Date: July 24, 2012

To: Dr. Agnes Kane, Chair
U.S. Environmental Protection Agency Science Advisory Board (SAB)
Libby Amphibole Asbestos Review Panel

From: David Bussard
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RE: Questions and clarifications related to SAB draft report reviewing EPA's Draft Assessment entitled "Toxicological Review of Libby Amphibole Asbestos"

EPA is pleased to have had a chance to read the SAB Panel's July 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 Wednesday, July 25, 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.

Issue / Section	Recommendation/comment from SAB Panel draft report	EPA question/clarification
1) Noncancer RfC: LPT as predictive of other health effects Letter to the Administrator: First page, lines 38-42 Exec. Summary, page 2, lines 12-14 Response to Charge Questions: page 19, lines 24 – 26.	The SAB agrees that localized pleural thickening is an appropriate health endpoint for the derivation of the RfC and one that is predictive of risk for other asbestos-related diseases, including asbestosis, mesothelioma, and lung cancer. The SAB has identified additional references and recommends that the agency conduct a more detailed review of the literature to further support this conclusion. Moreover, the presence of LPT itself is predictive of risk for other asbestos-related diseases, including asbestosis, mesothelioma and lung cancer − a point that the EPA should include as well. Additionally, the presence of LPT itself is predictive of risk for other asbestos-related diseases, including asbestosis, mesothelioma and lung cancer, a point that the EPA should include.	EPA would appreciate if the Panel could clarify what is meant by 'predictive' and how that might differ from 'associated'? The same exposure may cause two different endpoints, resulting in a statistical association solely by the nature of their shared exposure. Does the Panel mean that LPT predicts cancer endpoints conditional on exposure? The EPA appreciates the list of additional references offered on pages 13-14. However, if the panel's view is that LPT predicts other health effects even after controlling for exposure, EPA would appreciate an indication of which of the listed human studies the panel would cite as supporting such a relationship. It would be helpful to the EPA if the Panel could identify any additional references to support its conclusion that localized pleural thickening is predictive of other asbestos-related diseases, controlling for exposure.

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2) Noncancer RfC: Justification of LPT as critical effect Letter to the Administrator: First page, lines 38-42 Exec. Summary, page 2, lines 8-9 Exec. Summary, page 2, lines 12-14 Response to Charge Questions: page 19, lines 24 – 26.	The SAB agrees that localized pleural thickening is an appropriate health endpoint for the derivation of the RfC and one that is predictive of risk for other asbestos-related diseases, including asbestosis, mesothelioma, and lung cancer. The SAB has identified additional references and recommends that the agency conduct a more detailed review of the literature to further support this conclusion. The SAB agrees that the radiographic evidence of LPT in humans is the appropriate adverse critical effect for the derivation of the RfC. Moreover, the presence of LPT itself is predictive of risk for other asbestos-related diseases, including asbestosis, mesothelioma and lung cancer − a point that the EPA should include as well. Additionally, the presence of LPT itself is predictive of risk for other asbestos-related diseases, including asbestosis, mesothelioma and lung cancer, a point that the EPA should include.	It would be helpful for EPA if the Panel could clarify whether it considers LPT to be an appropriate health endpoint for the derivation of the RfC regardless of any potential association with other health outcomes (including cancer risk), or only to the extent it is predictive of other effects. With the wording about 'predictive' it may be unclear in the current text whether the panel considers the endpoint adverse in and of itself.
3) Fiber dimension information for study descriptions Exec. Summary: page 3, lines 36-40. Response to Charge Questions: page 18, lines 11-14	The SAB agrees that the database of laboratory animal and mechanistic studies pertaining to LAA is appropriately presented for support of the analysis of the human effects observed. However, the SAB finds the document deficient in not citing all that is known about the dimensions of the administered fibers, as 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. Furthermore, the results of the various studies cited in this section are almost all very difficult to interpret with respect to the toxic effects that were, or were not, reported, since no information was provided on the key dosimetric factor of fiber dimensions.	The information on the dimensions of the fibers of which EPA is aware, is presented in Appendix D. EPA can make linkages to that information on fiber characteristics more explicit or summarize it in the main text; however it would be helpful if the Panel could clarify what specific information it would like to see in the main text that was not there, and what specific information (if any) it would suggest EPA add to the Appendix, if the Panel continues to believe "the document", was deficient with respect to such data.

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4) Noncancer E-R modeling: Michaelis-Menten Model Response to Charge Questions: Page 28, lines 35 – 45 and following to page 29. Response to Charge Questions: Page 31, lines 30 – 31.	The SAB also finds that the method for incorporating TSFE into the full cohort analysis is not well justified and recommends that the analysis be revised. Currently, the EPA uses TSFE as a predictor for the plateau in the Cumulative Normal Michaelis-Menten model. The plateau provides the maximum proportion of the population that would experience LPT given sufficient exposure and time to develop the disease. No biological justification is given for why this maximum proportion would vary with TSFE. The SAB concludes that a more natural way to incorporate TSFE into the model would be to allow it to affect the rate of change in the probability of LPT; by including it directly in the linear predictor portion of the model alongside cumulative exposure; and/or by using an alternative exposure metric such as residence time weighting (RTW) that more heavily weights exposure in the distant past. The functional form of TSFE could then be selected using standard approaches (e.g., comparing AICs). Since adding TSFE to the model should affect the coefficient of cumulative exposure, the EPA should replace the Michaelis-Menten model with a dichotomous Hill model which allows the slope to be estimated. Finally, the SAB recommends following the approaches for the subcohort analysis, such as fixing the plateau using literature values as recommended in the response to charge question 2 in Section 3.2.5.2 of this report. The SAB states "The analyses based on the Cumulative Normal Michaelis-Menten model should be removed from the document."	EPA thanks the Panel for their responses to this charge question and their suggestions for additional procedures to either incorporate TSFE into the model or to use various other exposure metrics such as residence time-weighted (RTW) exposure to explain the contribution of exposure timing to the risk of LPT. The panel has recommended that EPA should replace the Michaelis-Menten model with a dichotomous Hill model which allows the slope to be estimated and the inclusion of TSFE as a covariate. Could the Panel clarify -- does it recommend EPA should not use the Cumulative Normal Michaelis-Menten if, after evaluating the dichotomous Hill model with a fixed plateau, the Cumulative Normal Michaelis-Menten provides the best fit to these data? EPA requests that the Panel consider alternative wording to allow EPA to consider a full range of analytic techniques (including the Cumulative Normal Michaelis-Menten model) with the understanding that any methods used should be well justified in terms of fit as well as biological/epidemiological plausibility and include the dichotomous Hill model as an evaluated model.

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5) Noncancer E-R modeling: additional analysis of covariates Response to Charge Questions: Page 29, Potential Confounders and Covariates	The SAB recommends a revised strategy for evaluation of covariates. The target of inference for the analyses of the Marysville cohort is the POD (BMCL). The evaluation of the various covariates should be made with respect to this target of inference. The SAB suggests the covariates fall into two classes: *exposure-related covariates* (alternative exposure metrics and TSFE) and *non-exposure-related covariates* (age, body mass index (BMI), gender, and smoking status). We provide recommended revised strategies for considering these two classes of covariates that follow directly from consideration of the target of inference. Non-exposure-related covariates: A decision on whether to control for the non-exposure-related covariates should account for how the EPA wishes to determine and apply the RfC. The SAB suggests a BMCL most directly applicable to all members of the general population is most appropriate. This implies that the BMCL should be estimated from a model that includes exposure covariate(s) but that is otherwise unadjusted. This is the same approach used in the current draft document; only the rationale for the approach is different. As sensitivity analyses, the SAB suggests it would be informative to understand how the BMCL varies conditional on subgroups defined by covariate values (e.g., older males or smokers).	EPA appreciates the new rationale for the evaluation of covariates which can be made with respect to the target of inference. Does EPA correctly understand that the Panel believes what EPA has done is one appropriate approach and that this revised strategy is an alternative to the current method? EPA is not clear on exactly how to implement this strategy. It would be helpful if the Panel could provide citations from the literature detailing the application of such methods – especially references pertaining to implementing such a strategy to obtain confidence intervals (BMCL estimates).

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6) Cancer IUR: Interval statistics Response to Charge Questions: page 36, line 33-46 and onto page 37	The SAB recognizes that the agency's effort to focus on good quality exposures specific to LAA has led to reliance solely on the Libby worker subcohort. This rationale is understandable but at the same time, it is important to acknowledge that this small subcohort may have its own limitations as a basis for modeling exposure-response relationships for a larger population over a lifetime. As a sensitivity analysis to evaluate the potential impact of omitting the Libby workers hired before 1959, the SAB recommends analyzing the entire Libby cohort using interval statistics (Nguyen et al 2012; Manski 2003; inter alia) or other traditional approaches for data censoring in predictors (cf. Küchenhoff et al., 2007). It is inappropriate to use midpoint substitution (as described in section 5.4.6.1.2) that assumes poorly measured or missing predictors have some constant value. Interval statistics and traditional censoring approaches to measurement uncertainty would, in essence, replace point values with interval ranges. When the intervals are narrow, as they might be for 21% of the early hires for which jobs titles are available, there might be a good deal of recoverable information present. When the intervals are much wider, there would be accordingly less information. Whatever empirical information may be present, it is worth evaluating whether its inclusion is better than leaving out the data entirely, which in principle amounts to replacing them with intervals that are completely vacuous, from zero to infinity.	The SAB report provides several references for interval statistics and one reference for data censoring in predictors, for use in a sensitivity analysis of the Libby workers hired before 1959. EPA reviewed the provided references and found that none of the references on interval analysis specifically addresses survival analysis with censoring. EPA would appreciate if the panel could offer references along with specific suggestion on how to apply interval statistics to the survival data.
7) Cancer IUR: assumption of independence Response to Charge Questions: page 39, lines 12-13 Response to Charge Questions: page 39, lines 23-25	The SAB found the description of the procedure used to be clear but considered the justification for independence assumption to be lacking in depth. One approach might be to undertake bounding analysis using the Fréchet inequality for disjunctions (Fréchet, 1935) that makes no assumption about the nature of the dependence. This analysis could reveal how large the impact of dependence might be.	The Panel recommended using the Fréchet inequality for disjunctions, for a bounding analysis of the independence assumption in combining risks of lung cancer and mesothelioma. As EPA understands the procedure, this method can be used for probabilities. It would be helpful if the SAB could provide a reference that clarifies the specific application of this method to confidence bounds (which are needed for combining risks of lung cancer and mesothelioma to derive an IUR) vs. combining probabilities?