended as the critical effect for deriving the RfC, please identify this effect and provide scientific support for this choice.*

Response:

The report carefully documents the various grades of radiographic changes observed following exposure to Libby asbestos and similar materials, and the selection of localized pleural thickening as the critical effect was explained. This is actually a less severe endpoint than other types or extents of change observed, which is consistent with the recommendation of the risk assessment guidelines to select the least severe endpoint which is considered adverse as the basis for the RfC.

The report also describes the association of this radiological observation with measurable defects in lung function, clearly identifying this endpoint as adverse in character. I think it is worth pointing out that although this endpoint was the least severe of the radiological endpoints considered, when looking at both the pathology demonstrated in the X-ray photographs and the functional deficits observed clinically this endpoint is really quite seriously adverse. This is not unusual for clinical evaluations used as the basis for epidemiological evaluation of health effects: the changes which are consistently observable in a clinical setting are often quite severe compared, for instance, to the sort of changes which would routinely be considered adverse endpoints in animal toxicology studies. Thus, U.S. EPA's (and Cal/EPA's) guidelines identify "Degenerative or necrotic tissue changes with no apparent decrement in organ function" as level 6, which is considered a severe effect. The clinical and radiographic observations in the Marysville workers could reasonably be described as "Pathological changes with definite organ dysfunction which are unlikely to be fully reversible", which would be level 8, a frank effect level, if it were in an animal study. It is important that this degree of severity be considered in selecting benchmark response rates and/or uncertainty factors when deriving the RfC, in order to maintain comparability with other RfCs in the database.

- 3. The database of laboratory animal and mechanistic studies of Libby Amphibole asbestos is summarized in the draft assessment (see Section 4.2 and 4.3, details in Appendix D) to inform the mechanisms of the biological response to Libby Amphibole asbestos and support the epidemiology studies used for derivation of the RfC. Please comment on whether the laboratory animal and mechanistic information presented is used appropriately in the draft assessment.*

Response:

The reported findings are appropriately presented in support of the analysis of the human effects observed: these studies are informative in identifying similar processes and progression of symptoms in animals as are seen in humans, and also help in establishing the extent to which similar pathological effects are seen with various different but related amphibole minerals. Although as noted earlier the mechanistic studies fall short of delineating a complete mechanism of action they are useful in identifying some common themes and potential key processes in asbestos toxicity, which will undoubtedly be valuable in directing future research on this topic.

B. Carcinogenicity:

- 1. Under EPA's Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005; www.epa.gov/iris/backgrd.html), the draft IRIS assessment characterizes Libby Amphibole asbestos as "carcinogenic to humans" by the inhalation route of exposure. Please comment on whether the cancer weight of evidence characterization is scientifically supported and clearly described.*

Response:

Based on the evidence presented on Libby asbestos, and the other amphiboles whose relationship to this material has been explained, this conclusion is clearly justified. Supporting evidence from animal studies and mechanistic research on Libby asbestos and other amphiboles reinforces this conclusion.

- 2. Due to the limitations of the data available, the draft assessment concludes that there is insufficient information to identify the mode of carcinogenic action of Libby Amphibole asbestos. Please comment on whether this determination is appropriate and clearly described. Note that in the absence of information to establish a mode of action, a linear low dose extrapolation is recommended by the Guidelines for Carcinogen Risk Assessment (U.S., EPA, 2005; Section 3.3). If it is judged that a mode of action can be established for Libby Amphibole asbestos, please identify the mode of action and its scientific support (i.e., studies that support the key events, and specific data available to inform the shape of the exposure-response curve at low doses).*

Response:

Neither the fairly limited amount of research on Libby asbestos itself which is described in the assessment report, nor the more extensive body of published work on other asbestiform minerals which is also summarized, lead to clear conclusions as to a single mechanism of carcinogenic action. Several key properties, such as fiber size and geometry, and the durability of the fibers *in vivo* have been identified, and probably

important processes such as macrophage cytotoxicity, fiber transport and stimulation of reactive oxygen generation have been extensively investigated. However no complete mechanistic analysis is available: It is likely that several mechanisms, some of which might be considered “mutagenic” and others not, contribute to the overall effects observed following exposure to amphiboles. In view of these complexities and uncertainties, the default linear extrapolation at low doses is therefore appropriate as a policy choice.

To the extent that the data permit it appears that the epidemiological evidence for Libby Asbestos is consistent with this assumption, so there are no empirical grounds for questioning it. An important further source of information addressing this question is the extensive epidemiological data on effects of other asbestos minerals, especially amphiboles. U.S. EPA in their 1986 review of asbestos health effects³ examined the linearity of the dose-response relationships in a variety of studies of asbestos exposure, and concluded that although the slope factor varied considerably between studies depending on the nature of the material, the characteristics of the population, and details of the exposure assessment methodology, many of the studies examined showed clear linear dose-response relationships for lung cancer and cumulative exposure. They noted in particular several studies: Dement et al., 1982; Henderson and Enterline, 1979; McDonald et al., 1980, a983a and 1983b; Finkelstein, 1983; Seidman 1984 (see US EPA, 1986 for these citations) where a linear relationship between lung cancer and cumulative exposure to asbestos dust was demonstrable, and a number of other studies which were consistent with this conclusion although lacking the power or precision to demonstrate linearity independently.

The situation for mesothelioma is more complex, because the incidence of this tumor shows a marked dependence on time following exposure. Peto et al. (1982)⁴ showed that tumor incidence varied with approximately time to the power of 3.5, and that this dependence was (at least for adults) independent of age at first exposure. This is consistent with the multistage model proposed by Armitage and Doll, but considerably complicates the analysis of exposed cohorts where exposure was for substantially less than lifetime and started at various times prior to evaluation of health status or appearance of tumors. It should be noted however that this same multistage model explicitly predicts that for whole-life, constant and continuous exposures, a linear dose-response relationship is expected at low doses. Thus for the case which is assumed in default uses of the unit risk factor the assumption of a linear relationship between cumulative exposure and lifetime risk is supported. This does, however, point out that a more complex, time-dependent analysis is necessary to provide a proper risk estimate for shorter-term exposures, especially at younger ages where the duration of post-exposure observation is greater. Although this is not so clearly revealed in the lung cancer data this may also be true to some extent for that endpoint.

³³ U.S EPA (1986). Airborne Asbestos Health Assessment Update. Office of Health and Environmental Assessment, Washington, DC, June 1986. EPA/600/8-003F

⁴. Peto J, Seidman H, Selikoff IJ (1982). Mesothelioma Mortality in Asbestos Workers: Implications for Models of Carcinogenesis and Risk Assessment. Br. J. Cancer 45: 124-135.

It is therefore important to note that although the decision to use a linear extrapolation model for dose response in the case of Libby asbestos has only a limited basis in those specific data, the analogy with other asbestos minerals provides powerful support for this assumption.

3. *An occupational cohort of workers from Libby, MT exposed to Libby Amphibole asbestos (i.e., the Libby worker cohort) was selected as the basis for the derivation of the inhalation unit risk (IUR). Please comment on whether the selection of this study population is scientifically supported and clearly described. If a different study population is recommended as the basis for the IUR, please identify this study and provide scientific support for this choice.*

Response:

This is the only well-documented cohort with sufficient numbers and duration, substantial disease incidence and clearly documented severity of exposure to this specific type of asbestos. Non-occupational groups such as Libby community members in general had lower exposures and disease incidence, and their exposures appear to have been much more variable and uncertain than the occupational cohort. The Libby occupational cohort is necessarily the best choice for the study population in determining the IUR, although comparison with other populations such as those examined in the EPA's earlier general asbestos assessment is helpful. These considerations are adequately explored and explained in the report.

4. *Mortality from lung tumors and mesothelioma in the Libby worker cohort was selected to serve as the basis for the derivation of the IUR. Please comment on whether this selection is scientifically supported and clearly described. If a different health endpoint is recommended for deriving the IUR, please identify this endpoint and provide scientific support for this choice.*

Response:

Given that these tumors are the principal cancer observations in the cohort, and the key concerns based on analogy with other asbestos-exposed cohorts, this choice is clearly the appropriate choice as the basis of the IUR for practical and scientific reasons. Given that both types of tumor contribute substantially to the mortality in the cohort, analysis of their joint effect is an appropriate basis for the IUR: it would only have been appropriate to confine the IUR to one site and tumor type if there was one tumor site which was of overriding importance relative to all others. Selection of mortality rather than incidence of the basis is less desirable in principle, but in practice the mortality data are what is available, and given that these tumors are both rapidly lethal after diagnosis the use of mortality data will not have a large effect. The risk assessment report does a thorough job of reviewing, explaining and justifying these choices.

5. *The database of laboratory animal and mechanistic studies of Libby Amphibole asbestos is summarized in this draft assessment (see Section 4.2 and 4.3, details in Appendix D) to inform the mechanisms of the biological response to Libby Amphibole asbestos and support the epidemiology studies used for derivation of the IUR. Please comment on the use of laboratory animal and mechanistic information in the draft assessment.*

Response:

This information is adequately described and well analyzed in the report. Its use in the risk assessment is confined to a supporting role, which is useful but not pivotal. The human evidence from Libby and related sites, as well as the extensive literature on human carcinogenesis by other forms of asbestos, are the crucial data which drive the risk assessment of Libby asbestos, and none of the conclusions would be substantially different if the animal evidence were not available. The report properly examines the mechanistic data from animal studies and experiments *in vitro*, but since these studies fall short of identifying a mechanism of action the final impact on the assessment is limited. Thus the risk assessment takes proper notice of these supporting data, but their role is primarily to provide reassurance that the human data are plausible and consistent.

III. Exposure-Response Assessment

A. Inhalation Reference Concentration (RfC):

1. *Exposures to Libby Amphibole asbestos for workers in the Marysville, OH facility were reconstructed based on industrial hygiene data collected in the facility from 1972 to 1994. Exposures from 1957 to 1971 were estimated based on extrapolation from the available industrial hygiene data. The information used for the exposure reconstruction was based on employee interviews, court and company records, and the expert judgment of the researchers. Is the methodology used for the exposure reconstruction reported in Appendix F and the subsequent development of exposure estimates used in the analyses scientifically supported and clearly described?*

Response:

The approaches used are a reasonable response to the data available, and are clearly described in the report. Obviously the reconstruction of exposures prior to 1972 is subject to a lot more uncertainties than for the later period, since it is only after 1972 that actual measured levels are available, and the extrapolation to earlier periods is complicated by substantial changes in workplace operations and dust control technology. It is therefore not surprising that the subsequent analysis found poor correspondence between extrapolated exposures and response levels, but it is not clear to me that anything specific could be done about this deficiency. There may be a subset of individual cases from the earlier period where better exposure estimates could be made rather than concentrating on the whole of this part of the dataset, which might make a basis for a comparison to see if this exercise added anything to the analysis. The newer data on the other hand appear to be sufficiently well founded on actual measurements and evidently do provide a suitable basis for exposure-response assessment.

2. *Exposure-response modeling was conducted using the incidence of localized pleural thickening in workers and cumulative exposure to estimate the point of departure (POD) for derivation of the RfC. EPA's estimate of the POD is based upon a Michaelis-Menten model applied to the subcohort of workers examined in 2002-2005 and first exposed to Libby Amphibole asbestos in 1972 (when measurements of fiber levels in the workplace began) or later with cumulative exposure as the explanatory variable. Is the selection of the model scientifically justified and clearly described? Has the modeling and the choice of a benchmark response (BMR) for the POD of 10% extra risk of localized pleural thickening been clearly described and appropriately conducted according to EPA's Draft Benchmark Dose Technical Guidance (U.S. EPA, 2000b)?*

Response:

The application of a best fitting mathematical model to the exposure response data has been carefully described and analyzed. Selection of the subcohort first exposed in or after 1972 is explained and justified based on the observation that the earlier portion of the cohort essentially provides no information on the exposure-response relationship due to the considerable uncertainty in the exposure levels during this earlier period. Selection of the model based on quality of fit to the data uses objective statistical criteria, is in line with recommended practice and is clearly described. The approach was to evaluate the fit of a considerable number of models covering different mathematical forms, plausible alternative exposure metrics, and alternate assumptions about the time dependence of the mortality following first exposure. Having thus covered the range of possibilities considered scientifically justifiable (or recommended in previous analyses of asbestos health effects), the best fitting exposure metric and dose/temporal exposure-response model was selected. This was applied to the later subcohort since the full dataset was found to give poor fit and reduced information because of the great uncertainty about actual exposures during the earlier period. This analysis objectively considered all the reasonable possibilities and took into account the significant uncertainties implicit in the data. It might be helpful to the reader to provide at least some graphical examples of the quality of model fit for the chosen model and others considered relevant for comparison, either in the main text or Appendix E. Visual examination of the quality of fit in the region of the proposed benchmark is one of the evaluation techniques for model selection recommended by EPA's benchmark dose guidelines.

The selection of 10% as a benchmark response rate is represented as being in line with the recommendations of the Benchmark Dose Technical Guidance, but I am not convinced that this choice was made sufficiently carefully. In the first place, the recommendation to use a 10% response rate is generally considered to apply specifically to the analysis of quantal datasets from animal studies (which is the context in which it was developed). Even in this case, various analysts (including those responsible for several EPA assessments) have found that a 5% BMR is more appropriate in defining a POD which is to be treated similar to the classic NOAEL in terms of uncertainty factors etc. Analysis of epidemiological data generally requires much more specific consideration of the particular dataset, and should involve consideration *inter alia* of the actual size of the minimum response rate which could be statistically detected with reasonable confidence, the range of exposures with responses covered by the data, and

the nature of the critical endpoint. I have commented earlier that the localized pleural thickening selected as the endpoint in this study is actually a fairly severe endpoint, especially in comparison to those used in animal studies. This needs to be reflected either in the choice of BMR (to the extent that the statistical power and range of the available data permit) and/or the uncertainty factors applied in developing an RfC. Given the complexity of the issues with this sort of dataset, the treatment of BMR selection with a statement that the analysts are “following the guidelines”, and a brief statement that the 10% response rate was “considered minimally biologically significant” (section 5.2.3.3) with little further discussion, is inadequate.

- 3. EPA’s assessment also provides the results of alternative modeling approaches to derive a POD for localized pleural thickening. This modeling used the full Marysville worker data set with exposures from 1957 and later and a Cumulative Normal Michaelis-Menten model that incorporates both cumulative exposure and time from first exposure as explanatory variables. Please comment on whether EPA’s rationale for presenting these alternative approaches is scientifically justified and clearly described. Please identify and provide the rationale if a different approach for identifying the most appropriate population within the cohort of Marysville workers is recommended as the basis for estimating a POD.*

Response:

The presentation of these alternatives was explained and justified on the basis that although these were not the approaches which provided the optimal fit to the data they are representative of the range of sustainable alternative model choices, and evaluating these is important in establishing the range of uncertainty in the final conclusion resulting from model uncertainty. This is an important undertaking: too often risk assessments go to great lengths to establish and evaluate a “best fit” model but are less careful to explore the implications of alternative “nearly as good”, or even “less likely but still plausible” model choices. This applies both to alternative forms of dose/response model and dose metrics, but also to mechanistic assumptions which may drive policy-based choices in the dose response modeling process. The model uncertainty can only be quantified by actually running and presenting the alternative models. It is reassuring that although the chosen model represents the optimal choice, the selection of alternative model forms, exposure metrics and cohort restrictions has a relatively modest impact on the final value of the RfC. In particular, not only does the choice of the more recent sub-cohort rather than the full cohort appear justified since the improvement in exposure measurement outweighs the loss of power due to smaller numbers and shorter durations, but also one would not have reached a markedly different conclusion if the alternative approach were to have been chosen.

4. *EPA has evaluated potential confounders and covariates where data are available. Specifically, EPA has explored the influence of age, body mass index, smoking status, time since first exposure, gender, and alternative exposure metrics on model fit and evaluated their association with the modeled health outcomes (see Section 5.3). Are these analyses clearly described and appropriately conducted? Are the results of these analyses appropriately considered in the RfC derivation? Additionally, there is a possibility of exposure-dependent censoring in participant selection for the update of the Marysville cohort (Rohs et al., 2008) but no evidence of selection bias. Does the panel have any specific recommendations for evaluating and, if appropriate, quantitatively addressing exposure-dependent censoring in these analyses?*

Response:

In general the analysis appears to have taken a reasonable and effective approach to the evaluation of confounders and covariates, and has, within the limits of the data, apparently minimized these effects. Remaining uncertainties are identified and evaluated. My only comment on this issue is that although effects of smoking are considered their evaluation is necessarily limited by the fact that only a basic smoking status question was used (current/former/never). It is well established that such simplistic questions are insufficient to quantify tobacco smoke exposure: such quantification requires not only intensity data (e.g. pack-years) for active smoking but also consideration of passive smoke exposure both at home and at work. Clearly the studies available lack the power to assess in detail the impact of cigarette smoking as either a confounder or an effect modifier, which is an inevitable uncertainty, although not a fatal flaw, in the analysis.

5. *The modeled POD estimate is based on cumulative exposure estimates for the worker cohort examined. For the derivation of the RfC, this cumulative exposure is prorated over the period of environmental exposure (lifetime or shorter duration chronic exposure when appropriate). The RfC is provided in units of continuous air concentration. Is the basis of this conversion clearly explained and scientifically justified?*

Response:

This correction was sufficiently explained and justified in the report. Such corrections are standard practice in RfC derivations.

6. *Please comment on the rationale for the selection of the uncertainty factors (UFs) applied to the POD for the derivation of the RfC. Are the UFs appropriate based on A Review of the Reference Dose and Reference Concentration Processes (U.S. EPA, 2002; Section 4.4.5) and clearly described? If changes to the selected UFs are proposed, please identify and provide scientific support. Specifically, please comment on the rationale for the selection of the database uncertainty factor (UFD) of 10 applied in the derivation of the RfC. The database uncertainty factor accounts for the lack of data on effects other than in the respiratory system, including other effects observed in community and laboratory animal studies (cardiovascular disease and autoimmune effects) that have not been well-studied (See Section 5.2.3 of the Toxicological Review); and lack of health data assessed at later time points. Is the rationale for the UFD appropriate and clearly described? Please provide the rationale if a change in the UFD is proposed.*

Response:

Uncertainty factors were selected in accordance with the usual procedures laid out in EPA risk assessment guidelines: a value of 10 was selected for UF_H (human interindividual diversity) and UF_D (database uncertainty) with a value of 1 for all others. Use of a UF_H of at least 10 is standard in considering health protective levels based on effects in the workforce, who are generally healthier and less diverse than the general population. In fact arguments have been made that this is an insufficiently large factor to cover all sensitive sub-populations, especially children. Some treatment of this question is offered in the later summary of conclusions (Section 6): in view of the very limited evidence on non-cancer effects in children it seems unlikely that a departure from the default guidelines would be justified. Selection of a UF_D of 10 is explained and justified based on the limited number of studies of exposure to Libby asbestos (Libby workers, ATSDR community study and Marysville workers) and the lack of evaluation of potentially more sensitive alternative endpoints. This seems reasonable and consistent with the guidelines. However, I do have a concern that the BMR of 10% which was chosen for what is undoubtedly a fairly severe endpoint is not reflected by the choice of a UF_L of 1. It would in my view be appropriate to consider either a lower BMR, or the application of a larger UF_L (3 or 10) for this endpoint. An argument could be made that some allowance has been made for this concern in the choice of the UF_D , but it is debatable whether this is sufficient, given the other matters to which that UF is also assigned. At the very least this question deserves more consideration and analysis that it receives in the assessment report.

7. *Please comment on whether the document adequately describes the uncertainties and limitations in the methodology used to derive the RfC and whether this information is presented in a transparent manner.*

Response:

The document presents a thorough and detailed analysis of the various uncertainties in the analysis, which is laid out in a logical and intelligible manner. Apart from the issues of children's sensitivity (to cancer and non-cancer effects) and severity of the endpoint

used for the RfC, which I note elsewhere, the relevant areas of uncertainty are adequately addressed. The effort to quantify uncertainties based on choice of alternative models is notable, and praiseworthy, since this type of uncertainty is frequently present but insufficiently addressed in risk assessments. A more integrated presentation of the overall uncertainty and identification of the key contributors to this would be helpful.

B. Inhalation Unit Risk (IUR):

- 1. Exposure-response modeling was conducted separately for lung cancer and mesothelioma mortality. The POD estimates for these endpoints are based upon analysis of the subcohort of workers first exposed after 1959 when the exposure data were judged to be better characterized. The exposure-response modeling included consideration of a variety of exposure metrics that varied with time and incorporated different lag and decay parameters. Based on the results of the exposure-response modeling, a lifetable analysis was used to determine the PODs for each type of cancer for the various exposure metrics. Have the exposure-response modeling and determination of the PODs from lifetable analysis been appropriately conducted and clearly described? If a different approach to exposure-response analysis is recommended as the basis for the estimating the IUR, please identify the recommended methods and provide a rationale for this choice.*

Response:

The analysis presented is a fairly complex one, but it is clearly and logically presented and the various model assumptions tested are well explained. The basic method is to try the various models of response to exposure over time which were considered potentially appropriate based on the epidemiological, toxicokinetic and mechanistic data available, or were recommended in previous risk assessments of asbestos. The selection of the models considered in the final determination of the POD is based on the fit to the data – an objective criterion. As in the case of the non-cancer analysis, exposure estimates early in the potential study period are too unreliable for these times to be considered in the analysis. The methods used are appropriate and generally in line with those used by other published analysts of this type of data. Application of a “latency” period is a fairly common strategy to deal with late-appearing tumors: this is of course a simplification since the delay between the initiating exposure and the appearance of a tumor is in fact going to be variable and best characterized by a distribution rather than a fixed time. However, to fully determine this distribution is probably beyond the capacity of the data to specify, and its incorporation into the analysis would add so much complexity that the overall uncertainty would be increased rather than decreased. Use of a decay time for fiber persistence as part of the model is plausible on biological grounds, but it should be recognized that this choice is (as per benchmark modeling theory) basically a mathematical choice to achieve a best-fitting model: it should not be supposed that the data actually have sufficient precision for it to be argued that this decay half-life is an accurate representation of biological reality.

It is important to note that the policy default of linear extrapolation over time was used to adjust from the period of observation in the cohort to the whole life (70 year) basis of the

IUR. This is correct, since the model used to fit the data is only valid within the range of the observations on which it is based. The subcohort data used to determine the IUR cover a relatively abbreviated fraction of a lifetime, and do not contain sufficient information about time dependence for the fitted model to be used in this way. Although the approach used is strictly in line with guidelines, and importantly provides an “unbiased” IUR which can be independently compared with that derived for other forms of amphibole, it would be interesting for the uncertainty analysis to include other possible time dependence assumptions such as the $t^{3.5}$ relationship identified by Peto et al (1982) for mesothelioma in insulation workers (primarily exposed to amosite) in this extrapolation.

- 2. Smoking is a strong independent risk factor for lung cancer and may be an important confounder of the lung cancer mortality analysis. Data on individual smoking habits and history were largely missing and could not be used to control for potential confounding in regression analyses. However, EPA used three approaches to evaluate the confounding issue, including restriction of the cohort and two analytic evaluations of the potential for confounding by smoking (see Section 5.4.3.6.5). Please comment on whether the methods and analyses are clearly presented and scientifically justified. If additional analyses are recommended, please identify the methods and scientific rationale.*

Response:

EPA has taken what steps it can to isolate and identify any confounding effect of smoking on the lung cancer mortality component of the IUR. The conclusion from two independent approaches (restriction of the cohort to the newer data for which the proportionality test in the Cox model is met, and the Richardson method) to evaluate confounding by smoking as a contributor to lung cancer mortality is that this potential for confounding has not been realized, especially in the restricted recent sub-cohort for whom smoking habits are likely to be better determined and more similar. This does not of course address the potential for smoking as an effect modifier of lung cancer, which is very likely to be the case given the results of other studies on asbestos-induced lung cancer and smoking. However, to the extent that the smoking habits of the Libby workers are somewhat typical of those of the general population (likely true at least over the study period) this does not imply an error in the final value of the IUR for that general population.

It is well established that simple categorical reporting of active smoking status provides an extremely crude and uncertain estimate of tobacco smoke exposure, being subject to potential recall bias, paying no attention to intensity of active smoking and neglecting the important impacts of passive smoking entirely. Under these circumstances it is appropriate that the EPA analysts took steps to show that notionally possible confounding is not an important factor in the overall mortality data, but realistically the data set does not have the power to identify any real effects of smoking on asbestos-related lung cancer.

3. *In order to derive an IUR which represents the combined risk of mortality from lung cancer or mesothelioma, a cancer-specific unit risk for each tumor type was calculated according to the Guidelines for Carcinogen Risk Assessment (U.S., EPA, 2005; Sections 3.2 and 3.3) by linear extrapolation from the corresponding POD (i.e., the lower 95% confidence limit on the exposure associated with 1% extra risk of lung cancer or 1% absolute risk of mesothelioma mortality). The IUR was then determined as a combined upper bound risk estimate for mortality considering both cancers. Has this approach been appropriately conducted and clearly described?*

Response:

This procedure is clearly justified by the data, which show that both mesothelioma and lung cancer contribute substantially to the overall cancer-related mortality in the study cohort. The description of the procedure used is clear and sufficient to determine that the analysis was correctly conducted. Since the two endpoints are clearly independent (different site, no progression or significant interference) the calculation of the two risk estimates separately and then addition of the two estimate distributions to obtain MLE and 95% upper confidence limit estimates for the joint distribution is the correct way to do it. The relatively straightforward approach to calculating the confidence limits on the combined estimate works in this case because both the Poisson and Cox proportional models result in a normal density function for the likelihood estimate. It is worth noting that this condition is not necessarily fulfilled when some other models (including multistage polynomials) are used to fit tumor incidence data.

4. *Please comment on the adjustment for mesothelioma mortality underascertainment. Is this adjustment scientifically supported and clearly described? If another adjustment approach is recommended as the basis for the IUR, please identify that approach and provide the scientific rationale.*

Response:

This adjustment appears to me to be well described and scientifically justifiable.

5. *Please comment on whether the document adequately describes the uncertainties and limitations in the methodology used to derive the IUR and whether this information is presented in a transparent manner.*

Response:

Similar to what was done for the RfC, the document authors have gone to considerable lengths to lay out the various elements of uncertainty in the estimate clearly and thoroughly, in a way that can be understood by the technical reader. The only area in which I have some concern is whether the question of childhood sensitivity to cancer effects has been sufficiently addressed, on the basis of my earlier comments about the use (or not) of age sensitivity factors. Although individual sources of uncertainty are well considered and described, it would be helpful to the reader if an overall summary of the likely uncertainty, and the contribution of certain key assumptions such as model choice, were provided. In particular, looking at the models evaluated in the report and most previously published analysts, it does not appear that the choice of model type (whether by optimal fit to the data, or based on mechanistic hypothesis) makes a huge difference to

the final value of the IUR. This is in itself an important conclusion contributing to the confidence in the chosen value.

This sort of thorough but straightforward presentation of uncertainties is very helpful, and I hope it encourages users of the document to read and consider the points made rather than simply taking the IUR as a “black box” number.

Dr. Lianne Sheppard

Overall I found this document to be thorough and thoughtful. In sections that I reviewed in much more careful detail (particularly pertaining to the RfC calculation), I had a number of questions and consequently an interest in seeing additional details. I am concerned that the proposed RfC is too high (note correction from my preliminary comments). I elaborate on these points below.

Brief comments in response to selected charge questions:

Charge section II

A.1. An occupational cohort of workers in a Marysville, OH facility exposed to Libby Amphibole asbestos (Lockey et al., 1984; Rohs et al., 2008) was selected as the basis for the derivation of the reference concentration (RfC). Please comment on whether the selection of this study population is scientifically supported (**Yes**) and clearly described (**Yes**). If a different study population is recommended as the basis for the RfC, please identify this study and provide scientific support for this choice.

The choice of this study population was scientifically well supported based on a number of important factors, including few exposures outside the occupational environment, reasonably good ability to reconstruct worker exposure histories (along with substantial effort in this regard), relatively low cumulative exposures in a range that provides good data for the RfC estimate, and some additional covariate data available on the study population. The choice of population was reasonably described.

A.2. Radiographic evidence of localized pleural thickening in humans was concluded by EPA to be an adverse effect and was selected as the critical effect for the derivation of the RfC. Pleural thickening is associated with restrictive lung function, breathlessness during exercise and, for some individuals, chronic chest pain. Please comment on whether the selection of this critical effect and its characterization is scientifically supported (**Yes**) and clearly described (**Yes**). If a different health endpoint is recommended as the critical effect for deriving the RfC, please identify this effect and provide scientific support for this choice.

This was reasonably described and appropriately justified.

I wonder if an alternative outcome could be defined as any anomaly identified on Xray (LPT, DPT, small opacity). All were clearly described as resulting from asbestos exposure. While any anomaly is a mixed outcome physiologically, humans are not restricted to how they respond and thus for purposes of risk assessment it seems more appropriate than limiting attention to only the most common outcome from the Xray findings.

Charge section III

A.1. Exposures to Libby Amphibole asbestos for workers in the Marysville, OH facility were reconstructed based on industrial hygiene data collected in the facility from 1972 to

1994. Exposures from 1957 to 1971 were estimated based on extrapolation from the available industrial hygiene data. The information used for the exposure reconstruction was based on employee interviews, court and company records, and the expert judgment of the researchers. Is the methodology used for the exposure reconstruction reported in Appendix F and the subsequent development of exposure estimates used in the analyses scientifically supported and clearly described?

My sense is that the researchers did the best they could with limited useful data. My only additional suggestion is that if any such data are available anywhere, that industrial hygiene data from other exfoliation/expansion plants that process vermiculite might be used to come up with alternative plausible estimates for asbestos concentrations in the Marysville plant during the pre-1972 period.

In addition to the specific thrust of this question, the exposure reconstruction evaluation should address exposure metric choice. I suggest

1. Showing relationships between the exposure metrics, such as by scatterplots of unlagged CEEH vs. other measures (separately by cohort). (Thanks to EPA for providing some of this with short turn-around time.)
2. Consideration in sensitivity analyses of additional exposure metrics such as: no exposure since 1980 in any cohort members (based on end date of processing of Libby vermiculite), alternative weighting schemes (particularly ones weighting earlier life exposures more heavily given the importance of time since first exposure, e.g. RTW – residence time weighting). (See Group 2 comments for additional details.)
3. Addition of a few words about lagging in the report so a reader understands what was done and its utility given the outcome is a measure of prevalence.

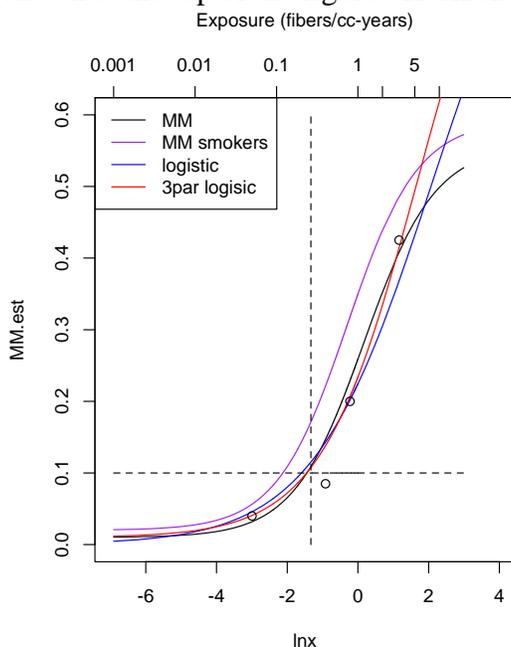
A.2. Exposure-response modeling was conducted using the incidence of localized pleural thickening in workers and cumulative exposure to estimate the point of departure (POD) for derivation of the RfC. EPA's estimate of the POD is based upon a Michaelis-Menten model applied to the subcohort of workers examined in 2002-2005 and first exposed to Libby Amphibole asbestos in 1972 (when measurements of fiber levels in the workplace began) or later with cumulative exposure as the explanatory variable. Is the selection of the model scientifically justified (**Not really, based on some basic plausibility arguments**) and clearly described (**Yes**)? Has the modeling and the choice of a benchmark response (BMR) for the POD of 10% extra risk of localized pleural thickening been clearly described (**No – too limited detail on BMR**) and appropriately conducted according to EPA's *Draft Benchmark Dose Technical Guidance* (U.S. EPA, 2000b) (**Not completely. See Group 2 comments and detailed comments below the responses to charge questions**)?

Overall I had a number of questions about the dose-response modeling and choices that were made in the calculation of the RfC.

1. Repeat measures data were not used but could potentially have been informative.
2. Given the analysis dataset, individually many choices appear to be reasonable in the sense that when altered alone it appears that they would not have affected the RfC estimate (at least within an order of magnitude) and thus could potentially be ignored. However, these have not been evaluated in concert and taken together they could have a greater impact.

3. Of particular concern to me was the choice of the dose-response model, specifically the sensitivity of the results to the use of a model with an estimated plateau (in both the subcohort and the full cohort). However, thanks to the additional information provided by EPA, I was able to compare the fitted curves and assess that for the BMR of 10% (shown slightly too low on the graph), this does not appear to be an issue here. (see graph inserted below)
4. I wish to see more detailed data description of the data, both pure description of the dataset and summaries that relate to the modeling results and that can help inform one's interpretation of the results. More thorough description of the data and results will help readers trust the analysis more. (See additional comments from Group 2)
5. The work should be improved by the inclusion of more sensitivity analyses.

(Figure comments: Predicted curves based on parameter estimates provided by EPA. Raw data for quartiles estimated from visual inspection of Figure 5-2. X-axis scale shown as log exposure to enhance visual understanding; Original units shown at the top of the figure. Horizontal line not adjusted for background.)



A.3. EPA's assessment also provides the results of alternative modeling approaches to derive a POD for localized pleural thickening. This modeling used the full Marysville worker data set with exposures from 1957 and later and a Cumulative Normal Michaelis-Menten model that incorporates both cumulative exposure and time from first exposure as explanatory variables. Please comment on whether EPA's rationale for presenting these alternative approaches is scientifically justified (**No: Rationale for presenting approaches is OK but the rationale for selecting the approaches used is not well justified**) and clearly described (**partly**). Please identify and provide the rationale if a different approach for identifying the most appropriate population within the cohort of Marysville workers is recommended as the basis for estimating a POD.

The full cohort is a reasonable alternative. It is preferable because of the larger number of events but it suffers from the speculative nature of much of the

historical exposure estimates. It is also a more complex dataset with much more variability in exposure and time since first exposure. It is useful to include this analysis as a way to substantiate the RfC estimate obtained from a small dataset.

I have the greatest difficulty with the analysis and results of the full Marysville cohort. Some of my reasons follow. See also Group 2's summary comments.

- It isn't clear what time since first exposure (TSFE) represents scientifically in general and also specifically in the context of the structure of this dataset. For instance, from a general scientific perspective, is it some imperfect measure of latency until disease is detectable, an additional measure of exposure, or both? In this dataset there is clearly some association between cumulative exposure and TSFE as suggested by the (limited) data summaries presented (e.g. Figure E-2) and the historical exposure patterns in the plant.
- From a biological perspective I don't understand why TSFE should influence the plateau in the model. What is the meaning of the plateau? I view it as an indication of the maximum proportion of the population that would experience LPT given sufficient exposure and time to develop the disease. What biological basis is there for this to vary by TSFE?
- I would not call TSFE as an explanatory variable in the model in the traditional sense of explanatory variables. The alternative model incorporates TSFE in a model for the plateau (using a cumulative normal distribution). As was already evident in the subcohort analysis (see e.g. Figure 5-2), there are limited data to inform the value of the plateau, and I am not convinced the plateau parameter can be estimated from the available data, even in the full cohort. In addition, I think it makes more sense to include TSFE as a predictor that would affect the rate of increase in the probability of LPT. This suggests TSFE should be included in the "linear predictor" part of the model rather than as part of parameterization of the plateau. (Specifically, this would mean replacing $\beta \cdot f(\text{TSFE})$ for $\beta \cdot \text{Smoke}$ in model (2) on page E-7. For $f()$, first consider TSFE as a linear term, then consider more complex functions.) Related to this change in the model, I would consider fixing the plateau based on scientific evidence (e.g. Lillis et al 1991 suggesting the highest prevalence of LPT in a high exposed population is 85%).
- Another set of sensitivity analyses would consider alternative exposure metrics
- The full cohort model results are quite sensitive to the value of the TSFE. Thus I conclude that:
 - Further revised analysis of the full cohort is needed before proposing the RfC.
 - The alternative modeling is suggestive that the RfC should be set lower than the proposed value based on the subcohort. (See Figure E-4)
 - Any additional information that can be used to support the modeling approach should be incorporated from other studies.

A. 4. EPA has evaluated potential confounders and covariates where data are available. Specifically, EPA has explored the influence of age, body mass index, smoking status, time since first exposure, gender, and alternative exposure metrics on model fit and evaluated their association with the modeled health outcomes (see Section 5.3). Are these analyses clearly described (**Yes**) and appropriately conducted (**it depends**)? Are the results of these analyses appropriately considered in the RfC derivation (**Not completely**)? Additionally, there is a possibility of exposure-dependent censoring in

participant selection for the update of the Marysville cohort (Rohs et al., 2008) but no evidence of selection bias. Does the panel have any specific recommendations for evaluating and, if appropriate, quantitatively addressing exposure-dependent censoring in these analyses? **(Based on the information presented I don't think exposure-dependent censoring is present.)**

Confounder and covariate analyses:

1. Given the purpose of the analysis is to estimate a BMC and eventually RfC, inclusion of several of the covariates predictive of the outcome should be considered at least in part based on whether they impact the BMC estimate rather than assessing p-values for how well they improve the predictive quality of the model. In particular, smokers are a sensitive subgroup and thus should be considered in the RfC estimate. BMI is a more challenging covariate since it impacts outcome assessment more than the actual outcome. Fortunately in this dataset adjustment for BMI does not appear to be important.
2. In general, appropriate assessment of confounding has to do with evaluating its impact on the estimate of a regression parameter of interest both from a scientific perspective and in the specific dataset. The focus of this analysis is not on estimation a regression parameter. Consider revising the presentation to clarify this issue.
3. See previous comments on TSFE handling in the model.

Exposure-dependent censoring: This discussion is based on results from Rohs et al that inappropriately separates deceased non-participants from the remaining non-participants. I don't believe there is evidence of exposure-dependent censoring once all non-participants are combined. (see further comments below)

A.5. The modeled POD estimate is based on cumulative exposure estimates for the worker cohort examined. For the derivation of the RfC, this cumulative exposure is prorated over the period of environmental exposure (lifetime or shorter duration chronic exposure when appropriate). The RfC is provided in units of continuous air concentration. Is the basis of this conversion clearly explained (**Yes**) and scientifically justified (**No**)?

The approach is reasonably explained. I think the most recent period of exposure should not be discounted in the calculation (by using e.g. 70-10 years for a lifetime, justified in the document by use of 10-year lagged exposure in the modeling) given that 1) the exposure metric is arbitrarily related to the prevalence data so lagging does not have real meaning in the context of time to event, 2) the model is based on much shorter than lifetime exposures, and 3) many of the exposure histories of the workers are highest in the distant past and far from constant over time.

A.6. Please comment on the rationale for the selection of the uncertainty factors (UFs) applied to the POD for the derivation of the RfC. Are the UFs appropriate based on *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002; Section 4.4.5) and clearly described? (**Mostly**) If changes to the selected UFs are proposed, please identify and provide scientific support. Specifically, please comment on the rationale for the selection of the database uncertainty factor (UF_D) of 10 applied in the derivation of the RfC. The database uncertainty factor accounts for the lack of data on effects other than in the respiratory system, including other effects observed in

community and laboratory animal studies (cardiovascular disease and autoimmune effects) that have not been well-studied (See Section 5.2.3 of the Toxicological Review); and lack of health data assessed at later time points. Is the rationale for the UF_D appropriate and clearly described? Please provide the rationale if a change in the UF_D is proposed.

Use of uncertainty factors in estimating the RfC:

- I would use a subchronic-to-chronic uncertainty factor higher than 1 given the mean and maximum exposure duration in this study are both well below the lifetime exposure of interest.
- I agree with the database uncertainty factor of 10. I would not reduce this to 3 in the full cohort analysis.

A.7. Please comment on whether the document adequately describes the uncertainties and limitations in the methodology used to derive the RfC and whether this information is presented in a transparent manner.

The approach taken is to describe a category of uncertainty and then address different features of uncertainty in that category, highlighting its strengths and weaknesses. For several uncertainty categories (exposure reconstruction, TSFE, background rate of LPT, model functional form, effect of smoking) it would be possible to conduct additional sensitivity analyses by assuming specific conditions in the data or model and determining the impact of the particular feature on the BMCL. Some of this was done (e.g. assessing the impact of smoking, understanding the estimated vs. predetermined background level), but the approach could be applied more extensively (and even in these cases it could be more extensive). I attempt to lay out some recommendations below; see also detailed summary recommendations by Group 2.

To help substantiate the RfC, some additional discussion could be added. In particular, Alexander et al (2012) estimate increased risk due to background asbestos exposures (also reference other papers from this study). This study has background exposures that appear to be in the ballpark of the RfC (assuming I've done various conversions correctly).

A key consideration is whether the estimated RfC is too high to be adequately protective. Given the impact of TSFE on the POD estimates, additional work should be done to understand what features may lead to lower BMCL and RfC estimates.

General Charge Questions:

1. Is the Toxicological Review logical, clear, and concise? Has EPA clearly, and in sufficient detail, presented and synthesized the scientific evidence for health hazards from Libby Amphibole asbestos?

- Generally yes. As an expert with little specific knowledge of minerals, I found the early chapters in the document to provide very helpful background.
- Please provide more information on modeling in the appendices with the intent of giving an educated reader better insight into the work that was done and the results being reported.

- Please harmonize the presentations between the non-cancer and cancer endpoints to the degree reasonable. For instance, 1) consider some exposure metrics for RfC that were considered for cancer and 2) consider similar sources of uncertainty in the two sets of modeling appropriate to the degree appropriate.

2. Please identify any additional peer-reviewed studies from the primary literature that should be considered in the assessment of noncancer and cancer health effects of Libby Amphibole asbestos.

In addition to the papers discussed at the meeting, I suggest papers on other topics that weren't cited in the report but may be of interest:

Measurement error papers

Szpiro AS, Sheppard L, Lumley T. Efficient measurement error correction with spatially misaligned data. *Biostatistics*, 2011, 12:610-23. [PMID: 21252080

Sheppard L, Burnett RT, Szpiro AA, Kim S-Y, Jerrett M, Pope CA III, Brunekreef B. Confounding and exposure measurement error in air pollution epidemiology, *Air Quality, Atmosphere & Health*, 2011, [March 23 Epub ahead of print].

Szpiro AA, Paciorek C, Sheppard L. Does more accurate exposure prediction necessarily improve health effect estimates? *Epidemiology*, 2011, 22:680-685. PMID: 21716114

Low-dose effects: It may be useful to cite recently emerging evidence that low-dose effects have a higher dose-response than high-dose effects, with possible consideration of this perspective for health effects of asbestos:

- Health effects of lead
 - I suggest contacting Bruce Lanphear for the best references
- Health effects of particulate matter
 - Pope, CA3rd et al, Cardiovascular Mortality and Exposure to Airborne Fine Particulate Matter and Cigarette Smoke: Shape of the Exposure-Response Relationship. *Circulation*. 2009; 120: 941-948
 - Pope CA 3rd, Burnett RT, Krewski D, Jerrett M, Shi Y, Calle EE, Thun MJ. Cardiovascular mortality and exposure to airborne fine particulate matter and cigarette smoke: shape of the exposure-response relationship. *Circulation*. 2009 Sep 15;120(11):941-8.

More detailed comments on the modeling approaches and some suggested additions/alternations: (see also Group 2 summary comments)

- Data description: It would be helpful to have a much better sense of the richness of the data. Here are some details I would like to see:
 - Additional details on the distribution of exposure, e.g. a rich set of univariate statistics or histogram, scatterplot vs. TSFE, comparisons of distributions for the various lags. Provide summaries so it is possible to understand features of different data subsets. For instance, what is the distribution of exposure among smokers vs. nonsmokers in the various (sub)cohorts.
 - Include description of the exposure distribution (not just the mean and range) for participants vs. nonparticipants in the Rohs et al follow-up study. (More information is provided by Rohs et al; this can be updated using the new

- exposure estimates and enriched with more detail.) Also give details for deceased non-participants.
- Add the exposure coefficient estimate and standard error in Table E-1. For consideration of BMI in that table, it would be helpful to be able to compare the AIC with the AIC of the model with exposure alone (and the same number of observations).
 - It would be helpful to add the cross-tabulation of counts for the bins of exposure with TSFE. I expect one reason for low/0 prevalences in some bins of TSFE by CHEEC in Figure E-2 is that there is no or very little data in those bins.
 - Include the median in the tables accompanying Figure E-2.
 - On Figure 5-2 please add a rug plot showing the distribution of the CHEEC in the dataset. Also show a smooth curve fit to the raw data as an alternative to the binned prevalence estimates. This curve would be more helpful to the viewer if the bottom portion were blown up (for prevalence below .2 and CHEEC below 2). Consider also showing exposure on the $\ln(\text{CHEEC})$ scale. Finally, (in an appendix) it would be helpful to see the predicted curves for some of the competing models.
 - It isn't clear from any of the material presented how much difference there is in the distributions of the lagged exposures. (It would also be helpful to include, either in Chapter 5 or Appendix F, a description of the approach to lagging exposure so readers can be reassured that it was done correctly.)
- Model assessment by AIC: While the AIC allows comparisons across models with different functional forms, it does not allow comparisons that are focused on the range of exposure most relevant for this exercise. I think it should be de-emphasized as a model selection criterion. Poor model fit in areas of high exposure (but of relatively little importance in the range of exposure consistent with the BMR) may be very influential from an overall fit perspective, but should not drive the final choice of the model. Given competing models have essentially the same AIC estimates, there should be more consideration of important differences in their estimates near the BMR.
 - Model form and parameterization:
 - The top models are nearly all of a logistic form with (depending on the model) inclusion of a background (3-parameter log-logistic and Michaelis-Menten), or plateau (Michaelis-Menten), and in one case after excluding estimation of a slope parameter (Michaelis-Menten). In other words, the background is constrained to equal 0 in the logistic, the plateau is constrained to equal 1 in the logistic and 3-parameter logistic, and the slope for the effect of exposure is constrained to equal 1 in the Michaelis-Menten. I suggest biological considerations, combined with understanding of the richness of the data, are much more important than AIC in determining the choice between these models. I would argue against constraining the slope parameter to 1. This implies that the scaling of the exposure is irrelevant since the slope parameter remains unchanged under rescaling of the exposure. I would also argue against estimating a plateau from a cohort of individuals with low exposure. (see next point) For evaluation of the best fit near the BMR, I would compare predictions from these models to the data near the BMR. For visual understanding, it would be helpful to see a local smoother estimated directly from the data and compare it to the predicted curves from the various models, again in the vicinity of the BMR.
 - It would be helpful to see a table of model parameter estimates (including also the fixed values as appropriate) for the set of related models.
 - For assessment of smoking, the smoking variable is included the “linear predictor” part of the model as an additional term. While it is not an effect modifier in the

“linear predictor”, it still impacts the BMCL. Smokers are a sensitive subgroup and their POD is lower.

- Estimation of the plateau:
 - Given there are relatively little data available to estimate the plateau, it is noteworthy that the estimate of this parameter has a big impact on the BMCL. In the subcohort, the plateau is estimated to be .56, implying that with arbitrarily large asbestos exposure, only 56% of the population would experience this most sensitive of outcomes as a result of asbestos exposure. I suggest this value is too low and may not be consistent with biological understanding.
 - The 75th percentile of the exposure distribution is 1.92 fibers/cc-years (based on information in Table 2 of Rohs et al). There is very little information in the subcohort with which to estimate the plateau or even justify the assumption that a plateau exists.
- Sensitivity to background: Several different values were mentioned in the report, including several that had been estimated in other published studies. It would be helpful to show the BMCL for a range of different background values. (It is helpful that this was given for the estimated as well as fixed background value.)
- Impact of selection:
 - Most of the analyses are based on the data from the Rohs et al study. This study had significant non-participation, due to death, refusal, non-response, and other reasons. The discussion by Rohs et al of nonparticipation of the cohort from the Lockey et al study is confined to living non-participants. This biases the comparisons by excluding deceased individuals; these individuals were on average, older, had been hired, earlier, and had higher exposures. If weighted averages are calculated to get averages among all non-participants (using data in Table 1 of Rohs et al), there is little difference in exposure or percentage hired before 1974 in participants and non-participants. It does not appear that selection bias is present as implied in the text.
 - It would be helpful to understand the reasons for death among the 82 deceased individuals described by Rohs et al. If a large fraction of these deaths were related to asbestos exposure this would suggest a lower RfC would be appropriate. Even some “what if” sensitivity analyses that include simulated exposures and outcomes for this deceased group (based on the Lockey data and other information) would help give insight into the potential impact on the RfC estimate of this missing information.
- Possible sensitivity analyses:
 - See priorities proposed by Group 2
 - Emphasize alternative exposure metrics
 - Allow the exposure slope parameter to be estimated in consideration of alternative exposure metrics
 - Consider how to include TSFE in the model for the full cohort
 - Assess the importance of the fixed value of the background
 - Assess the importance of estimating vs. fixing the plateau; consider some alternative values for the fixed plateau
 - Assess the BMCL for sensitive subgroups (at least smokers)
 - Expand the outcome definition to include any Xray anomaly likely to be caused by asbestos exposure
- Consideration of confounding:
 - P. 5-11: If small opacities are a direct consequence of asbestos exposure and not a natural consequence of aging, adjustment for age in an analysis of asbestos exposure will risk overadjustment and should be done with caution. More caution regarding

- the discussion of the results reported by Amandus et al should be incorporated into the text.
- P. 5-34: It is not appropriate to assess potential confounding by evaluating the statistical significance of the added variables. Predictors are confounders when they are associated with both the exposure and the outcome, not in the causal pathway, and affect the estimate of the exposure effect parameter of interest.
 - P. E-7: Smokers are a susceptible subgroup and so it would make sense to estimate the RfC for them regardless of the statistical significance of including a smoking term in the model.
- **Impact of exclusions:** The Marysville dataset had several exclusions including dropping of one Xray result for individuals with two Xray examinations and omitting workers with other occupational exposures.
 - It would be helpful to know whether the results for the cohort are affected by exclusion of the workers who had exposures in other locations. Is it known how large these other exposures were?
 - It would be informative to expand the analysis to include the repeat measures within individuals.

Additional comments:

- P. 5-13: If the reference group is exposed, this is more likely to bias the results rather than be a source of uncertainty.
- P. E-7: Clarify whether the models below Table E-4 are written correctly. (Are the added terms for smoking outside of the exponential function? If so, what constrains the probabilities to between 0 and 1?)
- P. E-10: I think the figures E-2 are overinterpreted somewhat (lines 21-22). The degree of flattening depends on exposure. Also the exposure distribution exacerbates the graphical sense of flattening given the large difference in the exposure mean for the fourth vs. all the other quartiles. It would help to add 95% CIs for each of the proportions displayed in Figures E-2.
- Table E-6: Are there typographical errors for the BMC in the >1972 cohort and exposure lags of 10-20? They don't vary with T. Why are some BMCL estimates not provided?

Additional Reference

Lilis R, Miller A, Godbold J, et al. Radiographic abnormalities in asbestos insulators: effects of duration from onset of exposure and smoking: relationships of dyspnea with parenchymal and pleural fibrosis. Am J Ind Med 1991; 20:1-15.

Dr. Randall Southard

Figure 2-4 (d) caption.

Chrysotile formula should be $Mg_3Si_2O_5(OH)_4$

Vermiculite formula should be $(Mg,Fe,Al)_3(Al,Si)_4O_{10}(OH)_2 \cdot 4H_2O$

The vermiculite structure should also indicate the presence of interlayer cations, not currently represented in the formula above.

Top of page 2-7, the identification of the amphibole groups presented here is a bit different from the scheme in Leake et al (1997). Generally, the groupings are based on B site composition.

PCM section on page 2-10 is a bit unclear regarding identification of particle morphology. PCM can differentiate fiber from non-fiber (which to me is morphology) but can't identify composition (elemental or mineralogical).

Electron microscopy section on page 2-11 could be clarified. SEM and TEM provide higher magnification to allow better particle morphological analysis. Electron diffraction allows mineralogical assessment. Energy dispersive X-ray analysis allows elemental composition determination, which can corroborate the mineralogical determination. X-ray diffraction (XRD) mentioned in this section is useful for bulk sample mineralogy measurements.

Page 2-12. Composition of vermiculite should be as above.

Table 2-1. Composition of vermiculite should be as above. Mohs hardness is about 2 (looks like a typo in the table).

Page 2-18. Seems the particle size distribution of the ore samples will depend in part on how energetic the sample prep was. Might be good to point that out here, and emphasize in Appendix C.

Figure 2-9 was missing in the version I downloaded.

Dr. Katherine D. Walker

General Charge Questions:

1. Is the Toxicological Review logical, clear, and concise? Has EPA clearly, and in sufficient detail, presented and synthesized the scientific evidence for health hazards from Libby Amphibole asbestos?

The document generally well-written well-organized along the lines of evidence relevant to the risk assessment and to the guidance criteria by which judgments about the evidence and its use have been made. These types of narrative weight of evidence documents are difficult to make concise but the HERO connections do make it easier to leave out some detail.

The document is in some places lengthier than it might need to be if it were not serving multiple audiences. For example, Chapter 3 is useful background for the likely end-users of this document who may have little in depth experience with fiber toxicokinetics in general. However, for scientists interested assessing the basis for the development of an IUR and RfC for Libby Amphibole asbestos, it could be much shorter and focused on helping to understand how fibers characteristic of the Libby Amphibole asbestos might behave. The reader is now left to infer the relevance of the general material on fiber deposition, clearance and translocation.

2. Please identify any additional peer-reviewed studies from the primary literature that should be considered in the assessment of noncancer and cancer health effects of Libby Amphibole asbestos.

An older but thorough review of the literature that should be cited is the 1991 Health Effects Institute – Asbestos Research study, “Asbestos in Public Buildings and Commercial Buildings: A Literature Review and Synthesis of Current Knowledge” and the subsequent follow-up, “Supplementary Analyses of Selected Data Previously Considered by the Literature Review Panel.” 1992. It was the product of a distinguished panel, chaired by Arthur Upton, which carefully evaluated the evidence for risks associated with different types of asbestos. Many of the same issues raised in the SAB meetings, for example on which statistical models should be used to describe cancer and mesothelioma risk were evaluated here as well. Dr. Peto was also a member of this panel. Both documents are available from HEI.

II.B.1. Under EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005; www.epa.gov/iris/backgrd.html), the draft IRIS assessment characterizes Libby Amphibole asbestos as "carcinogenic to humans" by the inhalation route of exposure. Please comment on whether the cancer weight of evidence characterization is scientifically supported and clearly described.

- *This descriptor is appropriate when there is convincing epidemiologic evidence of a causal association between human exposure and cancer.*

This is the primary criterion against which I made an evaluation of the weight of evidence determination in this document. Where within my area of expertise, I made a preliminary assessment of the quality of the studies, but focused particularly on whether they provided evidence for Libby Amphibole asbestos directly or for other forms of asbestos more generally.

In its assessment of the weight of evidence for carcinogenicity (chapter 4), the review has primarily focused on the epidemiologic evidence for Libby Amphibole asbestos, the set of studies involving occupational and community exposures to Libby Amphibole asbestos specifically. They have noted secondary evidence of increased risk of pleural and malignant mesothelioma from community exposures to soils containing other naturally occurring mixtures of asbestos that include tremolite (6% of LAA) as one component. Given that there appears to be limited evidence for understanding what it is about the composition or characteristics (e.g. fiber length and aspect ratio) of Libby Amphibole Asbestos (as geologically defined) that specifically accounts for its toxicity, it is difficult to know how to weigh this latter evidence. The conclusion on p 4-2 that these community studies represent tremolite exposure does not seem appropriate.

The occupational studies appeared most persuasive at showing dose related increased risk of lung cancer and mesothelioma among workers exposed by inhalation. However, the numbers of cases are small, particularly in the subcohort used from the Marysville, Ohio plant and at lower estimated levels of exposure. The case series in the community, while supportive, do not provide the same level of evidence for an association, or for the strength of the association.

Nonetheless, the epidemiologic evidence from the occupational studies does appear to support the choice of descriptor "carcinogenic to humans by the inhalation route" for Libby Amphibole asbestos under the conditions of exposure in those studies. Pending our discussions of the strength of the epidemiologic evidence, I also looked at the supportive evidence required by the guidelines when the epidemiologic

evidence is not so strong. This information is also useful for considering responses to later questions on mode of action.

b) the guidelines call for “extensive evidence for carcinogenicity in animals.” The review itself characterizes the experimental data on toxicity mechanisms as “limited” for Libby Amphibole asbestos although the results for the studies cited in two lab species are, as the review suggests, “consistent” with the findings of cancer and mesothelioma.

c) the guidelines asks that the “mode(s) of carcinogenic action and associated key precursor events have been identified in animals.” While the review has a hypothesis for the mode of action and has identified a series of studies that provide supportive evidence, the review concludes “Due to the limited data specific to Libby Amphibole asbestos, the mode of action of Libby Amphibole asbestos for lung cancer and mesothelioma following inhalation exposure cannot be established.” P 4-80.

d) the guidelines ask for “strong evidence for key precursor events.” The review identifies supporting evidence for key events (ROS production, genotoxicity) but itself concludes that “multiple key events for one MOA have not been identified”, again concluding the mode of action cannot be identified.

II.B.2. Due to the limitations of the data available, the draft assessment concludes that there is insufficient information to identify the mode of carcinogenic action of Libby Amphibole asbestos. Please comment on whether this determination is appropriate and clearly described. Note that in the absence of information to establish a mode of action, a linear low dose extrapolation is recommended by the *Guidelines for Carcinogen Risk Assessment* (U.S., EPA, 2005; Section 3.3). If it is judged that a mode of action can be established for Libby Amphibole asbestos, please identify the mode of action and its scientific support (i.e., studies that support the key events, and specific data available to inform the shape of the exposure-response curve at low doses).

The section 4.6.2.1 does describe the limitations of the existing data that would plausibly preclude identification of mode of action (lack of characterization of individual fibers and cell types, non physiologically relevant routes of exposure, etc). It would be helpful here if the text could refer back to the preceding sections that provide the evidence on which these conclusions are based. As written, it refers

primarily to reviews on mode of action whose relationship to the studies for this assessment are not immediately clear.

II.B.5. The database of laboratory animal and mechanistic studies of Libby Amphibole asbestos is summarized in this draft assessment (see Section 4.2 and 4.3, details in Appendix D) to inform the mechanisms of the biological response to Libby Amphibole asbestos and support the epidemiology studies used for derivation of the IUR. Please comment on the use of laboratory animal and mechanistic information in the draft assessment.

My response here follows somewhat from my comments on mode of action above. In general, I think the document has done a good job of identifying appropriate laboratory animal and other studies that provide supporting evidence. The particular challenge EPA faces is that having made the effort to make this risk assessment specific to LAA, it has to be careful to identify studies that inform inferences about LAA. For example, the reliance on exposures to tremolite, which is one component of LAA, as representative of LAA is not well justified. Without reviewing each study in detail, I cannot say whether the document has accurately portrayed all limitations or alternative interpretation of individual studies. But the document at least appeared to have identified key limitations where they exist. These are of course subject to some interpretation.

III.B. 5. Please comment on whether the document adequately describes the uncertainties and limitations in the methodology used to derive the IUR and whether this information is presented in a transparent manner.

In chapter 5, Section 5.4.6.1 EPA is to be doing a thorough job of describing many sources of uncertainty and in some cases the potential magnitude of the underestimation or over estimation.

The enumeration of possible sources of uncertainty and the possible direction of any bias they might create for the IUR is an important step. But without any quantitative characterization of how probable these are and what the magnitude of their effects might be (either individually or particularly, collectively), they leave the risk assessor who is ultimately tasked with characterizing the full uncertainty in human health risk, and the decision maker with little sense of how probable the risks are. In that sense, the uncertainty analysis is not as transparent.

The general assertion that “the selected combined IUR from of mesothelioma and lung-cancer mortality **accounts for** (emphasis added) both the demonstrated cross-metric uncertainty as well as several additional uncertainties, which could have resulted in underestimates of the mesothelioma and lung-cancer mortality risks” (p 5-105, lines 1-5) is not actually explicitly demonstrated except for the exposure metrics. It is well established in the literature that qualitative expressions of

probability or likelihood have very different quantitative meaning to different people. In practice, therefore, the IUR is likely to be treated as essentially certain by risk assessors in application (Section 6.3).

That said, I think EPA has done a good job of assessing the impact of varying exposure metrics on estimation of the unit risks, given the choice of the data set and the model for estimating them.

But a major uncertainty that is not necessarily reflected in the conservatism imbedded into the IUR (with the use of the 95% UCL) is in the choice of the statistical model, particularly for mesothelioma. Based on model fit criteria, a Poisson model was used to fit the data and a number of sensitivity analyses run to evaluate assumptions about the lengths of cumulative exposure – this is primarily the “within-metric” uncertainty. There is an adjustment for potential underascertainment of cases of mesothelioma from death certificates, but I did not see any discussion of potential underascertainment resulting from the assumption that risk of mesothelioma increases linearly with dose, rather than as some power function of time since first exposure as has been posited by some investigators (Peto, Nicholson). This is the basic argument about models that the SAB was having during the meeting.

I recognize that the EPA did fit the Peto model to the Libby cohort data, that it was not a good fit according your criteria, and that the IUR you derived using that model was not that different from the one selected for this risk assessment. But even application in a risk assessment of an IUR based on fit of the Peto model would not, as I understand it, really deal with this question of time since first exposure. Currently the guidance does not recommend any particular adjustments of for early lifetime exposure as is recommended for the general asbestos risk assessment. An analyst would simply be applying the IUR to a lifetime averaged daily dose, regardless of when the exposure occurred.

Despite what we heard at the meeting, it is not clear that all scientists agree that there is one right model for mesothelioma. The HEI-AR (1991) document notes:

The model for mesothelioma was proposed to explain the observation that mesothelioma incidence is independent of age and is approximately proportional to the third power of time since first exposure (or more equivalently, to the square of time since first exposure minus 10 years) (Peto 1979; Peto et al., 1982), but neither the predicted relationship to duration nor the assumption of the linear dose response has been adequately tested. In spite of its widespread adoption as a basis for risk assessment, the model has been formally fitted in only one cohort in which individual exposure data were available (page 6-18)."

But, it appears that the same criticism might be leveled at the application of the one model to the subcohort of the Marysville, Ohio worker population. The reality is that we don't know and that model fit, while reassuring for the range of data and types of exposure in the subcohort, is no guarantee of certainty that we have the only 'right' model.

At a minimum, EPA needs to address the question of why the epidemiologic evidence and modeling approaches used now for modeling asbestos under other guidance, provides essentially no information that is useful to the Libby Amphibole Asbestos assessment. What is it that makes it OK to consider toxicologic and other evidence developed with exposures to asbestos that are not strictly Libby AA, but analogous, but to give no weight to evidence from these other epidemiologic

studies? There may be good reasons relating to the types of asbestos, the high exposures, etc, that might make use of the Peto studies for example, more dubious for the Libby AA case. But going back to Chapters 2 and 3, given that we don't really know what it is about Libby AA that makes it more or less toxic, it's unclear why these other studies should be completely ruled out.

I recognize that EPA guidance favors selection of a "best" study for the purposes of developing RfCs and IURs that are unlikely to underestimate risks. The downside to this approach is that it can work against a broader consideration of the weight of evidence. And in this case, it raises the question as to whether or not mesothelioma cases might be underestimated.

A more straightforward and transparent treatment of uncertainty about the rate at which mesothelioma cases arise over time would be to estimate risks using both approaches. Then we truly could see how much difference this model assumption makes.

Section 6.3- Application of RfC and IUR

The comments from the previous section then apply to the application of the IUR in risk assessment, in particular in regards the estimation of risk from less-than-lifetime exposures. Is the standard Superfund assumption that risks from less-than-lifetime exposures can be computed by simple calculations of average lifetime exposure concentrations X IUR consistent with the weight of evidence for Libby AA? For situations when Libby AA may not be the only form of asbestos present or suspected to have been present?

Dr. James S. Webber

Chapter 2- Geology, Use, and Exposure

General Charge Questions:

1. Is the Toxicological Review logical, clear, and concise? Has EPA clearly, and in sufficient detail, presented and synthesized the scientific evidence for health hazards from Libby Amphibole asbestos?

Response:

This question is not applicable to Chapter 2.

2. Please identify any additional peer-reviewed studies from the primary literature that should be considered in the assessment of noncancer and cancer health effects of Libby Amphibole asbestos.

Response:

Add after the last sentence of line 4 on page 2-20: *Elutriation of respirable fibers by Webber et al. produced a fiber-size distributions similar to those in Figure 2-11.*

Add after the last sentence of line 11 on page 2-20: *Webber et al. found no difference in elemental ratios between fiber dimensions, indicating that the different mineral types were not segregated by fiber dimensions.*

Add the reference:

Webber, J.S., D.J. Blake, T.J. Ward, and J.C. Pfau. 2008. Separation and Characterization of Respirable Amphibole Fibers from Libby, Montana. *Inhal. Toxicol.* 20:8, 733 — 740.

I. Background

A. Mineralogy and Toxicokinetics

1. In order to inform the hazard identification and dose response of Libby Amphibole asbestos, background material is included in the document briefly describing the mineralogy and toxicokinetics of asbestos and related mineral fibers (Section 2 and 3):

- a. Please comment on whether the presentation of the available data on the mineralogy of Libby Amphibole asbestos is clear, concise and accurate.

Response:

Discussion of mineralogy is good

The discussion of mineralogy of Libby Amphibole asbestos is generally clear, concise, and accurate. Discussions of mineralogy and morphology are good, with appropriate discrimination between methods/definitions that are applied to field samples versus terms/definitions that are applied to environmental samples delineated (lines 4 and 5 of page 2-10).

Discussion shortcomings

Discussion on page 2-10 glosses over a serious shortcoming of PCM: its inability to detect fibers narrower than $\sim 0.25 \mu\text{m}$. These thin fibers are the most biologically potent according to the Stanton-Pott hypothesis. The fact that only a third of the TEM-visible Libby fibers were PCM-visible is buried in McDonald *et al.* 1986a. Furthermore, Text Box 2-2 does not adequately contrast the capability of EM versus PCM. EM's capability to yield elemental composition via EDS provides information to identify different asbestos types. PCM's, in contrast, can't even determine if the fiber is mineral. Furthermore, the SAED capability of TEM allows determination of crystalline structure, e.g., amphibole versus serpentine. Finally, Box 2-2 incorrectly states that *SEM produces three-dimensional (3-D) images*. Rather, SEM produces 2-D images that reveal surface structure of particles.

Chapter 5- Exposure-Reponses Assessments

Sections 5.2 and 5.3- Inhalation Reference Concentration (RfC) and Uncertainties

III. Exposure-Response Assessment

A. Inhalation Reference Concentration (RfC):

1. Exposures to Libby Amphibole asbestos for workers in the Marysville, OH facility were reconstructed based on industrial hygiene data collected in the facility from 1972 to 1994. Exposures from 1957 to 1971 were estimated based on extrapolation from the available industrial hygiene data. The information used for the exposure reconstruction was based on employee interviews, court and company records, and the expert judgment of the researchers. Is the methodology used for the exposure reconstruction reported in Appendix F and the subsequent development of exposure estimates used in the analyses scientifically supported and clearly described?

Response:

Report correctly excludes 1957 to 1971 data

F-13, line 17 *...twice as high...* is not a convincing multiplication factor for determining airborne fiber concentrations before 1972. It would be impossible for workers to objectively determine that *dust exposures in trionizing were at least two times higher in the 1960's* in that any visual estimation would be fraught with uncertainty. Furthermore, pre-1972 estimates are based on a *weighted* (page F-10, line 7) fiber ratio of 10:1 in the mixed Libby/South Carolina vermiculite. This would add further uncertainty to reconstructing fiber concentrations. Hence the report appropriately limits its final evaluation to 1972 and later, when measured airborne fiber concentrations were available.

Chapter 5- Exposure-Responses Assessments

Sections 5.2 and 5.3- Inhalation Reference Concentration (RfC) and Uncertainties

III. Exposure-Response Assessment

A. Inhalation Reference Concentration (RfC):

7. Please comment on whether the document adequately describes the uncertainties and limitations in the methodology used to derive the RfC and whether this information is presented in a transparent manner.

Response:

Use of log transformation underestimates exposure

I have modified my response on the basis of the data provided by the EPA on February 1, 2012.

F-12, line 6: *The data were log-transformed.* No rationale or explanation is given for this transformation. While this transformation apparently (Figure F-1) provided normally distributed populations for modeling purposes, the bias of the log transformation was not clearly removed post-modeling for determination of the RfC. Log transformation creates bias in populations by decreasing the significance of the highest numbers. (Note that these were natural logs, rather than base 10 as presented in the original EPA report. This only came out in the amended caption for Figure F-1 that was provided February 1.)

F-12, line 10: *For each year, the annual exposure estimate was determined by exponentiation of the value from the curve.* For 1973, I have calculated the natural-log-mean as 1.19 fibers/cc, which is consistent with Figure F-1. However, the arithmetic mean of 7.38 fibers/cc that I calculated does not appear in the EPA report: Table F-4 reports 3.007 f/cc for 1973 and Figure 5-1 shows ~3 f/cc for 1973). 3.007 f/cc, and certainly 1.19 fibers/cc, do not represent what a worker would have been exposed to in 1973 (7.38 fibers/cc), assuming that he breathed equal portions of the 39 samples that were reported for that year. To put it another way, a worker's lung does not selectively inhale fibers in a log-transformed manner. This could potentially create a bias of as much as a factor of 2 to 4.

Adjust PCM Exposure Values

Page 5-118, Lines 22-33 discusses the two-fold under-reporting of fibers because of the poorer resolution, 0.44 μm versus 0.25 μm today, of the analysis during the 1970's. Because today's analysts have no protocol for discriminating fibers $> 0.44 \mu\text{m}$ from the entire population of resolvable fibers, the exposure data from the 1970's used for modeling should be doubled so that the RfC will reflect fiber concentrations as measured today.

Confusing statements

F-5, line 20: *plotted..and found to be visually similar* Were these viewed as raw data or as log plots. If they were log plots, as shown in Figure F-1, the data would look similar even if they weren't. That's what log plots do.

Table F-1: Where did *COMBINED* come from? There is no discussion of it in the text.

F-12, line 8: *...mean values of years having at least 40 exposures measurements (1973, 1976, and 1978)*. Table F-2 shows 1977 with 68 *Trionize* samples. Was 1977 included in drawing the line?

F-21, line 34: *Tables 5-7 provide a list of all 280 subjects participating in the 2004 Marysville health update (Rohs et al., 2008)*. The Rohs article available from HERO only goes up to Table 4. I was unable to locate Tables 5-7.

Inclusion of the recent Adgate et al. data

Because the exposure data in this paper are extrapolations and not based on PCM measurements, this cohort should not be used in developing risk models.

Section 6.3- Application of RfC and IUR

General Charge Questions:

1. Is the Toxicological Review logical, clear, and concise? Has EPA clearly, and in sufficient detail, presented and synthesized the scientific evidence for health hazards from Libby Amphibole asbestos?

Response:

This section establishes appropriate limits on interpretations and applications of the study. It correctly concedes that no risks concerning fiber size or type can be made because of the limitations of its source (PCM) data and, furthermore, that the study result's applicability is limited to those environments where Libby asbestos predominates.

I am concerned about the confusion that will be caused by *the dimensions of the PCM fibers for the Libby Amphibole asbestos unit risk are defined as fibers $\geq 5 \mu\text{m}$ in length with an aspect ratio of 3:1 or greater and a width $> 0.4 \mu\text{m}$* (page 6-29, line 27). While it may be true that PCM during the 1970s generally lacked resolution below $0.4 \mu\text{m}$, there are two reasons why there is no easy work-around for applying the 1970's-based RfC to today's environments. One is that there has been no determination of the expected ratio of the fibers in the 0.2 to $0.4\text{-}\mu\text{m}$ range versus the total population of fibers in the $>0.2\text{-}\mu\text{m}$ range. Second, today's analysts have no protocol for determining a $0.4\text{-}\mu\text{m}$ cut-point in fiber width. So I repeat my earlier recommendation that exposure data from the 1970's be doubled to accommodate the reality of today's analytical method.

Dr. Susan Woskie

Chapter 4 Hazard Identification

General Charge questions 1 & 2 for this section:

Section 4.1 on Studies in Humans-Epidemiology, provides a comprehensive review. There are no additional peer-reviewed studies I am aware of. I would suggest some modifications to the organization and presentation to aid the reader in following the material more easily.:

Section 4.1.1.2 Exposure Estimation would benefit from a more detailed discussion in the text clearly organized by cohort: NIOSH cohort (Amandus papers) with description of modifications for Sullivan and Moolgavkar papers. Then ATSDR cohort (Larson papers) what were the similarities or differences in exposure assessment compared to Amandus and Sullivan. Then McGill cohort (McDonald papers). Finally, the Marysville cohort, first the Lockey paper approach and then discussion of the modifications described in the Appendix. Then a summary that discusses similarities and differences in these studies would be helpful.

For Table 4-1 it would help to have a consistent format: Years when potential exposure to workers. Sampling method: PCM for fibers ≥ 5 μ m and $> 3:1$ aspect ratio or TEM/SEM for PCM equivalent measure; Years when PCM sample results available; Number of PCM personal and area samples (can combine with years if not concurrent); Sampling method for dust: midget impinger with microscopy counting for mmpcf metric; Years for dust sampling; Number of dust personal and area samples (can combine with years if not concurrent); Conversion ratio for dust to PCM equivalent; Exposures categorized by: location or job group using mean or geometric mean (specify); Cumulative exposure metric used. Also Table 4-1 only has the info on sampling from original Lockey et al paper, 1984 and should also include a summary of material in Appendix F

In addition to Table 4-2 for the Libby mining and milling operation it would be helpful to have a similar table showing the source of sample data and years for the Marysville OH data set in Lockey and the material in Appendix F

Note that Table 4-1 lists two epidemiologic papers that are not discussed in the text that is titled Description of cohorts: Moolgavkar et al, 2010 using the NIOSH Amandus/Sullivan cohort (also not included in Table 4-4) and Rohs et al, 2008 using the Lockey Marysville cohort. This section is not correctly named...it is more a description of the respiratory cancer cohorts. I would prefer to see a summary section on all the cohorts used in all human studies with population size and gender, years covered, inclusion criteria, design details including exposure metric used, then a column with # deaths or cases, mean/median duration of work, mean/median cumulative exposure in a consistent fashion and then instead of the study results a series of columns (check boxes?) where it is indicated which cohorts were used for respiratory cancer mortality, mesothelioma, other cancers, asbestosis, non-malignant respiratory disease mortality, chest radiography, cardiovascular mortality etc. This type of table would aid in moving on to the results tables as it seems that now some details on the cohort are in some tables, some in others (see Table 4-1-; 4-4;4-5.4-7

Section 4.1 Studies in Humans-Epidemiology (charge questions IIA1 and II A2)

The occupational cohorts from both Libby Montana and Marysville, OH are well described in the document. However, the charge question asks if the selection of the Marysville cohort for the RfC derivation is clearly described and scientifically supported. Unfortunately, the discussion is in Chapter 5 not this chapter. Therefore this comment will be found under Chapter 5.

Likewise, the choice of localized pleural thickening in humans as the critical effect for derivation of the RfC was discussed in Chapter 5 not here so comments will be found there.

Chapter 5.2 and 5.3 Inhalation Reference Concentration (RfC) and Uncertainties
Selection of the occupational cohort of Marysville OH for the derivation of the RfC
(charge IIA1 moved from Chapter 4)

The rationale for the use of the Marysville OH cohort for development of the RfC was well described and scientifically supported. There are clear drawbacks in the exposure assessment of this cohort due to the lack of sampling prior to 1972, the use of self-reported work histories, the end of Libby vermiculite use in 1980 and the mixture of vermiculite sources used throughout the life of the plant. This concern is compounded by the fact that approximately 70% of the cohort were hired before 1972. Nevertheless, these drawbacks are offset by the solely occupational exposure of this cohort, the use of better quality radiographs taken for research purposes and the use of 2000 ILO standards for reading radiographs, and for the stated relevance of this organization, a preference for exposures closer to environmental levels (lower). The McDonald et al cohort (1986) also collected radiographs specifically for the study, though they were read using an older ILO standard; had a thorough exposure assessment, though like Marysville depended on qualitative information to reconstruct exposures prior to the start of sampling in 1956 and included dust to fiber conversion for the period of 1956-1969; did not rely on self-selection for cohort inclusion, avoiding the potential selection bias of the Rohs et al Marysville cohort; included currently exposed workers (1983), former workers hired before 1963 (1 yr tenure minimum) and unexposed, therefore more of the cohort work history was covered by sampling data compared to Marysville. However, exposures were high relative to environmental levels. On balance the factors that weighed most heavily in choosing the Marysville cohort appear to be minimal exposure outside the workplace for Marysville workers vs Libby workers, newer methods for radiographs and lower range of cumulative exposures. These are reasonable criteria.

Selection of localized pleural thickening as the critical effect for derivation of the RfC
(charge IIA2 moved from Chapter 4)

The evaluation of endpoints to use for derivation of the RfC was well described and scientifically supported. Evidence that both diffuse and localized pleural thickening (including plaques) are associated with decreased pulmonary functioning was presented. However, a final section in 5.2.2 is needed to discuss the rationale for focusing on localized pleural thickening. Presumably, the main rationale would be that the expected latency from time of hire to observed change for localized pleural thickening was reported as a median of 8.6 years in the Larson et al study (2010a) of the Libby Workers. Whereas diffuse pleural thickening had a median latency of 27 years. In Lockey et al (1984, 1985) the cohort had a mean employment duration of 10.2 years. However the Rohs et al (2008) study had up to 27 years of additional followup so would have had

adequate time to evaluate diffuse pleural thickening as well. Nevertheless, due to the shorter latency and the association with pleural plaques, localized pleural thickening is an earlier and therefore perhaps more sensitive endpoint for use in developing the RfC. Exposure reconstruction scientifically supported and clearly described (charge question IIIA1)

The approach described in the Appendix F is detailed and specific. The strengths and weaknesses of the approach are clearly laid out. However, this information should be summarized in the document in the Section 4 with the other cohort exposure descriptions. In addition, in the text there should be a table summarizing the changes in proportion of each type of vermiculite used (S.Carolina, Libby and African) at the Marysville plant throughout time frame represented by the cohort. It should explicitly discussed in this section that Libby vermiculite usage ended in 1980 and the fiber counts used in the cumulative exposure calculation for the production workers, though small are generally 1.5-6.3 times higher than background. These fibers are presumably from combinations of African/Virginia/South Carolina vermiculite that was used from 1980-2000. Likewise, the description of the calculation of the CHEEC in section 5.2.3.1 would benefit by addition of a version of the material on pg F-19 to clarify the correction factors, and breathing rate adjustments made due to extended work hours during some seasons. The approach used has the typical drawbacks of oversimplification of breathing rate (one size fits all) but is consistent with typical EPA approaches.

Exposure Response Modeling: Is selection of Michaelis-Menten model to estimate POD scientifically justified and clearly described and has choice of benchmark response for the POD of 10% extra risk been clearly described and appropriately conducted (charge question IIIA2)?

The determination to use the Michaelis-Menten model based on the AIC is adequately described in the document. The 10 year lag is reasonable since the work by Larson et al (2010) with the Libby worker cohort found that from time of hire to observed appearance of localized pleural thickening the median latency was 8.6yrs (1.4 and 14.7 for 25th and 75th percentile). Since several models had a similar fit +/- 2 units of AIC, other more commonly used models such as logistic would have produced BMCL's in a similar range and could be considered more parsimonious. Using the logistic model with ln CHEEC and 10 yr latency produced a 50% lower BMCL of 0.0591 fibers/cc-year vs the Michaelis Menten model result of 0.1177 fibers/cc-year. Nevertheless, the choice to use the model with the best fit is in line with the approach recommended by the EPA Benchmark Dose Technical Guidance Document.

It is interesting to note that although the radiographs were taken in 2002-2005, and Libby vermiculite exposures stopped in 1980, as the lags increase from 5-15 years for all the models, the BMCL decreases. So, presumably either the exposures accumulated from the non-Libby vermiculite exposures in the 1980-2002/2005 period have some impact on risk as well or TSFE is an important predictor of LPT, despite the statement in the document that there is "no association between risk of LPT and TSFE, age at XRay, gender or BMI". There is relatively little information on the background rate on non-occupational local plural thickening, although it appears that it does increase with age. Libby community members age 41-50 had a prevalence of 1.4% although older members had a high rate (likely due to environmental exposures). For diffuse plural thickening the background

ranged from 1.2% in NHANES I to 3.9% in NHANES II while military personnel had rates of ~ 2.3%. Therefore, the choice of a background rate of 1% is a reasonable and conservative approach for pleural thickening. The use of an excess risk of 10% fits with the default BMR approach described in the EPA Benchmark Dose Technical Guidance Document. The final exposure-response model produced a background rate of 3.12% and use of that background rate in calculating the BMCL/POD produced only ~15% difference(0.1349 fibers/cc-year compared to the fixed 1% model BMCL of 0.1177 fibers/cc-year).

Exposure Response Modeling: Is the rationale for presenting the alternative model to estimate a POD scientifically justified and clearly described (charge question IIIA3)?

It was difficult to follow the rationale and approach for the modeling done with the combined radiographs from 1980 (Lockey 1984) and 2002-2005 (Rohs 2008). For example, in a previous section 5.2.3.3 where the rationale for a background rate was discussed, it was stated that “in general, pleural thickening increases with both age and time since first exposure (TSFE) in a population” and data from Weill, 2011 is used to show that LPT in Libby community members with no reported exposure increases with age. Yet in the main subcohort analysis discussed in 5.2.3.3.1 it is stated that there was “no association between risk of LPT and TSFE, age at XRay, gender or BMI”. While for the combined dataset TSFE is considered a key covariate. The TSFE to Xray for the combined cohort is 0.4-47 years, while for the sub-cohort it is 23.2-32.7 years. As mentioned previously, Larson et al (2010) with the Libby worker cohort found that from time of hire to observed appearance of localized pleural thickening the median latency was 8.6yrs (1.4 and 14.7 for 25th and 75th percentile). So, is the issue with the combined cohort simply that there are some workers with too little TSFE? Might it be better to simply drop those individuals? In addition, it does not appear the repeated measures nature of the combined cohort has been accounted for. Overall, this addition to the document was more confusing than clarifying.

Cumulative Exposure: Is the basis for the conversion from cumulative exposure to RfC continuous exposure concentration clearly explained and scientifically justified? (charge question IIIA5)?

It is important to remember that for the Marysville subcohort only workers whose exposure to Libby amphibole asbestos began after 1972 (when sampling began) were included and that exposures ended when use of Libby vermiculite ended in 1980, although fiber exposure continued after that date in the plant and were included in cumulative exposure estimates. Thus it is difficult to estimate a lifetime exposure when the maximum length of exposure to Libby vermiculite was only 8 years. The approach used to estimate the lifetime BMCL/POD was to divide the BMLC by 70 years of exposure-10 years of lag resulting in 1.96×10^{-3} fibers/cc. However other approaches were tried as well to see if dividing the BMCL either by the average employment duration (18.7 years) or using the individual worker average exposure in modeling produced different results. Modeling the average exposure, which assumes duration of exposure is not important, produced the highest worklife BMCL/POD of 8.5×10^{-3} fibers/cc (~4 fold higher). Thus the lifetime BMCL/POD can be defended as a more conservative approach. To estimate the RfC, this lifetime BMCL/POD is divided by an uncertainty factor of 100 resulting in 1.96×10^{-5} fibers/cc ~ 2×10^{-5} fibers/cc