

## **Compilation of Comments from the SAB Libby Amphibole Asbestos Panel Members on the Draft Report (4/30/2012):**

Overarching comment:

It is not possible to conduct “confirmatory” analyses for the RfC or to validate the primary analyses. Analyses of the full Marysville cohort and other cohorts will only provide additional supporting evidence to *substantiate* rather than confirm the RfC. They are providing evidence to support the RfC, not establishing its truth or proving it is correct.

### **Cover Letter:**

p ii, line 6,7, delete “lung cancer”

p ii, line 19, change “consider additional data and analyses for the” to “re-consider the need for an”

p ii line 31 insert “and justification” after “discussion”

p i, line 43: insert an acknowledgement that this revised outcome measure may be important in future analyses but is not likely to change the primary Marysville subcohort analysis results. For instance, insert at the end of the sentence: “recognizing this change will have little impact on the current analysis but could be an important feature in future analyses.”

p i, line 43: Replace “confirmatory analyses” with “additional analyses to substantiate the RfC”

p ii, l 16-20: I understand the recommendation to reevaluate uncertainty factors as discussed on pages 29-31 to apply to more than the database uncertainty factor.

p iii, line 15: Delete “However”. Replace “important” with “additional”.

p iii, line 17-18: Revise sentence to read: “The SAB recommends that this source of model uncertainty can be evaluated using a straightforward and transparent approach by estimating risks ....”

### **Executive Summary:**

p1, line 30: “Chrysotile asbestos fibers are very different from amphibole fibers in terms of their airborne concentration measurement errors and uncertainties, much lower biopersistence, clearance and translocation pathways, and health risks”. This sentence could use some clarification. What is meant by ‘airborne concentration errors and uncertainties’? Also, the term ‘lower’ precedes ‘biopersistence’, but is this also meant to convey lower clearance and lower health risks? It is important to be clear on this issue as chrysotile, while likely less carcinogenic and fibrogenic compared to amphiboles such as tremolite, is nonetheless associated with pleural disease and asbestosis.

p1, line 44 change “was” to “were”

p 1, line 45: replace “confirmatory” with “additional substantiating”

p2, line 15 insert a comma after “publications”

p2, line 23 change “LA” to “LAA”

p2, line 23: “While inhalation is regarded as the most physiologically relevant mean of fiber exposure in animals, there is no published study using this route of exposure in experimental animals”. This sentence should be revised to clearly state “...there is no published study using this route of exposure for delivery of LAA to experimental animals.” As it reads, one might conclude that inhalation studies in rodents have not been performed for any kind of asbestos, when in fact inhalation studies have been performed for amphiboles (tremolite, crocidolite) and chrysotile asbestos.

p2, line 24 insert “for LAA” after “exposure”

p2, line 26: “The relative potency of inhaled LAA should be compared with that of tremolite to add new information for refining the RfC for LAA.” Should add “in rodents” just after the term ‘tremolite’ for clarification.

p3, line 6: “...evidence for the mode of action of LAA based on laboratory studies is weak”. While true, the SAB also discussed the fact that there is abundant mode of action (MOA) data for other amphiboles such as crocidolite and tremolite that are likely similar to the MOA for LAA.

p3, line 7 change “by” to “in”

p3, line 7 change “LA” to “LAA”

p3, line 34 change “LA” to “LAA”

p 4, lines 2–4, A thoughtful uncertainty analysis might be able to rescue some of those estimates which are probably not valueless.

p 4, line 3-4: replace “measured exposures” with “exposure estimates based on measured concentrations”

p 4, line 10-11: After reading the longer discussion on page 24, the reason behind this statement is clear. As it appears alone it is less clear. Perhaps some additional explanation or a revision to this sentence will make it clear out of context?

p4, line 22 change “s are all” to “is”

p4, line 31 change “an important role” to “important roles”

p. 4, lines 21-22: I recommend revising to read "...the lower 95% confidence limits on the benchmark doses (BMDLs) are all within a factor of three."

p. 4, lines 31: delete the extra "g" at the end of "determiningg"

p4, line 34 change "fixing" to "adjusting"

p 4, line 38: Why is there mention of "in cancer modeling" here? Remove or clarify.

p. 4, line 38: delete "in cancer modeling"; this section refers to models for LPT.

p4 line 43 change "which" to "that"

p. 5, line 2: replace "recommends" with "agrees that"

p 5, line 2-4: This sentence is unclear. Rewrite.

p5, line 3 insert "to" before "substitute"

p5, line 6 change "intendd" to "intended"

p5, line 13 change "which" to "that"

p5, line 14 change "fixing" to "adjusting"

p. 5, lines 31-33: The statement that males and females are expected to have a similar response to asbestos is an argument against effect modification not confounding. Confounding would not be expected if exposure levels were the same for males and females. The same comment applies to p. 28, lines 38-40.

p 5, line 41: insert "in this prevalence dataset" after "event".

p 6, lines 23-24, The sentences beginning "A key consideration..." are strange. How is whether the RfC is protective a key consideration for an uncertainty assessment? Of course, it's a key consideration for the assessment generally, but what's it got to do with uncertainty particularly?

p6, line 5 add "to justify" at end of line

p6, line 6 delete "for"

p6, line 39 insert "longer than 5, 10, and 20  $\mu\text{m}$ " after "fibers"

p7, line 2,3 move "a larger population over a lifetime should be considered" from line to end of line 3

- p. 7, line 7: replace “provides” with “provide”
- p. 7, line 8: replace “explains” with “explain”
- p 7, line 8: “explain”
- p. 7, line 15: add “e.g.,” before Weibull
- p 7, line 37: This is the only place in the executive summary where we refer to our detailed response to a charge question. Should that be revised?
- p7, line 41 change “which” to “that”
- p 8, line 12-13: move “than it needs to” to after “heavily”.
- p. 8, lines 12-13: put a comma after “p-values” and a comma after “significant”
- p8 , line 12 change “which” to “that”
- p8, line 13 delete “than it needs to”
- p8, line 20 change “used is not well” to “which is not”
- p 8, line 21: delete “reference”
- p 8, line 30-31: reword sentence

### **Section 3.1. General Charge Questions**

#### **Response to Question 1:**

- p10, line 9 insert “(LAA)” after “asbestos”
- p11, line 2 insert “amphibole” before “asbestos”
- p11, line 7 insert “with” before “asbestosis”
- p11, line 11 change “the outcome” to “outcomes, e.g.,”
- p11, line 18 insert “, including the Berman (2011) model” after “chosen”
- p11, line31 insert “that were used” after “criteria”
- p12, line3 insert “either” before “support”
- p12, line 10 insert “(especially length) after “dimension”

p12, line 27 insert “fiber” before “size”

p12, line27 insert “distribution” after “size”

p12, line27 change “comparison” to “in relation to”

p12, line29 insert “amphibole” before “asbestos”

p 11, line 7-8: parenthetical comment appears to refer to LPT but is intended to refer to smoking.

p 11, line 13: replace “validate” with “substantiate”

p 12, line 1-3: It would be helpful to add a sentence to this bullet recommending the desired tone.

### **Response to Question 2:**

p13, line7 insert “Berman DW (2011). Apples to apples: The origin and magnitude of differences in asbestos cancer risk estimates derived using varying protocols. Risk Assessment 31:1308-1326.”

### **Section 3.2.1. Mineralogy and Toxicokinetics**

#### **1.a.**

p14, line 2, change “One aspect” to “Aspects”

p14, line 3, change “and” to “are”

p14, line 8, “per se” should be italicized”

p14, line 9, change “by” to “through”

p 14, line 37: four are listed

p14, line 38, change “types” to “terms”

p14, line 40, change “be discussed too” to “also be discussed”

p15, line 1, insert “used” before “are”

p15, line 5 ,insert “and other fibers” after “particles”

p15, line 7, insert “which is” before “central”

p15, line 12, change “composition” to “compositions”

p15, line 16, insert “characterizations” after “irrelevant”

p15, line 19, change 2<sup>nd</sup> “the” to “available”

**1.b.**

p17, line 4, insert “for” before “up”

**Section 3.2.2. Noncancer Health Effects of Libby Amphibole Asbestos**

**Response to Question 1:**

p17, line 25, delete “and”

p17, line 28, change “was” to “were”

p 17, line 21: Insert “exposure” at the end of the line

p 17, line 29: Replace “confirmatory analyses ...” with “analyses to substantiate the subcohort findings” and move “has a clear and strong rationale” to line 27.

p 17, line 44: Add a sentence like: “Similarly, because the Libby workers have both environmental and occupational exposures, this cohort should not be used for primary RfC analysis.”

**Response to Question 2:**

p18, line 10, delete the 1<sup>st</sup> “effect”

p18, line 12, delete “and”

p18, line 20, change “The” to “Furthermore the”

p18, line 23, change “discussed” to “noted”

p18, line 25, delete the 1<sup>st</sup> “effect”

p18, line 34, change “include” to “included, along with”

p18, line 40, change “a significant reduction” to “significant reductions”

**Response to Question 3.**

p19, line 19, change “LA” to “LAA”

p19, line 33, change “LA” to “LAA”

- p19, line 41, insert “other” before “particles”
- p19, line 42 , change “Berstein” to Bernstein”
- p20, line 3, change “interaction” to “interactions”
- p20, line 19,change “have” to “be”
- p20 line 18, change “EPA” to “SAB”

p 20, line 20-22: This sentence is a bit cryptic. Clarify who the SAB is agreeing with. Add more perspective about how this fits in with the rest of the response.

### **Section 3.2.3. Carcinogenicity of Libby Amphibole Asbestos**

#### **Response to Question 1:**

p20, line 34 change “LA” to “LAA”

#### **Response to Question 2:**

p,21, line 36 change “LA” to “LAA”

#### **Response to Question 3:**

p22, line 25 insert “only” after “leaves”

p 22, line 4: Reword the parenthetical statement

p 22 line 5: Do limitations include the possible/probably environmental exposures to asbestos?

p 22 line 29: Clarify the “two cohorts” reference.

#### **Response to Question 4:**

p 22, line 44-45: Clarify the statement about smoking. Based on the implication earlier in the paragraph, it is not a confounder.

p 23, line 8: delete ”

p23, line 18 insert “amphibole” after “other”

#### **Response to Question 5:**

p23, line 33 change “LA” to “LAA”

p23, line 40 change “directing” to “guiding”

p 23 line 43: insert “by”

p24, line 11 change “LA” to “LAA”

p24, line 15 change “LA” to “LAA”

#### **Section 3.2.4. Inhalation Reference Concentration (RfC)**

##### **Response to Question 1:**

p24, lines 28–31: A thoughtful uncertainty analysis might be able to rescue some of those estimates which are probably not valueless.

p24, line 33 insert “re-examining the” after “for”

##### **Response to Question 2:**

p25, line 29 change “but” to “but, if so,”

p26, line 13 insert “that” before “often”

##### **Response to Question 3:**

p26, line 32 insert “and that” after “justified,”

##### **Response to Question 4:**

p28, line 27 insert “amphibole” after “of”

p28, line 32 insert “the” before “consideration”

p. 28, lines 38-40. The statement that males and females are expected to have a similar response to asbestos is an argument against effect modification not confounding. Confounding would not be expected if exposure levels were the same for males and females.

##### **Response to Question 6:**

p 30: the references are in the footnote here; use a consistent approach

p31, line 8, change “which” to “that”

p31, line 21, insert “draft” before “assessment”

##### **Response to Question 7:**

p 32, lines 5–6: The sentences beginning “A key consideration...” are strange. How is whether the RfC is protective a key consideration for an uncertainty assessment? Of course, it’s a key consideration for the assessment generally, but what’s it got to do with uncertainty particularly?

p 32 ,line 9: Move the parenthesis and refer to the Minneapolis cohort in a consistent fashion across the document.

#### **Section 3.2.5. Inhalation Unit Risk (IUR)**

##### **Response to Question 1:**

At one point the comments refer to other possible exposure-response models for cancer, such as the Weibull and two-stage clonal expansion models for consideration. It is entirely appropriate to review these alternatives as a way of delineating the range of possible model uncertainty. However it is important to note that these models are at least partly dependent on assumptions about mechanism of action (about which the Panel concluded that there was only limited evidence in the specific case of Libby asbestos), and on data from other exposures to possibly related materials. The Agency followed the appropriate risk assessment guidelines in using an initial approach to exposure-response modeling which was, to the extent possible, free of such external assumptions and based solely on the data being considered. This is the proper approach for determining a quantitative risk estimate for this specific material. The extent to which the result is consistent with other data sets and with assumptions about mechanism is of considerable interest: it also informs the analysis of possible uncertainties. However the data available from the Libby cohort have somewhat limited power to inform questions about the time-dependence of tumor appearance, or to distinguish between possible mechanistic alternatives. This is particular because of the relatively short period of exposures for which reasonably precise estimates of exposure are available.

p33, line 30, change “that” to “they”

p33, line 43, change “Is there” to “Did EPA have a”

p35, line 5, insert to” before “use”

p 34, lines 5–6: suggest adding this paragraph:

“The full Libby data set, including hires before 1959, could be handled using interval statistics (Nguyen et al 2012; Manski 2003; inter alia) or other traditional approaches for data censoring in the predictor covariates, which are strategies to handle large Berkson-type measurement error (cf. Küchenhoff et al. 2007). It is inappropriate to use midpoint substitution (as described in section 5.4.6.1.2) that pretends poorly measured or missing predictors have some constant value. Interval statistics and traditional censoring approaches to measurement uncertainty would, in essence, replace point values with interval ranges. When the intervals are narrow, as they might be for 21% of the early hires for which jobs titles are available, there may be a good deal of recoverable information present. When the intervals are much wider, there would be accordingly less information. Whatever empirical information may be present, it is surely better than leaving out the data entirely, which in principle amounts to replacing them with intervals that are completely vacuous, from zero to infinity. This approach can produce an interval range for the final outputs, which would provide the explicit quantitative uncertainty statement as recommended by previous National Academy of Science reviews.”

p 34, line 8: Add ‘lung’ before ‘cancer’, otherwise it sounds like you’re saying mesothelioma is not a kind of cancer.

p 34, lines 11–12: I thought you were going to use the phrase “unless there is evidence to the contrary”. Is there not evidence to the contrary for asbestos?

p 34, lines 15–19: Maybe the phrase “do not with what probability model uncertainty about” could be contracted to “cannot be confident that”. The “and” on line 18 could then become “or”, or the rest of the text could be broken into separate sentence.

p 34, line 18: I guess “from of” should be “from”.

p 34, lines 24–25: We might be a little tougher. I suggest replacing “Is this assumption consistent” with “This assumption is not consistent” and “If not” with “Therefore”.

p 34, line 26: The m-dash (without spaces) should replace both the n-dash and the two hyphens.

p 34, line 41: I suggest adding another bullet:

“ • Consider developing an ancillary analysis of the full Libby data set, including hires before 1959, using interval statistics or other traditional censoring methods (*not* simple midpoint substitution).”

p 34, line 40: Is “sub-” a typo?

p 34: Should the SAB also recommend that EPA carefully consider what disclaimers or caveats should be ascribed to the final IUR? EPA made several assumptions in its calculations (linearized, annualized, independent, etc.) that some consider troubling for asbestos. Yet once an EPA calculation enters IRIS, it seems likely to be used in ways that treat these assumptions as facts. Shouldn’t there at least be a footnote somewhere cautioning would-be users?

### **Response to Question 2:**

p 35, line 21–22: Use m-dashes.

p 35 line 28: Add a comma or move “than it needs to”.

p 35, line 28-31: Reword for clarity, possibly by replacing “which” with “; such models”

p35, line 33, insert a comma after “occurring”

p 35, line 37: Italicize the parenthetical “n”; it is a mathematical symbol.

### **Response to Question 3:**

p 36 discussion of the independence assumption: I would judge that in the same cohort competing risks are more likely to induce negative correlation since an increase in events in one type is likely to result in a decrease in events in the other. This would imply that the independence assumption leads to a wider confidence interval than accounting for the dependence. Note that assuming a random effects model implicitly assumes there is a positive correlation between events.

p36, line 33, change “risk” to “risks”

p 36, line 27: I suggest inserting, before the sentence beginning “At the very least...”, the following sentence:

“Alternatively, a simple bounding analysis using the Fréchet disjunction inequality (1935) that makes no assumption about the nature of the dependence could be undertaken. This would reveal how large the impact of dependence might be.”

p 36, line 34: I suggest “More specifically” should be “If appropriate”.

### **Response to Question 5:**

p 37, lines 43–44: Use m-dashes.

p 38, lines 4–5: We should specify what *other* models might be also be included. I think “Cox” might be redundant. Maybe it suffices to say “Poisson models”.

p 38, line 5: The sensitivity analysis could actually be a full uncertainty analysis (albeit not a probabilistic one) if it were constructed to be *integrated*, *comprehensive* with respect to the variety of uncertainty sources identified as important, and *quantitative* in the sense that the ranges of values and model options are propagated jointly. Given that a probabilistic uncertainty analysis would be onerous at this point, do we want to recommend—as we explicitly did during the meeting in Washington—that they undertake a (non-probabilistic) uncertainty analysis with these features?

(page iii, lines 13–22: If any of the suggestions above result in a change to the text, consider the implications for the cover letter to the Administrator.)

p 38, lines 16–17: For readability, the clause “the assumption is valid” should be moved to immediately after the word “Thus,”.

## **Section 4. Long Term Research Needs**

p 39: Would it be useful to bring forward into this section the recommendation to develop a TEM protocol for PMCE fibers for RfC purposes?

### **References:**

p 40: If needed add the following entries:

Fréchet, M. (1935) Généralisations du théorème des probabilités totales. *Fundamenta Mathematica* 25: 379-387.

Küchenhoff H; Bender R; Langner I. (2007) Effect of Berkson measurement error on parameter estimates in Cox regression models. *Lifetime Data Analysis* 13(2):261–72.

Nguyen H.T.; Kreinovich V.; Wu B.; Xiang G. (2012) *Computing Statistics under Interval and Fuzzy Uncertainty*. Springer, Berlin.

Manski, C.F. (2003). *Partial Identification of Probability Distributions*. Springer, New York.

## **Appendix B**

Does this belong in the document? It seems more appropriate to ask a few individuals to endorse these rather than the entire Committee.

## **Appendix:**

### **Compilation of Individual Member's Comments (as of 4/27/2012)**

#### ***Dr. Bonner:***

##### 1. Executive Summary

Page 1, line 30: "Chrysotile asbestos fibers are very different from amphibole fibers in terms of their airborne concentration measurement errors and uncertainties, much lower biopersistence, clearance and translocation pathways, and health risks". This sentence could use some clarification. What is meant by 'airborne concentration errors and uncertainties'? Also, the term 'lower' precedes 'biopersistence', but is this also meant to convey lower clearance and lower health risks? It is important to be clear on this issue as chrysotile, while likely less carcinogenic and fibrogenic compared to amphiboles such as tremolite, is nonetheless associated with pleural disease and asbestosis.

Page 2, line 23: "While inhalation is regarded as the most physiologically relevant mean of fiber exposure in animals, there is no published study using this route of exposure in experimental animals". This sentence should be revised to clearly state "...there is no published study using this route of exposure for delivery of LAA to experimental animals." As it reads, one might conclude that inhalation studies in rodents have not been performed for any kind of asbestos, when in fact inhalation studies have been performed for amphiboles (tremolite, crocidolite) and chrysotile asbestos.

Page 2, line 26: "The relative potency of inhaled LAA should be compared with that of tremolite to add new information for refining the RfC for LAA." Should add "in rodents" just after the term 'tremolite' for clarification.

Page 3, line 6: "...evidence for the mode of action of LAA based on laboratory studies is weak". While true, the SAB also discussed the fact that there is abundant mode of action (MOA) data for other amphiboles such as crocidolite and tremolite that are likely similar to the MOA for LAA.

#### ***Dr. Ferson:***

Page 4, lines 2–4, and page 24, lines 28–31: A thoughtful uncertainty analysis might be able to rescue some of those estimates which are probably not valueless.

Page 6, lines 23–24, and page 32, lines 5–6: The sentences beginning "A key consideration..." are strange. How is whether the RfC is protective a key consideration for an uncertainty assessment? Of course, it's a key consideration for the assessment generally, but what's it got to do with uncertainty particularly?

Page 34, lines 5–6: I suggest adding this paragraph:

“The full Libby data set, including hires before 1959, could be handled using interval statistics (Nguyen et al 2012; Manski 2003; inter alia) or other traditional approaches for data censoring in the predictor covariates, which are strategies to handle large Berkson-type measurement error (cf. Küchenhoff et al. 2007). It is inappropriate to use midpoint substitution (as described in section 5.4.6.1.2) that pretends poorly measured or missing predictors have some constant value. Interval statistics and traditional censoring approaches to measurement uncertainty would, in essence, replace point values with interval ranges. When the intervals are narrow, as they might be for 21% of the early hires for which jobs titles are available, there may be a good deal of recoverable information present. When the intervals are much wider, there would be accordingly less information. Whatever empirical information may be present, it is surely better than leaving out the data entirely, which in principle amounts to replacing them with intervals that are completely vacuous, from zero to infinity. This approach can produce an interval range for the final outputs, which would provide the explicit quantitative uncertainty statement as recommended by previous National Academy of Science reviews.”

Page 34, line 8: Add ‘lung’ before ‘cancer’, otherwise it sounds like you’re saying mesothelioma is not a kind of cancer.

Page 34, lines 11–12: I thought you were going to use the phrase “unless there is evidence to the contrary”. Is there not evidence to the contrary for asbestos?

Page 34, lines 15–19: Maybe the phrase “do not with what probability model uncertainty about” could be contracted to “cannot be confident that”. The “and” on line 18 could then become “or”, or the rest of the text could be broken into separate sentence.

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Page 34, line 26: The m-dash (without spaces) should replace both the n-dash and the two hyphens.

Page 34, line 41: I suggest adding another bullet:

“ • Consider developing an ancillary analysis of the full Libby data set, including hires before 1959, using interval statistics or other traditional censoring methods (*not* simple midpoint substitution).”

Page 34, line 40: Is “sub-” a typo?

Page 34: Should the SAB also recommend that EPA carefully consider what disclaimers or caveats should be ascribed to the final IUR? EPA made several assumptions in its calculations (linearized, annualized, independent, etc.) that some consider troubling for asbestos. Yet once an

EPA calculation enters IRIS, it seems likely to be used in ways that treat these assumptions as facts. Shouldn't there at least be a footnote somewhere cautioning would-be users?

Page 35, line 21–22: Use m-dashes.

Page 35, line 37: Italicize the parenthetical “n”; it is a mathematical symbol.

Page 36, line 27: I suggest inserting, before the sentence beginning “At the very least...”, the following sentence:

“Alternatively, a simple bounding analysis using the Fréchet disjunction inequality (1935) that makes no assumption about the nature of the dependence could be undertaken. This would reveal how large the impact of dependence might be.”

Page 36, line 34: I suggest “More specifically” should be “If appropriate”.

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***Dr. Lippmann:***

Cover letter

Page line(s) change

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Ii	19	change “consider additional data and analyses for the” to “re-consider the need for an”
Ii	31	insert “and justification” after “discussion”

Executive Summary

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4	31	change “an important role” to “important roles”
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17	25	delete “and”
17	28	change “was” to “were”
18	10	delete the 1 <sup>st</sup> “effect”
18	12	delete “and”
18	20	change “The” to “Furthermore the”
18	23	change “discussed” to “noted”
18	25	delete the 1 <sup>st</sup> “effect”
18	34	change “include” to “included, along with”
18	40	change “a significant reduction” to “significant reductions”
19	19	change “LA” to “LAA”
19	33	change “LA” to “LAA”
19	41	insert “other” before “particles”
19	42	change “Berstein” to Bernstein”
20	3	change “interaction” to “interactions”
20	19	change “have” to “be”
20	18	change “EPA” to “SAB”
20	34	change “LA” to “LAA”
21	36	change “LA” to “LAA”
22	25	insert “only” after “leaves”
23	18	insert “amphibole” after “other”
23	33	change “LA” to “LAA”
23	40	change “directing” to “guiding”
24	11	change “LA” to “LAA”
24	15	change “LA” to “LAA”
24	33	insert “re-examining the” after “for”
25	29	change “but” to “but, if so,”
26	13	insert “that” before “often”

26	32	insert “and that” after “justified,”
28	27	insert “amphibole” after “of”
28	32	insert “the” before “consideration”
31	8	change “which” to “that”
31	21	insert “draft” before “assessment”
33	30	change “that” to “they”
33	43	change “Is there” to “Did EPA have a”
35	5	insert to” before “use”
35	33	insert a comma after “occurring”
36	33	change “risk” to “risks”

***Dr. Pennell:***

**Major comments:**

- **p. 5, lines 31-33:** The statement that males and females are expected to have a similar response to asbestos is an argument against effect modification not confounding. Confounding would not be expected if exposure levels were the same for males and females. The same comment applies to p. 28, lines 38-40.

**Minor comments:**

- **p. 4, lines 21-22:** I recommend revising to read “...the lower 95% confidence limits on the benchmark doses (BMDLs) are all within a factor of three.”
- **p. 4, lines 31:** delete the extra “g” at the end of “determiningg”
- **p. 4, line 38:** delete “in cancer modeling”; this section refers to models for LPT.
- **p. 5, line 2:** replace “recommends” with “agrees that”
- **p. 7, line 7:** replace “provides” with “provide”
- **p. 7, line 8:** replace “explains” with “explain”
- **p. 7, line 15:** add “e.g.,” before Weibull
- **p. 8, lines 12-13:** put a comma after “p-values” and a comma after “significant”

***Dr. Andrew Salmon:***

In my opinion, the draft report accurately summarizes the issues identified and concerns expressed by the Panel. These concerns are primarily with points of detail and requests for further explanation in some areas: the comments appropriately support the overall approach and conclusions of the Agency in their draft report.

I note that at one point the comments refer to other possible exposure-response models for cancer, such as the Weibull and two-stage clonal expansion models for consideration. It is entirely appropriate to review these alternatives as a way of delineating the range of possible model uncertainty. However it is important to note that these models are at least partly

dependent on assumptions about mechanism of action (about which the Panel concluded that there was only limited evidence in the specific case of Libby asbestos), and on data from other exposures to possibly related materials. The Agency followed the appropriate risk assessment guidelines in using an initial approach to exposure-response modeling which was, to the extent possible, free of such external assumptions and based solely on the data being considered. This is the proper approach for determining a quantitative risk estimate for this specific material. The extent to which the result is consistent with other data sets and with assumptions about mechanism is of considerable interest: it also informs the analysis of possible uncertainties. However the data available from the Libby cohort have somewhat limited power to inform questions about the time-dependence of tumor appearance, or to distinguish between possible mechanistic alternatives. This is particular because of the relatively short period of exposures for which reasonably precise estimates of exposure are available.

***Dr. Sheppard:***

Overall this draft represents a good summary of the key points identified by the SAB. My comments are divided into three parts: one overarching comment, detailed comments and specific suggested edits, and minor details.

Overarching comment:

1. I don't think it is possible to conduct "confirmatory" analyses for the RfC or to validate the primary analyses. Analyses of the full Marysville cohort and other cohorts will only provide additional supporting evidence to *substantiate* rather than confirm the RfC. They are providing evidence to support the RFC, not establishing its truth or proving it is correct.

Detailed comments:

- P i, l 43: insert an acknowledgement that this revised outcome measure may be important in future analyses but is not likely to change the primary Marysville subcohort analysis results. For instance, insert at the end of the sentence: "recognizing this change will have little impact on the current analysis but could be an important feature in future analyses."
- P i, l 43: Replace "confirmatory analyses" with "additional analyses to substantiate the RfC"
- P ii, l 16-20: I understand the recommendation to reevaluate uncertainty factors as discussed on pages 29-31 to apply to more than the database uncertainty factor.
- P iii, l 15: Delete "However". Replace "important" with "additional".
- P iii, l 17-18: Revise sentence to read: "The SAB recommends that this source of model uncertainty can be evaluated using a straightforward and transparent approach by estimating risks ...."
- P vii: Either LA needs to be added, or references to LA in the document need to be replaced with LAA.
- P 1, l 45: replace "confirmatory" with "additional substantiating"
- P 4, l 3-4: replace "measured exposures" with "exposure estimates based on measured

concentrations”

- P 4, l 10-11: After reading the longer discussion on page 24, the reason behind this statement is clear. As it appears alone it is less clear. Perhaps some additional explanation or a revision to this sentence will make it clear out of context?
- P 4 l 38: Why is there mention of “in cancer modeling” here? Remove or clarify.
- P 5 l 2-4: This sentence is unclear. Rewrite.
- P 5, l 41: insert “in this prevalence dataset” after “event”.
- P 8, l 30-31: reword sentence
- P 11, l 7-8: parenthetical comment appears to refer to LPT but is intended to refer to smoking.
- P 11, l 13: replace “validate” with “substantiate”
- P 12 l 1-3: It would be helpful to add a sentence to this bullet recommending the desired tone.
- P 17, l 21: Insert “exposure” at the end of the line
- P 17, l 29: Replace “confirmatory analyses ...” with “analyses to substantiate the subcohort findings” and move “has a clear and strong rationale” to line 27.
- P 17, l 44: Add a sentence like: “Similarly, because the Libby workers have both environmental and occupational exposures, this cohort should not be used for primary RfC analysis.”
- P 20 l 20-22: This sentence is a bit cryptic. Clarify who the SAB is agreeing with. Add more perspective about how this fits in with the rest of the response.
- P 22 l 4: Reword the parenthetical statement
- P 22 l 5: Do limitations include the possible/probably environmental exposures to asbestos?
- P 22 l 29: Clarify the “two cohorts” reference.
- P 22 l 44-45: Clarify the statement about smoking. Based on the implication earlier in the paragraph, it is not a confounder.
- P 36 discussion of the independence assumption: I would judge that in the same cohort competing risks are more likely to induce negative correlation since an increase in events in one type is likely to result in a decrease in events in the other. This would imply that the independence assumption leads to a wider confidence interval than accounting for the dependence. Note that assuming a random effects model implicitly assumes there is a positive correlation between events.
- P 39: Would it be useful to bring forward into this section the recommendation to develop a TEM protocol for PMCE fibers for RfC purposes?
- Appendix B: Does this belong in the document? It seems more appropriate to ask a few individuals to endorse these rather than the entire Committee.

Minor:

- P 7, l 8: “explain”
- P 7 l 37: This is the only place in the executive summary where we refer to our detailed response to a charge question. Should that be revised?
- P 8, l 12-13: move “than it needs to” to after “heavily”.
- P 8, l 21: delete “reference”
- P 14, l 37: four are listed

- P 18 1 12: delete “and”
- P 23 1 8: delete ”
- P 23 1 43: insert “by”
- P 30: the references are in the footnote here; use a consistent approach
- P 32 1 9: Move the parenthesis and refer to the Minneapolis cohort in a consistent fashion across the document.
- P 3 1 28-31: Reword for clarity, possibly by replacing “which” with “; such models”
- P 35 1 28: Add a comma or move “than it needs to”.