

**Preliminary Comments from Members of the Chartered SAB on the SAB  
Draft Report Review (August 30, 2012) of EPA's Draft Assessment entitled  
*Toxicological Review of Libby Amphibole Asbestos (August 2011)***

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## **Comments from lead reviewers**

### **Comments from Dr. Thomas Burke**

1. This draft review is very comprehensive and responds very well to each of the charge questions. Each question is addressed, including recommendations to improve the clarity and justification for findings and conclusions.
2. Within the limits of my expertise, I feel there are no technical errors in the report.
3. The draft is well written, but in some places there are contradictions that are confusing. Taken as a whole it appears to be a favorable review, with general recommendation for improving clarity and justification for key methods and assumptions. However there are many places where wording such as “erroneous and irrelevant” or “notable misstatements or omissions” that present confusing answers to the questions and appear to require new research initiatives. In addition, it is not really evident if the recommendations would lead to changes in the key findings of the document.
4. It is not clear just what the conclusions of the report are. There are an excellent set of recommendations made, but many require extensive reworking of the analyses, and a rethinking of challenging risk assessment issues such as uncertainty factor justification, critical study selection, and modeling of epidemiologic findings with limited exposure and sample sizes.

#### General comments:

The style and approach taken by the committee is very comprehensive. Each charge question is explored in great depth, including identification of many uncertainties associated with each step of the risk assessment process.

Almost each section begins with complimentary positive statements followed by a however and sometimes harsh and contradicting criticism. For example on page 11 “well written, logical and appropriately referenced..... extraneous and repetitive materials could be deleted” Mixed messages.

The report could benefit with editorial changes to present a more consistent format for each question and section. Some are very terse with bulleted recommendations others have recommendations nested within lengthy paragraphs.

The inclusion of many recommendations for additional research, including long-term research, may be outside the charge of the committee, and may reflect a misunderstanding of the role of an IRIS assessment.

Emphasis of the key finding and a conclusion (“bottom line”)for each charge question would enhance the report and make it clearer just what is expected of the Agency to finalize the document.

## Comments from Dr. Michael Dourson

### 1. Were the charge questions adequately addressed?

I agree that the charge questions were adequately addressed for the most part. The following points, however, should be reconsidered by the panel:

Page: 18, line 42. The panel's suggestion to combine effects does not seem unreasonable, but combining outcomes also means combining background incidences. Do we know such backgrounds for other endpoints? For example, an assumption of 1% incidence each for all 3 endpoints, which would be consistent with EPA's assumption for 1% for 1 endpoint (LPTs), may not be appropriate.

Page: 21, line 19. I would be more comfortable with the panel's conclusion, if it requested EPA to conduct a more formal MOA-key event analysis using its current guidance (EPA, 2005) and that of the International Programme on Chemical Safety (IPCS), developed in part by EPA senior staff (numerous publications here). We appear to have sufficient understanding of asbestos to analyze several possible MOAs, including direct mutagenesis, formation of reactive oxygen species, immune suppression, inhibition of spindle formation, and regenerative regrowth due to cell necrosis. Key events for these various MOAs should be sought and analyzed within the established frameworks that others are now routinely using. Carcinogenesis from foreign body implants, a well-known phenomenon, should also be explored. The physical characteristics of LAA and the type and timing of tumor appearance are also highly relevant in the determination of MOA, as per EPA (2005) guidelines. Such a formal MOA analysis would be preferred, I should think, to statements that the mechanisms by which LAA produces malignancy and fibrosis are complex and likely multifactorial.

Page: 24, line 12. EPA (2005) cancer guidelines specifically caution against asking for a "mechanism of action" for cancer evaluations. Rather EPA guidance dictates use of the Mode of Action (MOA) concept. Thus, the relevant question for the panel should be: are the data sufficient to determine one or more MOAs, or can the available data be used to exclude one or more MOAs. This is why a more formal MOA analysis would be helpful, as per the previous comment.

Page: 26, line 38. The panel's thoughts here are spot on. In addition to the visual fit, one of EPA's criteria suggested by the panel, EPA also has 3 additional criteria for BMD model selection. These are a model's p-value (where models with values of greater than 0.1 are selected), scaled residuals in the area of the BMCL (where models with absolute values of 2 or less are selected) and the ratio of BMC to BMCL (where models with lower values are selected). These criteria should be similarly analyzed.

Page: 27, line 8. This is yet another good suggestion by the panel, and if taken up, would then necessitate some consideration for reducing the default uncertainty factor of 10-fold for within human variability. This is because this uncertainty factor accounts for human variability as does reduction in the Benchmark Response (BMR) used to determine the point of departure.

Page: 31, line 24. I do not understand the panel's comment here, probably because I do not understand epidemiology terms. The terminology that EPA uses for this conversion, "fibers/cc-year," can be interpreted as "fibers per cc per year," similar to the commonly used

toxicological term "mg/kg-day" which is interpreted as "mg per kg per day." Is "fibers per cc per year" what is meant? If not, what does the term mean?

Clarification of this terminology is important since one either then divides or multiplies by 60 or 70 years, or uses an uncertainty factor to adjust for partial lifetime exposures.

Page: 32, line 29. I would be more comfortable with the panel's conclusion, if it could convinced me that some other effect might occur up to 10-fold lower than the BMCL of the chosen critical effect of LPT. This evidence might be theoretical (e.g., expected asbestos distribution and accumulation in another organ) or actual (e.g., community data indicate more immune suppression occurring than lung effects). Since the lung is already known to be impacted early in the pathogenic process by this lung-accumulating chemical---correct?---the evidence for another, more sensitive effect, should be compelling. EPA's justifications for this factor are not inappropriate scientific speculations, but the choice of 10-fold does not followed EPA (2002) guidance, nor practice. For example, lack of chronic duration is not an appropriate justification for the database uncertainty factor, as the SAB panel correctly points out. This uncertainty is addressed in the factor for subchronic to chronic where EPA has judged that a value of 1-fold is appropriate.

Page: 34, line 20. I only scanned the EPA text, but is the panel stating that EPA has only one study from which to select in order to determine the RfC? Or is it that multiple studies exist and only 1 has been selected? If it is the former, then do the recently published studies on two other cohorts, suggested by the panel for EPA to consider, obviate this concern? If it is the latter, this is the current practice by risk assessors everywhere.

2. Are there are any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report?

I would value an enhancement to the Administrator's letter on page 2, line 8, along the lines of requesting a more formal MOA analysis using EPA current guidance and that of the International Programme on Chemical Safety (IPCS). The specific text to be enhanced is:

- The SAB agrees that the weight of evidence for LAA supports the descriptor "Carcinogenic to Humans by the Inhalation Route" in accordance with EPA's *Guidelines for Carcinogen Risk Assessment*. The SAB views the mode of carcinogenic action of LAA as complex, and therefore the default linear extrapolation at low doses is appropriate.

3. Is the draft report clear and logical?

I agree that the draft report is clear and logical. The following items might be seen as enhancements:

Page: 2, line 9. It appears that several of the expert public comments disagree with this judgment of the critical effect as Localized Pleural Thickening (LPT). What is the panel's response, for example, to the comments of Dr. Moolgavkar on this topic?

Page: 11, line 33. Do the "numerous publications on the mode of action of other amphiboles" suggest to the panel that the formation of reactive oxygen species, immune

suppression, and/or inhibition of spindle formation are likely Modes of Action (MOA) for the development of lung tumors or mesothelioma? If so, how likely are these MOAs to be operating with Libby Amphibole asbestos (LAA)?

Page: 17, line 31. An assumption was made by EPA for background incidence of LPTs of 1%, I believe. Does the panel recommend that EPA obtain a better estimate of background for this group, perhaps from hospital data in this area?

Page: 17, line 43. The panel raises another good point here. The modeling of LPTs from the Marysville cohort should be consistent with modeling of LPTs from other cohorts that might have less accuracy or exposure precision. Has EPA done this? If not, is the panel recommending that it does?

Page: 18, line 27. Does this paragraph represent the panel's response to public comments of Dr. Moolgavkar regarding LPTs as the critical effect for RfC development? If so, please acknowledge these comments. If not, what is the panel's response?

Page: 20, line 7. The panel's description of in vitro assays would enhance EPA's text on MOA analysis. Does the panel feel, however, that similar in vitro assays from other asbestos forms can shed insight with LAA? The MOA for cancer does not appear to be mutagenic, both from the available in vitro data on LAA, and from LAA's physical characteristics. An analysis of this mutagenic MOA as per EPA or IPCS guidelines would likely yield a negative finding, suggesting another, or multiple other, MOA. This points again to the request for a more formal MOA analysis.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

With the considerations of suggestions made in this review, and those of other SAB reviewers, this report will be a very important, and scientific credible response to a pressing Agency problem. Public health will be well served when EPA's report is revised.

## Comments from Dr. Gina Solomon

### Comments by Gina Solomon on the Toxicological Review of Libby Amphibole Asbestos (August 2011)

9/21/2012

1) *Were the charge questions to the committee adequately addressed?*

Overall, it appears clear that the committee put a lot of work into this review, and they presented a lengthy and detailed report. The committee did address all the charge questions, although sometimes the responses to the questions were “muddy” and the reader had to really search the text for the actual response to the question. The fact that the responses to the questions were somewhat buried in the report made the document difficult to read and somewhat confusing. This was a particular problem in the executive summary, which needs some work to make it more readable.

I also see a number of areas where the committee may have gone beyond their charge and made recommendations that – although they would be of academic interest – may not significantly improve the quality of the IRIS assessment. In particular, the committee recommended a considerable amount of additional modeling and analyses, addition of a slew of references, more text, and presentation of a number of additional tables of data. The committee did not justify why these recommendations are necessary, or exactly how they would contribute to the scientific basis of the actual numbers in the IRIS assessment. As a reviewer, it was very hard for me to see the reasoning behind many of the committee’s recommendations for additional work. In at least one area (analysis of new data from other cohorts to support derivation of the RfC), I only understood the rationale for the recommendation after reading the public comments, but not from the report itself.

In the end, the plethora of recommendations for additional analyses and additional data tables created confusion. When I read the review, it was very confusing to discover that on the one hand, the committee appears to support every single one of EPA’s major substantive assumptions and decisions (ie. the decision to calculate an RfC, use of LPT as a critical endpoint, the choice of cohorts for both the non-cancer and the cancer calculations, the cancer classification for LAA, the decision to use a linear model, etc). Yet, the committee wrote dozens of pages of critique that appear to this reviewer to be quibbling about fairly minor issues of presentation around the margins. As a result, the major conclusion that “there are many areas that need more consideration...” (cover letter, line 26; executive summary p. 1, line 12) is confusing and not very well supported by the overall substance of the report.

Therefore, in my view, the committee should do three things: (1) determine which of the recommendations for extra text, tables, references, and analyses are actually important to improving the basis for the RfC and the IUR numbers, and focus the report on those recommendations; (2) delete or de-emphasize recommendations that – although they might be interesting academic efforts - go beyond what is really necessary for improving the RfC and the IUR numbers; and (3) reassess the cover letter and the executive summary to clarify the fact that the committee supported all of EPA’s major assumptions and decisions, since the current version of the letter and executive summary sound significantly more negative than the actual content of the review seems to warrant. Of course, if I am misunderstanding the fact that the committee

supported all the major elements in the IRIS assessment, then the report would need to be rewritten in a somewhat different way to better clarify the basis for the dissatisfaction and help the reader understand the major problems.

2) *Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?*

The section on localized pleural thickening (LPT) should be strengthened. This is clearly a controversial issue, so the committee needs to demonstrate that it gave careful consideration to the arguments on both sides. In particular, the sentence on page 18, lines 36-37 is weak and should be rewritten and clarified. It's not appropriate in this context to say that "the SAB believes that large cohort studies have shown significant reduction in lung function, including diminished diffusing capacity and vital capacity associated with LPT" (emphasis added); this is an important statement that is either true or false and not a matter of belief. If it can't be substantiated it should be deleted.

The section on Selection of Uncertainty Factors on p. 32 has a statement in lines 19-21 that "arguments have been made that a factor of 10 is not sufficient to cover all sensitive sub-populations, especially children" (emphasis added); this statement requires a reference, and it really shouldn't be in the passive voice. Perhaps the committee is referring here to data on the range of sensitivity within the population to other pulmonary toxicants that cause chronic oxidative stress such as ozone? If so, that should be clarified. It's fine to keep this point in, but it should either be referenced or clarified.

The section on the use of laboratory animal and mechanistic studies is also a bit confusing. For example, the statement: "An understanding of the basic carcinogenic mechanisms of LAA will be extremely useful in deriving a realistic risk assessment" (p. 4, lines 1-2) seems a bit bizarre; research on various forms of asbestos has been ongoing for many decades and there's an almost overwhelming amount of information on carcinogenic mechanisms. The problem is that there are likely multiple relevant mechanisms, and that despite all the data there's no clear scientific consensus on mechanisms of action. This statement and the following recommendations make it unclear what the committee is recommending. It almost appears that they are recommending more research "to fill the gaps in knowledge" (p. 4, line 3) prior to finalizing the assessment. I don't think this is what the committee intends to say (or at least I hope it isn't, since clear answers to this ages-old question aren't likely to emerge anytime soon). So this section needs to be corrected and clarified.

The response to the question on confounding by smoking (p. 37-38) fails to refer to the data on synergy between asbestos exposure and smoking with regard to lung cancer risk. There's quite a lot of literature on this, although I don't know if any of it is directly on LAA, rather than on other forms of asbestos. At any rate, it seems like it would be appropriate to at least entertain the hypothesis that there may be a synergistic relationship, and discuss how that might affect the analysis. As a reader who knows something about asbestos, but very little specifically about LAA, this seemed to be a significant omission to me.

3) *Is the draft report clear and logical?*

See above for general comments. Overall, the report is densely written, major recommendations are not separated from more minor suggestions, and the rationale for the recommendations is not presented clearly in the body of the report. These problems carry through into the executive summary, which is quite confusing (more details on that below). Only the cover letter seems to prioritize some key issues. These problems aren't fatal, but they do make the report more confusing than it needs to be for the reader.

4) *Are the conclusions drawn or recommendations provided supported by the body of the draft report?*

The cover letter is remarkably clear given the confusing nature of the report itself. However, as stated above, the committee should rethink the overall tone of the conclusions given the fact that they appear to support EPA's judgment in about 90% of areas in the assessment, and seem to be quibbling about things that aren't likely to change the final results. Does the committee really think that "there are many areas that need more consideration?" Does this bottom-line conclusion really comport with what the committee seems to be saying in the report itself?

The executive summary requires more work than does the cover letter. I was utterly incapable of deciphering what the committee was trying to say about minerology (p. 1, lines 18-30), and reading the response to charge question 3.2.1 didn't help much; it appears that the main issue here was with various minor details, and with shortcomings of microscopy. The latter point is important, but is lost in all the additional minor text and totally falls out in the executive summary.

The section discussing recommendations regarding the RfC derivation fails to mention the small number of workers in the Marysville cohort with LPT as the rationale for recommending additional analyses in other cohorts; this rationale is fairly compelling, but the reviewer only understood it after reviewing public comment letters, not from the committee's report itself. Most of the text on "Use of Animal and Mechanistic Studies" on p. 2, lines 27-37 appears to contribute very little and be devoid of significant recommendations. This could be deleted. The section on Weight of Evidence Characterization at the bottom of p.2 starts with saying that the "SAB agrees...." but then lists a number of things that don't really support that conclusion and in fact appear to undermine it (ie. "the number of mesothelioma cases is small", "the case series in the community...does not provide the same level of evidence..."). The reader ends up confused about the real justification for the committee's concerns here. It's also odd to see such uncertain language about the carcinogenicity of asbestos, given the vast database on the carcinogenicity of this substance.

There is a lot of repetition in the executive summary on p. 5, with repeated mentions of the committee's preference for the Hill model (line 5, line25) which don't need to be repeated; and concerns about the use of time since first exposure (TSFE) (lines 18-19, 42-45) which are confusing because they appear to be somewhat contradictory. In particular, the recommendations around TSFE should be clarified in the executive summary.

The section on Selection of Uncertainty Factors is fairly clearly explained in the executive summary, but these points are not well-captured in the cover letter. The committee should mention in the cover letter bullet #4 the suggestion that EPA consider a factor higher than 1 for UFL.

Overall I do not think that the issues with this report are significant enough to merit returning it to the committee for major work and bringing it back before the Board for a second Quality Review. Instead, I think that there are some revisions and clarifications that would address my concerns and that the report could then be re-reviewed either by the Chair or by a designated group of Board members.

## Comments from Dr. Daniel Stram

### 1. Were the charge questions adequately answered?

Overall the report appears to be very thorough, although most of this is well out of my field of expertise. I have focused most of my review on those parts where I could contribute something useful; such as the implications of the risk analysis models chosen by EPA. In some cases more useful and insightful comments on the draft assessment could have been made.

**In discussion of the clarity of the mineralogy**, it is indicated that section 2.2 "needs significant modification". Right now there is only one sentence provided that indicates what the reviewers are pointing to in general terms, after that there several very specific suggestions about terminology and model formula, but this wouldn't seem to add up to "significant modification" ; This recommendation should be expanded on.

**Selection of localized pleural thickening in humans as the critical effect for RfC.** The reviewers agree with the EPA that LPT is the correct endpoint. Is LPT simply a convenient effect because it was available, associated with lung function, and not confounded by smoking? Ideally would LPT be used instead of lung function or other measurements if smoking was not a confounding factor? Is lung function loss due to fiber exposure in non-smokers highly associated with LPT or are there many non-smokers with exposure-related loss of lung function but not LPT? If the former then I would feel more comfortable with LPT. Are there other measurements or outcomes that would be used, if available, and if not confounded by smoking? The review recommends on page 18 (lines 19-25) that a further literature review should be provided in support of the choice of LPT. Is there any likelihood that such a review would not support the choice of LPT? I.e. is this recommendation simply given for the sake of completeness of the report, or is there uncertainty about the usefulness of LPT in the mind of the reviewers? This needs clarification

On page 20 lines 7-22 a "wish list" of additional in vitro assays is discussed, is this really relevant to the review of this report? If there are important studies that have not been evaluated in the EPA report this is be one thing, but if they have not been done would it be worth waiting for this report until such work is performed?

The discussion of charge questions (page 20 line 24-page page 21-line 36) concerning the overall weight of evidence for carcinogenicity of LAA (despite the limited direct evidence) as well as the lack of clear mode of action (and hence default linear dose response) seems convincing and logical.

**Critical endpoint and study selection for IUR determination:** The review comments on the choice of lung cancer and mesothelioma mortality as the appropriate endpoints for derivation of the IUR as "clearly appropriate" and "are scientifically supported and clearly described". While I am in agreement with these statements it would make sense to indicate whether other cancer effects have been hypothesized and if there is any epidemiological evidence of a relationship with other cancers. It is unclear for example (page 23 lines 8-11) whether the reviewers are recommending that the assessment include laryngeal or ovarian cancer in any analyses.

The review notes the potential problems with death certificates for ascertainment of these endpoints and the likelihood that mesothelioma in particular may be undercounted. Based on typical times to death from diagnosis the number of incident cases of lung cancer that would have gone uncounted (as of end of follow-up) should be small although this is not directly discussed.

The reviewers indicate that effects of LAA on mesothelioma (and the IUR) might be undercounted for two reasons, the first is problems with diagnosis (especially in the past) and the second is that follow-up times are not as long as the 60 or more years detected in other studies. Since an absolute increase in risk to 1% is used in the definition for the IUR of mesothelioma the first cause of undercount is valid. However the effect of limited follow-up on the IUR) is a bit more complicated. The models used to estimate excess involve estimation of excess risk at various ages and will do extrapolation based on the type of model used. The extrapolation to older ages or times since exposure is inherently variable but it is not clear that an underestimate of the effects of lifetime exposure is necessarily expected.

The reviewers agree with the EPA assessment's choice of the Libby cohort for IUR determination. The statement that "additional follow-up of both the occupationally and environmentally exposed populations would be helpful" appears. The intent of this is not clear. Is this simply a suggestion for future research or is there follow-up data available now that could be included in the assessment? Presumably this is a suggestion for future work, but this should be clarified. The review suggests that other LAA-exposed cohorts be summarized (page 23 lines 25-27) in a summary set of tables or figures. It would seem reasonable to include some information about other asbestos-exposed cohorts (for comparison's sake) as well.

### **Exposure response modeling for RfC determination**

I think there is some lack of clarity in the discussion by the reviewers of exposure response modeling, but this is mainly because of lack of clarity in the EPA assessment concerning the models that are used particularly the analysis of the full Marysville dataset with exposures from 1957.

For the post-1972 analysis the EPA assessment focuses on models with plateau effects of the general form

$$P(LPT=1) = bkg + (\text{Plateau} - bkg) f(x)$$

where  $x$  is cumulative dose and  $f(x)$  is monotonic ranging from 0 and 1 (e.g. of logistic, or normal CDF form etc.) and various transformations of dose (log unlogged, etc ) are considered. The main model used is the Michaelis-Menten (M-M) model with  $f(x) = x / (\exp(-a) + x)$ . This model has a slope equal to  $[\text{plateau} - bkg] * \exp(a)$  at zero dose and a slope of zero at  $x = \text{infinity}$  (e.g. is non-linear). The parameter  $a$  thus parameterizes the (starting) slope (change in probability per unit dose) in the model. In order to keep this same general form of model in the analysis of the full cohort the EPA assessment makes the plateau parameter a function of time since first exposure. One can speculate about what is really going on in these data; it seems likely that this change is used to model the observation that there is little or no effect of age for the unexposed but a very large effect of age in the heavily exposed and a lesser effect of age in the less heavily

exposed. This is my interpretation of Figure E-3 of the EPA assessment based on the assumption that most exposures start at around the same age.

When TSFE is used to modify the plateau then since the TSFE is always zero for the unexposed, there is no age dependency in the unexposed (and the strength of the age effect increases with dose). Thus the EPA assessment, by using TSFE as a modifier of the M-M plateau, incorporates this feature directly into the model.

Choosing (as in the EPA assessment) TSFE as a modifier is very awkward however, since intensity of the first exposure is not considered, a small first exposure near zero starts the TSFE "clock" as much as a large first exposure. Generally also it is harder to think about the predictions that are being made about models that include TSFE compared to ones that simply include age dependencies, and TSFE should only be used for a good reason.

There are several other, simpler, ways to modify the M-M model to include this general form of age dependency by only including age at exam (and not TSFE) in the model. For example if the plateau is made a function of age, such as logistic i.e.

$$P(LPT=1) = bkg + [\text{expit}(c+d*\text{age}) - bkg] [x / (\exp(-a) + x)]$$

then there will be no age dependency if  $x$  is 0 and a monotonic increase in the age dependency (parameters  $c$  and  $d$ ) as  $x$  increases. Another alternative is to make the parameter  $a$  a function of age. This would increase the rate (in dose) at which the plateau is reached with age, but not allow for higher plateaus for older ages. However if one set the plateau to one (or to a value closer to one) then over the range of actual doses the basic phenomenon (of larger age effects in the more heavily exposed) would still be exhibited by the model.

The review committee suggested using residence time weighted (RTW) dose as a possible alternative to TSFE, i.e. replacing cumulative dose  $x$  with RTW dose in the M-M model. This makes sense as well, again the plateau would have to be increased (which is also a suggestion of the reviewers) so that this model would fit the full dataset. Any of these changes would give a more easily interpretable model and the fit of such simpler models could be explored. Overall a clearer discussion by the reviewers of the practical implications involved in using either TSFE, age, or RTW dose, and in particular the age effects that are being implied, would be helpful.

It is not clear from the EPA assessment why these age effects (TSFE) effects do not seem to be present in the post-1972 data. This may be a power issue (due to smaller number of events or a smaller range in age at time of examination in the post 1972 cohort compared to the full)

2. Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report?

I did not identify technical errors as such. Some clarifications of use of models for IUR and RfC are described above but in general I find that the text provided is accurately technically (to the extent that I could judge)

### 3. Is the draft report clear and logical?

The draft report is structured according to the charge questions and provides answers to each one in turn. Overall the report reads well throughout

### 4. Are the conclusions drawn or recommendations provided supported in the body of the draft report?

I am in agreement with the recommendations that I was able to evaluate. For example I agree with the reviewers that the modeling procedure described is generally valid scientifically but should be enhanced in the ways suggested by the committee, for example by including graphical depictions of the data. The committee suggests using the dichotomous Hill model which differs from the M-M model in that cumulative dose  $x$  is replaced with a power of cumulative dose ( $x^b$ ) with  $b$  estimated from the data. It is not clear to me that this added complication (of estimating  $b$ ) provides very much flexibility. The comments of the reviewers (page 27 lines 1-3) that the benefits of this model is that

"..., the dichotomous Hill model is attractive because it allows estimation of an exposure slope parameter, allowing the exposure effect to scale as covariates are added, the exposure metric changed, or the plateau fixed."

Is not very clear to me that these are really very helpful. The M-M model is a special case of the Hill model and unless power transformations of dose are really needed to model the shape of the exposure response I would prefer the M-M model as easier to interpret. To me a change in the power  $b$  parameter as covariates are added to the model complicates the interpretation of the effect of those covariates. Later on (page 28 lines 12-150) it is said that using the dichotomous Hill model allows a slope parameter to be estimated. But the same is true for the M-M model, since the parameter  $a$  is estimated from the data. I do agree with the committee that a fixed plateau is preferable; I wonder in fact whether a plateau different than 1 (see above) is really desirable or preferable.

I agree completely with the reviewers that the choice of a 10 percent extra risk as the benchmark criteria (BMR) needs further justification: This is an absolute risk, not a relative risk, so that this is a much larger risk benchmark than implied by a 1 or even 10 percent increase in relative risk for an outcome that is moderately rare among the unexposed.

The suggestions made in 3.2.5.4 (page 29) regarding covariates are generally good, however, the effects of covariates in the data from Marysville seem to be very limited; with only smoking (not generally thought of as a cause of LPT) being anywhere close to statistical significance. I would recommend focusing only on smoking. In contradiction to the reviewers (and the report) I don't think that the BMCL most directly applicable to all members of the population is the one derived from a model without covariates such as smoking. Since smokers predominate in the Marysville data the Marysville BMCL using no covariate adjustment would reflect smokers risks not the population as a whole. Calculating BMCLs for smokers and BMCLs for nonsmokers and then weighting by the proportion of smokers and nonsmokers in the population would be the approach that would give the best estimate for the BMCL for the entire population.

I don't like the idea (same section) of estimating a risk score (for non-exposure related variables) and then using this as a single adjustment variable in the later modeling. As a general regression method it doesn't seem correct first fit a model with variables A and B in the model, then make a risk score for A and B combined and putting in the risk score when fitting variable C. This does not estimate the joint effects of A, B, and C properly (compared to putting each of A, B, and C in the model). The reviewers should further justify the approach. The idea of producing separate estimates of the BMCLs for subgroups defined by covariates is reasonable (although I think the only needed covariate is probably smoking), but this can be done from the results of the full model (exposure and non-exposure covariates).

The comments on page 30 on requiring EPA to examine alternative approaches to including the TSFE in modeling are reasonable, however I think the committee should go further and recommend examining other age-related variables as well as TSFE and RTW dose. The EPA should certainly examine age at exam as a modifier of the plateau and/or of the "slope" parameter  $a$  (after increasing the plateau) for example. Age at initial exposure (rather than TSFE) should also be considered as a modifier of the plateaus and "slopes" in the M-M model. TSFE and Age at initial exposure are somewhat difficult to interpret for extended exposures, so I think the main question is whether RTW weighted dose models are helpful compared with models that just use age at examination as a modifier (discussion above). If age is very important (which seems clear in the full cohort data) then the benchmarks derived from the full cohort need to be based on specific (presumably advanced) ages, where the dose response appears to be the strongest.

Exposure-dependent sampling. The reviewers (page 30-31) indicate that "The exposure dependent censoring discussion is based upon results from Rohs et al (2008) that inappropriately separated non-deceased non-participants from the remaining non-participants. Once all non-participants are combined there is no evidence of exposure-dependent censoring". These comments should be expanded. My reading of the Rohs et al article is that individuals with higher exposure (those hired before 1973) are more likely to participate than those hired after. Why is this not "exposure dependent sampling". In general exposure dependent sampling shouldn't bias regression results by themselves. Of much greater concern is differential sampling, i.e. sampling dependent upon the outcomes being analyzed. Exposure dependent sampling will bias some comparisons such as the risk in the upper and lower quantiles of exposure since the quantiles will not be the same in the sample as in the population as a whole. However this type of effect doesn't seem to be extremely important for the purposes that EPA is making of these data.

## Comments from Dr. Peter Thorne

### *1. Were the charge questions adequately addressed?*

- There were 23 questions posed including 2 general charge questions and 21 specific questions, many with multiple parts. All 23 charge questions were adequately addressed. The answers to these questions make up 32 pages of the Draft Assessment. This extensive, deliberative and carefully written SAB Draft Report states that the SAB agrees with the overall conclusion that the weight of evidence for LAA supports the descriptor ‘carcinogenic to humans by the inhalation route’ based mostly on occupational epidemiology reinforced by animal studies, while the evidence to identify a mode of carcinogenic action for LAA is weak. The Report identifies many areas for further consideration to strengthen the scientific basis for the LAA risk assessment and these are outlined and justified in some detail. The draft report also offers constructive suggestions to improve the clarity of the document. Importantly, the SAB Draft Report provides significant input to the process for development and justification of toxicity values for the IRIS database including the chronic inhalation reference concentration (RfC) and the Inhalation Unit Risk (IUR). The SAB Draft Report supports use of radiological evidence of localized pleural thickening (LPT) as the proper adverse effect for deriving the RfC citing its specificity and lack of confounding by smoking history. This is clearly described and well justified. Many concerns are raised (on pages 4 to 5) about exposure modeling in the Marysville, Ohio plant cohort dataset. Issues raised appear justified and are adequately explained, many can be addressed by straightforward evaluation of the raw data, testing alternative model assumptions and further description of decision criteria for model selection.

### *2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?*

The report is carefully written and extremely thorough. There are several issues that should be discussed by the SAB.

- (top of page 4): The SAB Draft Report recommends that studies be undertaken to elucidate physiological pathways to enhance the understanding of the carcinogenic mechanisms of LAA suggesting, among others, animal inhalation studies with LAA. Since the weight of evidence is sufficient to label LAA as a known human carcinogen, and inhalation studies have been done using tremolite, I question whether such studies would add to the risk assessment enough to justify their cost. In my opinion the SAB Draft Report does not establish a compelling rationale for such a study.
- (page 6, lines 6-9; page 31, lines 24-28; page 34, line 18): Perhaps I don’t thoroughly understand this issue. It would help the reader to provide the rationale for using a 70 yr lifetime instead of a 60 yr + 10 yr lagged exposure. What is meant by “given that the exposure metric is arbitrarily related to the prevalence data...”?
- (page 9, lines 23-27; page 15, lines 28-40; page 34, lines 34-40; pages 42-43, lines 31-41 and 1-3): Since PCM resolution is low compared to TEM an equivalent method would appear to involve exclusion of amphibole fibers below a defined diameter and length. Presumably this

would be used to adjust older PCM data to estimate total LAA exposure based on applying a multiplier derived from modern TEM methods. However, this would only be valid under the assumption that changes in production techniques, ventilation controls, or materials handling have not changed since the time the PCM-based exposure assessments were performed. This further requires that the particle size distribution of LAA fibers in air have remained the same. The development of such a retro method is recommended for EPA study and is also highlighted on page 42-43 as a long-term research need. However, the value of this for the LAA risk assessment is not stated. Nor is there a description of how such data would be applied to the exposure data in this cohort. This is described in four sections of the Draft Report which seems excessive, yet it is not convincing (*at least not to me*).

- (page 15, line 43): “resolution” should replace “magnification” as the descriptor for the improvement of electron microscopy over phase contrast microscopy.

### ***3. Is the draft report clear and logical?***

The draft report is clear in most sections and flows logically. There are a few areas where the clarity could be further enhanced.

- The executive summary captures the essential content and issues in the narrative response to the questions posed. However, at 9 pages, the Executive Summary seems too long. The discussion of modeling issues in the Executive Summary could be shortened as these issues are thoroughly described in the body of the report.
- (page 6, lines 19-23): The SAB recommends the addition of human data from community LAA exposures around an expansion plant in Minnesota and data from cohort studies of other amphiboles. This suggestion, if acted on, negates the suggestion on page 6, lines 41-42 to include an additional uncertainty factor for using a single study. This should be pointed out.
- (page 8, line 24-26; page 38, line 8-12): What is the evidence to support negative confounding of COPD and asbestos exposure? This should be explained (or deleted if there is none).
- (page 9, line 12-13; page 22, lines 30-33): Regarding the recommendation to calculate an SMR for the Libby Cohort based on Montana and U.S. data - why is this recommended and how would this be used in the risk assessment? For this cancer risk assessment, the major cohorts are identified as the Libby Workers, the ATSDR community study, and the Marysville, Ohio plant. The primary basis for the cancer risk assessment is the Libby Workers cohort (N=991 total and N=285 with exposure data). This cohort establishes the IUR based on lung cancer and mesothelioma. The Marysville plant is used in the non-cancer risk assessment to establish an LPT-based RfC (N=434 total with N=118 employed after 1972 with exposure and x-ray data). There is also discussion of the ATSDR Libby, MT community study (N=7307) but little is mentioned about that in the SAB Draft Report.
- (page 11, lines 17-19): “... that appears to offer nothing new, with no detailed exposure information and an exposed population, respectively.” The meaning of this sentences in unclear.

- (page 11, lines 32-36): The suggestion to consider human and animal data on other amphiboles for information on mode of action and model selection is appropriate and points out a deficiency in the document. The fact that LAA is 6% tremolite also supports this. Is there anything to be learned from comparison of the physicochemical characteristics and *in vitro* activities of richterite and winchite to tremolite?
- (page 25, lines 17-32): Regarding use of geometric mean (GM) vs. arithmetic mean (AM) vs. minimum variance unbiased estimation (MVUE): The SAB Draft Report states that use of the GM imparts a bias in that it decreases the significance of the highest exposures. If the industry targeted the “most exposed” workers for sampling, their use of arithmetic mean or MVUE would overestimate the exposure of average workers. Since there is apparently no information on the intent and design of the workplace exposure assessment, it is unclear how it can be determined which measure of central tendency best represents the true distribution of exposures.
- (pages 27-28): Regarding alternative modeling approaches to derive a point of departure (POD) for derivation of the RfC. This very thorough set of recommendations regarding derivation of the RfC should help EPA develop a defensible RfC value. The suggestion to use residence time weighting seems like a good idea (page 28, line 9). The rationale for using time since first exposure (TSFE) as a covariate versus date of first exposure is that earlier exposures are likely to have been higher than more recent exposures and TSFE doesn’t necessarily capture the earlier exposures. However, since neither TSFE nor date of first exposure are metrics of exposure duration it makes more sense to apply residence time weighting. An important question is are there data available for LAA to facilitate assigning meaningful weighting to the exposures?
- (page 35, lines 5-6): “Use TEM to identify and count asbestos fibers longer than 5, 10, and 20 um in air samples for RfC purposes. The Report should state to what air samples this refers. It was not clear if there are any air samples available to carry out this recommendation.
- (page 36, line 1-4): This statement sounds pejorative? I suggest that it be softened.
- (page 36, lines 9-22; page 37, lines 15-16): This is an excellent point. SAB should have a specific recommendation on what to do to address left censoring as an alternative to midpoint substitution. Options include use of Monte Carlo methods, Tobit models or some other imputation method).
- There were some minor typos I noticed:
  - page 26, line 24: “asTroy” should read “as Troy”
  - page 35, line 17: insert a line between paragraphs
  - page 42, line 5: “p > 0.1” should read “p < 0.1”
  - page 42, lines 7-8: “for the estimating” should read “for estimating”

**4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?**

Yes, the draft report does an excellent job of explaining the basis for the conclusions and recommendations. A few instances where this is not the case are discussed above. Dr. Scott Ferson is listed as not concurring with the Draft Report. Will he be preparing a minority report or is there need for a statement as to why he chose not to concur?

## Comments from Dr. John Vena.

1. Were the original charge questions to SAB Standing or Ad Hoc Committees adequately addressed?

I extend my compliments to the Panel for the comprehensiveness and thoroughness of their review. The review is exceptional in content and format. Explicit recommendations are made after very well written responses to the questions, thoughtful critique of document and justification for the recommendations that follow. In my opinion the two general charge questions and the specific charge questions on mineralogy, Toxicokinetics, Noncancer health effects, carcinogenicity of Libby amphibole asbestos, and inhalation reference concentration, and inhalation unit risk were very effectively answered. It is noteworthy that they developed well articulated responses and complemented them with very detailed feedback with superb comments and recommendations. The long-term research needs were well done. See below for specific comments and a few corrections.

2. Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the Committee's report?

None that I can tell based on my expertise.

3. Is the Committee's report clear and logical?

The **cover letter** is concise and the text very effectively highlights the major recommendations. The letter captures the sentiments of the full review report. A few minor points on cover letter: Page 1 around line 30 Add a bullet on the strong recommendation in the section on fiber toxicokinetics (pages 1 and 16).

Page 1 line 45. I recommend stating specifically what the guideline for epidemiologic data is.

Page 2 line 6 if reevaluate the default what does the panel recommend as substitute?

Page 2 lines 32-34 states the recommendation to consider epidemiologic studies of other amphiboles for model selection, may be helpful to state why. Also this recommendation is not in the executive summary as far as I could tell but is clearly stated and justified on page 11, section 3.1.1.

The **executive summary** is well done and provides an excellent overview of answers to charge questions and recommendations.

Page 3 lines 21-25. Upper part of paragraph agrees with selection of the Libby cohort. Seems awkward that the limitations are stated here and suggest deleting the lines.

Page 7 line 29 Why would other "models might have provided very different estimates of risk that are not discussed" This is not clear and should be rewritten and explained.

Page 7 lines 34-36 this recommendation seems reasonable but would it change the outcome? Is this done in all other IRSI documents?

Page 20 line 33 add "and mortality" after "incidence"??

4. Are the conclusions drawn or recommendations provided supported by the body of the Committee's report?

Yes. In my opinion the report is very well written and comprehensive in responses to the charge questions.

## Comments from other SAB Members

### Comments from Dr. George Alexeeff

Quality review comments on the draft report:

Review of EPA's Draft Assessment entitled *Toxicological Review of Libby Amphibole Asbestos* (August 2011).

#### **1. Were the original charge questions adequately addressed?**

The draft report contains a discussion of the general and specific charge questions, which are adequately addressed in the report.

#### **2. Are there any technical errors or omissions in the report or issues that are inadequately dealt with in the Panel's report?**

I have identified a number of areas in the report which could be clarified and improved.

The Panel's report on page 2 (and 17) states: "The SAB suggests that the EPA include any X-ray abnormalities as the outcome [localized pleural thickening (LPT), diffuse pleural thickening (DPT), or asbestosis]." The statement should indicate what outcome EPA used in their analysis by adding "in addition to localized pleural thickening." Further there is really no justification given for suggesting these additional analyses especially in light of the next comment. There is a suggestion that it may result in a more sensitive analysis. Yet, the Panel's report on page 2 (and 18) states: "The SAB agrees that the radiographic evidence of LPT in humans is the appropriate adverse critical effect for the derivation of the RfC. LPT has the appropriate specificity and is not confounded by cigarette smoking." In light of this strong support, why is Panel suggesting that analyses be done with poorer quality data? If the result is more sensitive how will the interpretation be affected by the use of less specific endpoints. Finally, the recommendation (page 19) and Executive Summary state that these analyses be "included." This is in contrast to the suggestion in the body of the report on page 18 which states: "The SAB also suggests that the

EPA consider looking at LPT, DPT and small opacity profusion score together as an outcome.” I suggest that the Executive Summary reflect the body of the report and use the term “consider.”

The Panel’s report on page 2 (and 18) states: “The relative potency of inhaled LAA should be compared with that of tremolite in rodents to add new information for refining the RfC for LAA.” It is not clear to this reviewer how the animal potency data can refine the human RfC data. I suggest the Panel report clarify how this tremolite information would be used, especially since most of LAA is in the amphibole form.

The Panel’s report on page 3 (and 24) states: “The SAB agrees that the database of laboratory animal and mechanistic studies pertaining to LAA is appropriately presented in the report and its Appendices for support of its analysis of the human effects observed. However, the SAB finds the body of the document deficient in not utilizing what is known about the dimensions of the administered fibers from Appendix D. It is now widely accepted that differences in biological potency among the various amphibole fiber types are due primarily to differences in dimensions, especially in fiber length distributions.” I am concerned about using the phrase “widely accepted” without references. The recommendation appears to overstate the consensus reached on the correlation between amphibole health effects and fiber dimensions, including length. Kane (1991) states: “In summary, both long and short crocidolite asbestos fibers are toxic in vitro via an oxidant-dependent mechanism. In vivo, short fibers are also toxic and carcinogenic if lymphatic clearance is prevented.” Aust *et al.* (2011) states: “Logic would therefore suggest that since fibers <5  $\mu\text{m}$  are the particle fraction more likely to be in extrapulmonary sites where asbestos related changes/tumors occur, these short fibers contribute to the pathogenicity/tumorigenicity at these sites. Contrasting opinions exist as to the potential contribution of short fibers to development of tumors; however, there are no published electron microscopy data that contradict their being the majority fiber size in extrapulmonary sites.” Broddus *et al.* (2011) states: “there is still much uncertainty concerning the contributions to disease of short, thin fibers that predominate in pleural fiber burden studies”.

The Panel’s report on page 4 states: “In light of the lack of data on the mode of action of LAA, the SAB recommends that action be taken to fill the gaps in knowledge by performing research in appropriate lung cell types *in vitro* (e.g., mesothelial cells, macrophages, fibroblasts) and in

rodents *in vivo* that will elucidate basic pathological pathways. Furthermore, animal inhalation studies should be performed with LAA concentrations relevant to human environmental and occupational exposures in order to identify key physical and chemical aspects of LAA that mediate disease, including the role of fiber length in initiating and exacerbating biological lesion formation and progression.” I was unable to find the basis of this statement in the full report. It is unclear to me why this research is being proposed and which charge question is being addressed.

The Panel’s report on page 16 refers to a number of inaccuracies in the EPA report. Further, the panel report states:

“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 (d) risks.” If this information is taken from the EPA report then I think we should cite the pages in the report; if the information comes from other references, and represents an inadequacy in the EPA report, then references for these statements should be added. I think this is especially important with regards to the reference to risk.

The Panel’s report on page 16 states: “The discussion of general fiber toxicokinetics is not clear, nor concise, especially since it fails to distinguish between chrysotile and amphibole fibers. Furthermore, it is inaccurate in too many places, as noted below...” Yet this reviewer does not think that one of the inaccuracies identified is necessarily inaccurate. The Panel report further states: “One rationale for the exclusion of chrysotile fibers from this document of the literature on risks associated with exposures to chrysotile is that most of the risks have been associated with amphibole fibers within the chrysotile ores than to the much more numerous chrysotile fibers that dominate the measured airborne fiber concentrations.” However, Hein *et al.* (2007) state: “The study plant, located in South Carolina, produced asbestos products beginning in 1896 and asbestos textile products beginning in 1909. The plant exclusively used chrysotile fibers obtained from Quebec, British Columbia and Rhodesia; however, small amounts of crocidolite yarn were used to make woven tape or braided packing from the 1950s until 1975. The total quantity of crocidolite used was approximately 2000 pounds compared to 6–8 million pounds per

year of chrysotile during the same time period. As the crocidolite was never carded, spun or twisted, and all weaving of crocidolite tapes was done wet on a single loom, the predominant exposure at the plant was to chrysotile.” In this study “Poisson regression modelling confirmed significant positive relations between estimated chrysotile exposure and lung cancer and asbestosis mortality observed in previous updates of this cohort.”

The positive results at this plant question the above risk statement. A study by Stayner et al. (2007) considered epidemiological evidence concerning this question fiber dimensions and toxicity and found: “Both lung cancer and asbestosis were most strongly associated with exposure to thin fibres (<0.25  $\mu\text{m}$ ). Longer (>10  $\mu\text{m}$ ) fibres were found to be the strongest predictors of lung cancer, but an inconsistent pattern with fibre length was observed for asbestosis.” Since this is a section on toxicokinetics, I suggest the discussion of risk be removed and that the section focus on toxicokinetics.

The Panel’s report on page 19 states: “However, since LAA also contains winchite (84%) and richterite (~11%), it would be prudent to determine whether these mineral forms contribute to the adverse health effects of LAA or whether there are interactive effects of winchite or richterite that modify the toxicity of tremolite.” It is not clear to this reviewer if there is a recommended action with the phrase “it would be prudent to determine.” I suggest rewording to clarify that it is an uncertainty.

The Panel’s report on page 20 states: “While inhalation studies have been conducted with tremolite (e.g., Bernstein et al., 2005), the relative potency of inhaled LAA should be compared to that of tremolite. This could add new information for refining the RfC for LAA.” This sounds like the Panel is suggesting that EPA conduct a research project. If so, I believe that is beyond the scope of the charge question. Page 18 states: “While inhalation is regarded as the most physiologically relevant means of fiber exposure in animals, there is no published study with the LAA mixture with this route of fiber administration in experimental animals.” Possibly the Panel is suggesting that the intratracheal installation potencies be compared. If so, it should be clarified and more information provided on how it could refine the human RfC.

The Panel's report on page 20 states: "It would be valuable for future research on LAA mode of action to focus on biomarkers that are more clearly and specifically related to non-cancer endpoints (i.e., asbestosis) or cancer endpoints (e.g., mesothelioma)." It is unclear why the panel is suggesting another research project. It appears to be beyond the scope of the charge question. I suggest it be deleted from the report.

### **3. Is the Panel's draft report clear and logical?**

The Panel's report is fairly clear and logical. My concerns about clarity are embedded in my comments to question 2.

### **4. Are the conclusions drawn or recommendations provided supported by the body of the Committee's report?**

As indicated above, some of the recommendations did not follow from the body of the document.

#### **References:**

- Aust AE, Cook PM, Dodson RF (2011). Morphological and chemical mechanisms of elongated mineral particle toxicities. *J Toxicol Environ Health B Crit Rev* 14(1-4): 40-75.
- Broaddus VC, Everitt JI, Black B, Kane AB (2011). Non-neoplastic and neoplastic pleural endpoints following fiber exposure. *J Toxicol Environ Health B Crit Rev* 14(1-4): 153-178.
- Hein MJ, Stayner LT, Lehman E, Dement JM (2007). Follow-up study of chrysotile textile workers: cohort mortality and exposure-response. *Occup Environ Med* 64(9): 616-625.
- Kane AB (1991). Fiber Dimensions and Mesothelioma: A Reappraisal of the Stanton Hypothesis in *Mechanisms in Fibre Carcinogenesis*, R.C. Brown, J.A. Hoskins, and N.F. Johnson, eds., Plenum Press, N.Y., 1991, pp. 131-140.
- Stayner L, Kuempel E, Gilbert S, Hein M, Dement J (2008). An epidemiological study of the role of chrysotile asbestos fibre dimensions in determining respiratory disease risk in exposed workers. *Occup Environ Med* 65(9): 613-619.



**Comments from Dr. Joseph Arvai**

***General comments:***

I appreciate that a great deal of work went into this report. Even though this is not my area, I found the report to be well written and easy to follow.

***1) Were the charge questions to the committee adequately addressed?***

*Yes.*

***2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?***

*To the best of my knowledge, no.*

***3) Is the draft report clear and logical?***

*The draft report is very clearly written, and it is quite methodically argued.*

***4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?***

*As far as I can tell, yes.*

## Comments from Dr. Terry Daniel

The review is impressive for its technical level and for having many detailed technical suggestions/recommendations. Indeed, one gets the impression that the authors of the EPA report did not do a very good job, though there is no such direct judgment leveled in the review. I assume that the level and intensity of technical detail is appropriate to a review of an IRIS assessment document, but I am also concerned that the asbestos assessment has been going on for some time and I assume there is some urgency for getting the assessment completed. Based on this SAB review, the EPA still has quite a bit of work to do before that can happen.

With regard to the specific QR question:

1. Were the charge questions adequately addressed?

Yes, and in great detail at a high technical level.

2. Are there are any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report?

There are no technical errors that this reviewer is competent to notice or comment upon.

3. Is the draft report clear and logical?

Yes, it is an excellent report in that regard.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Assuming that the cited literature and technical issues are accepted as correct, there is a clear and substantial basis for the recommendations (perhaps too many of which are represented as “suggestions”).

## Comments from Dr. George Daston

We were asked to address four specific questions as part of the quality review.

1. whether the original charge questions to SAB Standing or Ad Hoc Committees were adequately addressed;
2. whether there are any technical errors or omissions in the report or issues that are inadequately dealt with in the Committee's report;
3. whether the Committee's report is clear and logical; and
4. whether the conclusions drawn or recommendations provided are supported by the body of the Committee's report.

Question 1: I believe that all the charge questions were adequately addressed.

Question 2: The committee indicates that EPA may have gone against its guidance on benchmark dose analysis in setting a reference concentration for non-cancer health effects. Specifically, the committee questions the derivation of a 10% response level while guidance suggests that a 1% level may be appropriate for epidemiology data (p. 27, lines 8-14, and in the Executive Summary and cover letter). It should be noted that an overriding principle of benchmark dose analysis is to derive a benchmark dose (or concentration) that is within the range of the observed data, although it is usually possible to extrapolate a little beyond this range. The notion in the Agency's guidance that a 1% level may be more appropriate for epidemiology data is based on the assumption that most responses in human populations would be more in the 1% or less range. From the data in EPA's draft assessment, it appears that local pleural thickening was diagnosed at a higher rate than 10% and so that level may be appropriate for benchmark dose analysis and the selection of that risk level would be consistent with the overall guidance of selecting a dose within the observable range.

There are a number of places in the report that call for more animal studies including

- studies to determine how much winchite and richterite contribute to toxicity (p. 19, lines 13-21)
- an inhalation study with LAA to compare its potency with that of tremolite (p. 20, lines 2-5)
- inhalation studies to provide mechanistic and dose-response relationships (p. 42, lines 28-29 and the cover letter)

I am not convinced that any of these recommendations would affect the risk assessment in an important way. Winchite, richterite and tremolite are all present in LAA; whether the adverse effects are attributable to one, two or all three of the forms is immaterial when the forms are all present together in LAA, and it is LAA that people have been exposed to. Risk management decisions will be made on what to do about LAA exposure, not on exposure to each of the three forms. Regarding animal studies to further demonstrate dose-response relationships, this also seems less than essential, because the risk assessment is already based on human exposure-response information. While data from an animal study would provide more precision in dose-response, this would be balanced by the greater uncertainty in extrapolating the results to

humans. As for mechanistic studies, these would only be helpful in refining the risk assessment if they were to provide enough information to suggest a significantly different model for low-dose extrapolation of risk. No information is presented in the review as to the nature of the mechanistic studies and how they would change the outcome of the assessment.

My suggestion is to delete these recommendations from the report unless they can be much better justified.

Question 3: I found the report to be clearly and logically presented.

Question 4: I found the conclusions of the report to be well documented and supported, with the exception of the two recommendations I note in my response to question 2.

**Comments from Dr. Costel Denson**

General Comments. This report deals with a wide range of issues and questions around a topic of profound importance. The report is extremely well organized and written, especially so in view of the array and breadth of the charge questions.

1. Were the charge questions adequately addressed? Yes, the charge questions were all adequately addressed.
2. Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report? There were no errors or omissions that this reviewer identified, though human health and risk assessment are not a specialty or area of expertise for this reviewer.
3. Is the draft report clear and logical? A wide range of topics and issues are dealt with here. A superb effort in writing this report has resulted in a report that is clear and logical.
4. Are the conclusions drawn or recommendations provided supported by the body of the report? A firm foundation has been laid for supporting the conclusions drawn and recommendations provided in the report.

### Comments from Dr. David Dzombak

The draft report has provided numerous detailed comments that will strengthen the Draft Assessment. The report is well organized and well-written, but it is hard to follow the charge questions and how they are addressed. This can be remedied with relatively minor modification of the report.

1. Were the charge questions adequately addressed?

Yes, the charge questions are addressed adequately. The response to the charge questions is systematic in the body of the report (though the numbering of the charge questions is confusing), but in the Letter to the Administrator and in the Executive Summary, the charge questions are not mentioned. This needs to be remedied, especially for the Executive Summary. The outline for the Executive Summary follows the outline of the report, but it does not mention the charge questions and it is not clear from reading the Executive Summary how the charge questions are being addressed., i.e., it should follow the responses to the charge questions, in order, as in the report.

2. Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report?

I did not identify any technical errors or omissions in the draft report.

3. Is the draft report clear and logical?

The draft report is well written and well organized. It responds to the charge questions adequately and comprehensively.

As noted above, the response to the charge questions is systematic in the body of the report, but in the Letter to the Administrator and in the Executive Summary, the charge questions are not mentioned. This needs to be remedied, especially for the Executive Summary. The outline for the Executive Summary follows the outline of the report, but it does not mention the charge questions and it is not clear from reading the Executive Summary how the charge questions are being addressed., i.e., it should follow the responses to the charge questions, in order, as in the report.

A short-version of each charge question should be given in the ES preceding the summary of the response to the question. In the Letter to the Administrator, the charge to the panel should at least be given in summary form, and in the paragraphs summarizing the major points there should be some degree of mapping of the major points to components of the charge.

The absence of sequential numbering of the charge questions and the repetition of charge question numbers is confusing and is a problem. Perhaps the numbering cannot be modified as that is the way the charge questions were presented to the committee, but I recommend

renumbering the charge questions so that each charge question has a unique identifying number.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

The conclusions and recommendations are adequately supported in the body of the report. However, as noted above, the conclusions and recommendations developed in systematic response to the charge questions in the body of the report need to be mapped to the charge questions in the Letter to the Administrator and in the Executive Summary. In the Executive Summary, this mapping needs to be systematic as in the report. The Letter need not have the same structured format, but the relationship of the conclusions and recommendations presented to the charge questions needs to be discussed.

**Comments from Dr. Bernd Kahn**

The Review of the Draft Assessment of the Toxicological Review of Libby Amphibole Asbestos is extremely well written, clear, and to the point. My response to the four questions are, respectively, yes, no, yes, and yes. I have no suggested changes for the review. Minor typos that I found are:

p.42, p.8: skip line between paragraphs.

p.46, l.44: Delete '2009' repetition.

p. 44-50: Correct variations in reference format; for example, on p.49, l.28, delete periods after journal abbreviation; on p.50, l. 10, delete 'and' between authors;; on p.50, l. 17, replace semicolons with commas.

### Comments from Dr. Nancy Kim

The report was well done and I enjoyed reading it. I liked the concept of adding long-term research needs. Should this section be included with every IRIS report?

1) Were the charge questions to the committee adequately addressed?

Yes.

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

No.

3) Is the draft report clear and logical?

Yes.

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes, for the most part.

The letter contains 9 bullets with the SAB's major comments and recommendations. A letter that highlights 3 or 4 major recommendations would be clearer for the Administrator and the most important recommendations are likely to make a bigger impact. In reading the report, what came across as being important recommendations to me were about modeling, uncertainty analysis and uncertainty factors and that was not clear in the letter.

My recommendation would be to rewrite the letter, focusing on what the panel thought were the most 3 or 4 critical recommendations. All the major areas of agreement with the report could be summarized in one paragraph, if the panel thought those areas needed to be highlighted in the letter.

Page 12, line 20. This recommendation encourages the continued monitoring of relevant Libby residents for early onset asbestos associated diseases. It is also given later in the document with more detail. I would remove it from this section since it isn't clear here, but is later on, to whom the recommendation is made. When I first read it, I wasn't clear if the panel meant that the recommendation should be included in the review document or in IRIS? In addition, the report at this point hasn't provided enough information to support for the recommendation although it does later

Minor comments.

1. Page 12, line 31. Remove of between to and health.
2. Page 14, line 16. Would it be useful for the reader of the SAB report to provide information to understand the difference between field and environmental samples?

**Comments from Dr. James Mihelcic**

1) Were the charge questions to the committee adequately addressed?

Yes

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

Yes

3) Is the draft report clear and logical?

The report is well organized, clear, and logical.

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes, the conclusions and recommendations stand out, are useful, and are supported by relevant and peer reviewed science.