

April 30, 2012

MEMORANDUM

SUBJECT: Questions and Clarifications Related to the SAB Draft Report Reviewing EPA's Draft Assessment Entitled "Toxicological Review of Libby Amphibole Asbestos"

FROM: David Bussard, Director, Washington Division  
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TO: Dr. Agnes Kane, Chair  
Libby Amphibole Asbestos Review Panel  
U.S. Environmental Protection Agency Science Advisory Board (SAB)

EPA is pleased to have had a chance to read the SAB Panel's April 11, 2012 draft report reviewing EPA's draft "Toxicological Review of Libby Amphibole Asbestos." EPA sincerely appreciates the time and attention that the SAB Panel has taken in its review. EPA would like the opportunity to provide some questions seeking clarification of certain points in the Panel's draft report.

The following table identifies areas in the draft SAB Panel report where EPA would like additional clarification to help us better understand and respond to the panel's recommendations. EPA would appreciate your conveying the following questions and clarifications to the members of the SAB Panel in advance of the scheduled teleconference on Tuesday, May 1, 2012. These will also form the basis of my oral remarks to the Panel during the teleconference. EPA can also answer any questions from the Panel regarding our comments at that time.

Questions and clarifications regarding SAB Panels' draft report (April 11, 2012) for the peer review of EPA's draft Toxicological Review of Libby Amphibole Asbestos

Issue / Section	Recommendation/comment from SAB Panel draft report	EPA question/clarification
<p><b>Localized pleural thickening (LPT): the potential for effect modification by smoking</b></p> <p>Section 3.1</p> <p>Section 3.2.4</p>	<p><b>Formal Recommendation: (Executive Summary, Pg. 5)</b>            “Given that the purpose of the full set of analyses is to estimate the BMC and eventually RfC, the SAB recommends that several of the covariates predictive of the outcome be considered based on whether they impact the BMC estimate rather than merely assessing p-values for how well they improve the predictive quality of the model. <b>In particular, smokers are a sensitive subgroup and should be considered in the RfC estimate.</b>”<sup>1</sup> (also see Pg. 27)</p> <p><b>Formal Recommendation: (Pg. 29)</b>            “Revise consideration of the additional covariates to include their impact on the BMCL, particularly smoking as smokers are a sensitive subgroup. “</p> <p><b>Suggestions/issues in the associated text: (Executive Summary, Pg. 5)</b>            “LPT has the appropriate specificity and is not confounded by cigarette smoking.” (Pg. 2, Exec Sum., also see Pg. 18)</p> <p><b>Suggestions/issues in the associated text: (Pg. 28)</b>            “A distinction should be made regarding evidence for possible confounding between smoking and pleural effects and the role of smoking on the risk of pleural thickening. If smoking affects the risk of pleural thickening, regardless of whether it is also associated with asbestos exposure (i.e. as a confounder); it will decrease the estimated BMC. <b>Smokers may therefore be a sensitive subgroup and this should be addressed in consideration of the RfC.</b> The sensitivity analysis for smoking shown in Appendix E does suggest that smokers will have a higher risk for LPT and a concomitantly lower BMCL.”</p>	<p>As noted in the SAB Panel's draft report, localized pleural thickening (LPT) is not associated with smoking in the sense that the association between Libby Amphibole Asbestos (LAA) and LPT is not confounded by smoking. However, there may be effect modification as suggested by the lower benchmark concentration (BMC) in smokers (sensitivity analysis detailed in Section 5.3.6 and Appendix E, Section E.2). EPA believes this sensitivity analysis provides some indication that smokers may constitute a sensitive subgroup.</p> <p><b>Clarification requested:</b>            Is the statement in the draft Panel report that “smokers are a sensitive subgroup” based primarily on the sensitivity analysis suggesting effect modification (Section 5.3.6)? Is there additional literature to which the panel can direct EPA that further supports this statement?</p>

<sup>1</sup> Here and below, emphasis is EPA's, not SAB's



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<p><b>Review of amphibole literature</b></p> <p>Section 3.1</p>	<p><b>Formal Recommendation: (Pg. 11)</b>                      The toxicological review does not make clear the relevance of the extensive literature on the health effects of other amphibole fibers. Literature on other amphiboles should be included, particularly inhalation studies in rodents. There are numerous publications on the mode of action of other amphiboles, and epidemiological studies of populations exposed to amphiboles environmentally.</p>	<p>While incorporation of some of these data may be useful, expanding the current document to present and evaluate the extensive literature on amphibole fibers may change the scope of this effort and would be time and resources intensive.</p> <p>EPA would appreciate it if the Panel could clarify the intended scope of this recommendation.</p>
<p><b>Grouping all radiographic outcomes endpoints for E-R modeling</b></p> <p>Section 3.3.2 Subpart 2</p>	<p><b>Formal Recommendation: (Pg. 19)</b>                      In addition to LPT, include an analysis that uses all radiographic outcomes (LPT, DPT and small opacities).</p> <p><b>(Pg.18-19)</b>                      “The SAB also suggests that the EPA consider looking at LPT, DPT and small opacity profusion score together as an outcome. There is evidence that LPT is not always the first adverse effect that is detected on chest radiographs, and some individuals with Libby amphibole asbestos exposure can develop either diffuse pleural thickening or increased profusion of small opacities without developing evidence of LPT.”</p>	<p>Addition of small opacities to the exposure-response modeling is unlikely to inform the lower end of the exposure-response curve in the range of the BMC and BMC<sub>L</sub>. For example, considering the most recent study (Rohs et al., 2007); of the eight workers with small opacities, seven are in the highest exposure quartile, and one in the 3<sup>rd</sup> quartile. Additionally, of these eight workers with small opacities, six also had pleural effects (2 DPT and 4 LPT) (Rohs et al., 2007).</p> <p>EPA would appreciate it if the Panel could further clarify the intent of this analysis?</p>
<p><b>Exposure data used to calculate CHEEC</b></p> <p>Section 3.2.4 Subpart 1</p>	<p><b>Text Recommendation: (Pg. 24)</b>                      “Since the RfC is based on the transformed data, future use of the RfC at a given site should be based on the natural-log-transformed mean of all exposure measurements from that site.”</p>	<p>For clarification, the cumulative human equivalent exposure concentration (CHEEC) was not calculated with natural-log-transformed exposure data.</p>

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<p><b>Uncertainty factors (noncancer)</b></p> <p>Cover letter Page ii</p> <p>Section 3.2.4 Subpart 6</p>	<p><b>Letter to Administrator: (Pg. ii)</b>  A composite uncertainty factor of 100 was applied to the point of departure to obtain the RfC. The SAB supports the intraspecies uncertainty factor of 10 to account for human variability and sensitive subpopulations. However, the SAB recommends that the EPA consider additional data and analysis for the application of a database uncertainty factor of 10.</p> <p><b>Formal Recommendation: (Pg. 31)</b>  Review additional sources of uncertainty, i.e. timescale of cohort coverage, additional uncertainty resulting from target population diversity, and endpoint severity. Consider adjusting <math>UF_D</math>, <math>UF_C</math> or <math>UF_L</math> if necessary to accurately reflect the overall uncertainties in these categories: <b>provide specific justification for the choices made rather than claiming unsupported use of default values.</b></p> <p><b>Evaluation of <math>UF_H</math> in the Text: (Pg. 30)</b>  Use of a <math>UF_H</math> of at least 10 is standard in considering health protective levels based on effects in the workforce, who are generally healthier and less diverse than the general population. In fact, arguments have been made that this is an insufficiently large factor to cover all sensitive subpopulations, especially children. Some treatment of the question of inter-individual variability is offered in the later summary of conclusions (Section 6). There is no specific evidence on the relative sensitivity of children to the non-cancer effects of Libby asbestos, although some indications with other amphiboles suggest the possibility of enhanced effects following exposure at younger ages. <b>Overall, it seems unlikely that a departure from the default guideline value of <math>UF_H = 10</math> could be justified.</b></p> <p><b>Evaluation of <math>UF_D</math> in the Text: (Pg. 30)</b>  Selection of a <math>UF_D</math> of 10 is <b>explained and justified</b> based on the limited number of studies of exposure to Libby asbestos (Libby workers, ATSDR community study and Marysville workers) and the lack of evaluation of potentially more sensitive alternative endpoints. <b>This seems reasonable and consistent with the guidelines.</b> In particular, this uncertainty factor would not be reduced even if improved exposure estimates allowed consideration of the full cohorts (or a larger fraction thereof). However, some additional data have recently been published (for the community surrounding a Minnesota expansion plant (1, 2)).</p>	<p><b>Clarifications requested:</b></p> <p>1) Can the Panel further clarify which uncertainty factors represent the unsupported use default values, as stated in the recommendation and why these uncertainty factors are considered unsupported? What is the Panel seeking in terms of additional support?</p> <p>2) The recommendation indicates that “target population diversity” is not adequately addressed and additional uncertainty factors should be applied. As noted in the draft Panel report, the <math>UF_H</math> addresses human variability and states that data are not available to justify departure from the maximum default <math>UF_H=10</math>. EPA is seeking clarification on what would inform any additional uncertainty adjustment for target population diversity and how would it be applied if not as the <math>UF_H</math>?</p> <p>3) The formal recommendation indicates that “timescale of cohort coverage” is not addressed. However, the <math>UF_D</math> proposed by EPA specifically addresses this uncertainty as discussed in the draft document (see Section 5.2.4, pages 5-37 and 5-38.) Is the Panel recommending an application of an additional uncertainty factor above the <math>UF_D=10</math>?</p>

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<p><b>Model uncertainty</b> Cover letter Page iii</p> <p>Page iii and 7</p> <p>Page 7</p> <p><b>3.2.5.1 (IUR):</b> Page 33 Recommendations</p> <p><b>3.2.5.5 (IUR):</b> Page 38 Recommendations</p>	<p><b>Letter to Administrator:</b> “The SAB recommends that a more straightforward and transparent treatment of model uncertainty would be to estimate risks using a more complete set of plausible models for the exposure-response relationship, including the Cox and Poisson models.”</p> <p>“There are several competing models- Weibull, and the two stage clonal expansion (TSCE) - that could have been used ..., but these are not discussed”</p> <p><b>Letter to Administrator, Executive Summary (Pg. 7):</b> “The SAB recognized that the agency did conduct extensive sensitivity analyses of their chosen models ... However, these analyses rely on essentially the same underlying models. They do not address the fundamental question of model uncertainty.”</p> <p><b>Executive Summary (Pg. 7)</b> “Ultimately, there are many competing models that could have been used instead of the Poisson and Cox models which could have provided very different estimates of risk (e.g., parametric survival models, accelerated failure time models, additive models), but that are not discussed.”</p> <p><b>Formal recommendations (Pg. 33):</b> “The SAB recommends that a more straightforward and transparent treatment of model uncertainty would be to estimate risks using a more complete set of plausible models for the exposure-response relationship (discussed in response to question 1 in Section 3.2.5), including the Cox and Poisson models. This sensitivity analysis, while not a full uncertainty analysis, would make the implications of these key model choices explicit.”</p>	<p>Different models may be more or less plausible (or practical) depending upon the available data at hand. For example, multiparameter survival models may be less suited to data on rare events; two-stage clonal expansion (TSCE) models, while state-of-the-art, have only recently been applied to occupational epidemiology datasets. Richardson (2008) and Zeka et al. (2011) have demonstrated applications of such TSCE models – although EPA notes that in one instance, the model fitting a two-stage clonal expansion model to the Dement et al. (1994) study of lung cancer and asbestos exposure often did not converge.</p> <p>If after review, EPA finds that a limited number of models are both plausible and appropriate to the data, would a discussion of the models considered and their suitability, and the use of at least one additional model, meet the recommendation to address and illustrate model uncertainty? In addition, can the Panel clarify whether the specific models mentioned other than Poisson and Cox are a proscriptive list or examples of there being other models to consider?</p>

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<p><b>Assumption of independence</b></p> <p>Section 3.2.5</p> <p>Subsection 3</p>	<p><b>Executive Summary (Pgs. 7-8):</b>            “The SAB was divided on whether the independence assumption is fully satisfied. The estimation of the mesothelioma and lung cancer IURs from the same cohort by definition violates the assumption of independence. Violation of the independence assumption could result in either an inflated or deflated upper bound on the combined IUR. The SAB recommends that the EPA perform an analysis evaluating the independence assumption of the risk of mesothelioma and lung cancer mortality. The agency should fit a competing risk model to the data and use this model to calculate the correlation between the two potential event times.”</p> <p><b>Formal Recommendation: (Pg. 36)</b>            “... More specifically, they should fit a competing risk model to the data and use this model to calculate the correlation between the two potential event times (see Section 2.7 of Klein and Moeschberger, 2003). “</p> <p><b>Suggestions/issues in the associated text: (Pg. 36)</b>            “A better approach would be to jointly model the two outcomes using a Bayesian approach in which dependency could be introduced through a shared random effect in the regression models or a correlated prior for the exposure effects in each model. “</p> <p>“At the very least, this very restrictive assumption must be mentioned and the potential consequences of a violation of this assumption must be discussed.”</p>	<p>EPA reviewed Section 2.7 of Klein and Moeschberger (2003) and found the text of limited utility for the situation in the assessment, as no parametric form of joint survival is available for the Libby dataset. At the same time, EPA understands that the assumption of independence needs to be discussed in the assessment.</p> <p><b>Request of clarification:</b>            Can the panel clarify why it believes substantial errors might be introduced by statistical dependence and if so, can the Panel provide specific recommendations of applied examples where statistical dependence has been accounted for in a similar setting (e.g. when a similar amount of information to the Libby worker sub-cohort was available)? Has it been the panel's experiences that such competing risk models have yielded clear results for data similar in scope to that of the Libby sub-cohort?</p> <p>Note: For a similar situation with multiple tumors observed in an animal bioassay, National Research Council (1994) “Science and Judgement in Risk Assessment” stated that: “...a general assumption of statistical independence of tumor-type occurrences within animals is not likely to introduce substantial error in assessing carcinogenic potency.</p>

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<p><b>Request for full uncertainty assessment of cancer IUR exposure-response modeling</b></p>	<p><b>Letter to Administrator, Executive Summary (Pg. 8) and Formal Recommendation (Pg. 38)</b>            “The SAB recommends that a more straightforward and transparent treatment of model uncertainty would be to estimate risks using a more complete set of plausible models for the exposure-response relationship, including the Cox and Poisson models. This sensitivity analysis, while not a full uncertainty analysis, would make explicit the implications of these key model choices.”</p> <p><b>Formal Recommendation (Pg. 38):</b>            “The SAB recommends that the agency conduct a full uncertainty analysis by modeling the joint distributions of the major sources of uncertainty it has identified in its evaluation. However, the SAB recognizes the challenge of conducting such an analysis.”</p> <p><b>Slide presentation by SAB, February 8th</b></p> <ul style="list-style-type: none"> <li>•<b>Objective:</b> comprehensive uncertainty analysis               <ul style="list-style-type: none"> <li>–Quantitatively characterize major uncertainties, at least using interval ranges</li> <li>–Use an integrated (single) sensitivity analysis, to project all uncertainties simultaneously (e.g. Monte Carlo methods, info gap analysis)</li> </ul> </li> <li>•<b>Pragmatic:</b> individual sensitivity analysis               <ul style="list-style-type: none"> <li>–Be explicit about amount of uncertainty accounted for by guidance-driven assumptions</li> <li>–Give quantitative implications of key sources of uncertainty for IUR</li> </ul> </li> </ul>	<p>In discussion at the SAB meeting (e.g. slide referenced in the left column), EPA understood the Panel's interest in a more comprehensive examination of uncertainty. However, also reflected in the slide is the recognition of a range of analyses of different extent that could address this matter.</p> <p>In the draft report, there is a very specific recommendation that EPA conduct "... a full uncertainty analysis by modeling joint distributions ...". In EPA's preliminary consideration it is unclear if data exist to implement this recommendation, as written.</p> <p>EPA requests that the Panel consider alternative wording to allow EPA to consider a range of techniques and levels of analysis that could be applied in contributing to a more comprehensive uncertainty assessment.</p>