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Compilation of Individual Comments from Panel Members

(as of February 2, 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 potential 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.

No additional studies need be considered.

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

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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 judged to be reasonable.

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 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?

Preliminary comments:

- a) Section 4, pg 4-1: Libby 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 contains primarily winchite (84%), it would be prudent to determine whether this is a toxic component that contributes to the adverse health effects of Libby amphibole or whether there are interactive effects of winchite that modify the toxicity of tremolite.
 - 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 Turkey or Greece.
 - 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.

Preliminary 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, the predominant finding 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.

Preliminary comments:

- a) There are several additional 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.
- b) 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., Bernstein 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.

- c) 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 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 mode of action should be a top priority. Moreover, the identification of more appropriate biomarkers to predict human disease, and especially which subpopulation are at greatest risk, should have the highest 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

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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.

Preliminary comments: So far the rationale for the UFD is appropriate and clearly described, but modifications may be suggested after a full panel discussion to thoroughly evaluate this issue. As mentioned above, it is possible that the RfC could be refined with more information on susceptible populations, which could be identified by appropriate biomarkers of cancer and non-cancer disease.

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:

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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

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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.

Mr. John Harris

The fundamental component for all asbestos risk assessment is the underlying analytical protocol that defines which fibrous structures are counted and which are not. As an example, the RfC, or inhalation reference concentration (mg/m³), is a primary inhalation exposure measurement used to determine risk which is highly dependent on the accurate enumeration and sizing of asbestos structures.

The primary method used for risk assessment currently is the ISO 10312 direct method using transmission electron microscopy (TEM). Counting rules defined with the ISO 10312 method provide counts of asbestos structure by structure morphology and size. In addition, provisions within the method provide for PCM-size fibers to be counted which are critical for all risk assessments. This method has been in use since 1995 without any modifications.

In order to have accurate data for risk assessments, any analytical method must account for issues such as the accurate measurement of length, aspect, surface area, aerodynamic properties or bound state of asbestos fibers. With input from the risk assessment community, along with improvements in methodology, more accurate information will be available to risk assessors.

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 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 and concise. 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 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

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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?

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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.

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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. 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**) ?

These preliminary 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.

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:

1.

The 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. I think it 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 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., 4.1.4) and 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 obtained.

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.

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.

I have found no additional references at this time.

II.B.1.

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The weight of evidence for carcinogenicity is scientifically supported and clearly described. There is repetitiveness throughout this draft, however, that should be cleaned up.

II.B.2.

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. Despite this, or perhaps because of it, a linear low dose extrapolation of dose does seem warranted.

II.B.5.

This section seems overly complex. Laboratory animal data should be focused on the respiratory mode of exposure. However, 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, however, does not seem that useful. Autoimmune studies appear to add little or nothing new and perhaps should either be shortened or left out.

III.A.4.

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.

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.

II.B.3.

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.

II.B.4.

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

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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.B.2.

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.

III.B.4.

The mesothelioma undercount is adjusted for the entire lifespan (70 ÷ 54) and for the undercount in death certificates. The former seems quite logical and the latter requires more detailed statistical understanding to render a judgment.

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.

Dr. Lee S. Newman

January 30, 2012

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.

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.

I do not know of any relevant studies.

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

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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 Michaelis-Menton model with lag 5 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. The choice of the Cumulative Normal Michaelis-Menten model is valid. However, I had to come to this conclusion on my own by looking at the plots in the appendix which demonstrate a difference in plateaus of the dose-response curves for cumulative exposure by T; hence I recommend referring to this empirical evidence in the main document to make the justification more obvious.

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 uncertainty as to whether this POD or the others examined in the sensitivity analysis (i.e., the POD based on the average length of exposure in the data set and the POD based on dividing everyone's cumulative exposure by exposure duration) is more appropriate, their conversion method is justified given that it is the most conservative of the three—the EPA has omitted this reasoning and I think that it should be included.

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? 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. However, I think more appropriate methods are available for estimating the upper bound for the combined IUR. 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. Bootstrapping in theory would be more appropriate, but probably not for this data set given the small number of events of each type. Another approach would be to fit both the Poisson and Cox models using a Bayesian methodology; both the Cox and Poisson parameters would be sampled during the same MCMC and at each iteration, the sum of the unit risks would be computed. The 95 percentile of the sum of the unit risks across all saved iterations would then provide a valid upper bound on the combined IUR.

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 review is the choice of models for predicting the carcinogenic effects of lifetime asbestos exposure, particularly for mesothelioma. This is largely 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, it is inconsistent with the epidemiology of mesothelioma. The lifetime mesothelioma risk is much higher when asbestos exposure begins 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. 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 whether this has increased or reduced 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.

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 discuss national trends in smoking and lung cancer, and should include the epidemiological evidence on lung cancer patterns in other cohorts of workers exposed to amphibole asbestos.

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 cumulative dose would remain constant while the prevalence continues to rise. Again, the crucial assumptions implicit in the model should be identified and examined in relation to other data. Analysis of prevalence instead of incidence can underestimate the risk of asbestos-related signs and symptoms

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by an order of magnitude. This observation (together with a more appropriate model for mesothelioma) was published more than 30 years ago (Peto, Lancet i 484-9, 1978). In summary, I would have preferred a shorter document presenting and discussing predictions based on the models previously adopted by the EPA and many other agencies worldwide for asbestos risk assessment. This subset of the Libby workers cohort can be used to estimate dose-specific risks based on those models, but it is far too small to provide a basis for developing and evaluating new ones.

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 identified any additional primary references.

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.*

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.

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:

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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:

Unfortunately 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 the 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. 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 is consistent with this assumption, so there are no empirical grounds for questioning it.

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 this 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. 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.

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.

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.

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.

These preliminary 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.

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.

These preliminary 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.

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 low. I elaborate on these points below.

Brief comments on charge questions:

Charge section II

A.1. Appropriateness of the occupational cohort of workers in Marysville, OH as the basis for derivation of the RfC.

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. Appropriateness of LPT as the primary outcome for derivation of the RfC.

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.2. Exposure-response modeling and estimation of the POD based on a subcohort of exposed workers from the Rohs et al study.

Overall I had a number of questions about the dose-response modeling and choices that were made in the calculation of the RfC. Repeat measures data were not used but could potentially have been informative. 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. 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). I wish to see more detailed data description of the data, both pure data description and summaries that relate to the modeling results and that can help inform one's interpretation of the results. The work would be improved by the inclusion of more sensitivity analyses.

A.3. Results of alternative modeling using the full Marysville worker cohort that incorporates time from first exposure as an explanatory variable.

I have the greatest difficulty with this analysis and the results.

- It isn't clear what time since first exposure (TSFE) represents scientifically: is it some imperfect measure of latency until disease is detectable, an additional measure of exposure, or both? There is clearly some association between cumulative exposure and TSFE in this dataset 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. 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. In addition, I think it makes more sense to include TSFE as a parameter 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.
- 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)

A.5. Is the basis of converting the POD to the RfC reasonably explained and scientifically justified?

The approach is reasonably explained. I wonder if a lifetime of 70 years is too short and whether the most recent period of exposure should be discounted in the calculation (by using e.g. 70-10 years for a lifetime, justified by use of 10-year lagged exposure in the modeling) given that the model is based on much shorter than lifetime exposures and many of the exposure histories of the workers are highest in the distant past and far from constant over time.

A.7. Comment on the discussion of uncertainties and limitations in the RfC methodology.

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).

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.

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.

More detailed comments on the modeling approaches and some suggested additions/alternations:

- 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 there is as much selection bias as is 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.
- 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 in 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?

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?

My first read of the document is that it is generally well-written well-organized along the lines of evidence relevant to the risk assessment and 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.

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.

As I have focused on the methods more than the literature base, I have no comment currently on this question.

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.*
- *"[Carcinogenic to humans] can be used when [a lesser weight of epidemiologic evidence is available but] all of the following conditions are met:
(a) there is strong evidence of an association between human exposure and either cancer or the key precursor events of the agent's mode of action but not enough for a causal association, and
(b) there is extensive evidence of carcinogenicity in animals, and
(c) the mode(s) of carcinogenic action and associated key precursor events have been identified in animals, and
(d) there is strong evidence that the key precursor events that precede the cancer response in animals are anticipated to occur in humans and progress to tumors, based on available biological information."*

These are the criteria against which I evaluated 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 determination, the review appropriately focused on the epidemiologic evidence, the set of studies involving occupational and community exposures to Libby Amphibole asbestos. The occupational studies appeared most persuasive at showing dose related increased risk of lung cancer and mesothelioma among workers. However, the numbers of cases are small, and the CI on the RR's wide, particularly at lower estimated levels of exposure. (I will want to hear the more detailed assessments of the epidemiologists charged with those questions as well). 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" for 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 epi 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 studies that have insights into some piece of the puzzle. 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 and it will be helpful to hear the views of toxicologists on the panel.

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.

Ch. 6 Major Conclusions – Uncertainties

Dr. James S. Webber

Comments are embedded in Arial font below.

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:

None to add.

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-Reponses 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

Because the EPA has not yet responded to my request for the raw exposure data used in this report, it is difficult to evaluate the report's conclusion through reconstruction of the data set, as I've outlined below.

F-12, line 6: *The data were log-transformed.* No rationale or explanation is given for using this transformation. While this transformation apparently (Figure F-1) provided normally distributed populations for modeling purposes, the bias of the log transformation was not removed post-modeling when the RfC was determined. Log transformation creates bias in populations by decreasing the significance of the highest numbers.

F-12, line 10: *For each year, the annual exposure estimate was determined by exponentiation of the value from the curve.* Because my request for raw fiber concentrations from the EPA is yet unanswered, I used the data in Figure F-1. For 1973, the log-mean appears to be 1.1 fibers/cc on the y-axis, which would be a mean of 12.6 fibers/cc when exponentiated ($10^{1.1}$). (I did not see a value approximating 12.6 for 1973 anywhere in this 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, or even 12.6 fibers/cc, does not represent what a worker would have been exposed to in 1973, assuming that he breathed equal portions of the 40 samples that were collected that year. A rough calculation of mean concentration can be gleaned by looking at the highest five samples in Figure F-1. Log-transformed f/cc are approximately 4.1, 3.7, 3.6, 2.9, and 2.4. When exponentiated, these equal 12589, 5011, 3981, 794, and 251. These five values add up to 22,626, with decreasing contributions from the remaining 35 samples. Dividing this sum by the 40 samples for 1973 yields 453.

These preliminary 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.

Thus if a worker had breathed $1/40^{\text{th}}$ of a cc of each sample, he would have inhaled 453 fibers, not the 12.6 fibers (or maybe the 3.007 from Table F-4?) that the report is apparently using. 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 two orders of magnitude.

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.

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.

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