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September 18, 2012

VIA E-MAIL AND FIRST CLASS MAIL

Dr. Angela Nugent
Designated Federal Officer
EPA Science Advisory Board (1400R)
1200 Pennsylvania Avenue, N.W.
Mail Code: 1400R
Washington, DC 20460

Re: SAB Panel Report on Draft Libby Amphibole Asbestos IRIS Assessment

Dear Dr. Nugent:

We are providing this supplement to our June 25, 2012 letter to Dr. Diana Wong on behalf of W. R. Grace & Co. identifying procedural and substantive deficiencies concerning the SAB Draft Report ("Draft Report") on the Libby Amphibole Asbestos Draft IRIS Assessment ("Draft Assessment"). Given the importance of the issues we are raising regarding the scientific integrity of the Draft Report, I ask that you provide this letter and the attached June 25, 2012 letter promptly to all chartered SAB members for their consideration.[1] These letters contain information central to the question of whether the Draft Report (i) fulfills the SAB obligations regarding review of IRIS assessments, (ii) has been prepared consistent with public participation procedures that ensure the transparency and scientific soundness of IRIS reports, and (iii) provides EPA with clear advice grounded in objective and best available science. We respectfully request that the chartered SAB address in the course of its September 25, 2012 teleconference the fundamental issues set forth below.

In light of complex and controversial technical issues being addressed for the first time in the Draft Report, meaningful public participation in its development is of paramount importance. Considerable technical expertise regarding these issues exists outside of the SAB panel and should inform the deliberations of the SAB. Accordingly, we reiterate a request that has been made at each phase of the SAB panel ("Panel") review process: additional time should be allowed for technical experts and any other public commenters to present information to the chartered SAB at its September 25 teleconference. A three minute time period for an individual

[1] *See* Letter from Karl Bourdeau to Dr. Diana Wong (June 25, 2012), *attached hereto as* **Attachment A**.

presentation is patently inadequate, especially in light of the complexity of the issues at stake. We urge that the SAB allow outside scientific experts up to ten minutes to address the chartered SAB, and that it engage in a dialogue with commenters at an appropriate point during the teleconference to allow exploration of key issues and to demonstrate some consideration of public comments. In light of the limited number of speakers likely to present at the teleconference, these requests should not present a logistical problem. Moreover, such procedural safeguards are consistent with the augmented public participation measures to which the SAB Staff Office has recently committed for IRIS assessments, and would ensure that the input of highly qualified external technical experts is meaningful.

The importance of adequate public input concerning the chartered SAB's consideration of the Panel's Draft Report is illustrated by several fundamental procedural and substantive shortcomings concerning the Report that need to be brought to the chartered SAB's attention. Some of these deficiencies are summarized below and demonstrate why the chartered SAB should conduct a thorough review of the Report, informed by public comment, to ensure that the final Report presents to EPA clear scientific recommendations that are amply justified by the weight of best available scientific evidence.

1. RAW DATA UPON WHICH EPA BASES ITS DRAFT ASSESSMENT AND WHICH WERE NOT MADE AVAILABLE TO THE PUBLIC AND THE PANEL DURING THE PANEL'S DELIBERATIONS CLEARLY SHOULD BE CONSIDERED AND SUBJECTED TO PUBLIC COMMENT PRIOR TO FINALIZING THE REPORT

It is axiomatic that data underlying an IRIS assessment must be available in a timely fashion to ensure meaningful public participation.[2] As described below, key data upon which the Draft Assessment has been based have been unavailable to both the Panel and the public. In particular, based upon the record, it appears that no SAB panelist or member of the public had access to the full data sets from which the proposed RfC or IUR were derived (although one panelist seems to have obtained a restricted portion of one of the raw data sub-cohorts). The Panel should have received the data to support and enlighten their review, and the data should have been available for public comment.

To conduct a thorough scientific review of the Draft Assessment, we sought to obtain the complete set of data upon which the RfC and IUR are predicated. With respect to the RfC-related data, after pursuing the data without success from the SAB staff (which may not have the full data set), we received these data for the first time in late July 2012 from another source. To do so, we had to seek the data from a research institution (University of Cincinnati) and have the

[2] Access to such data is also required by EPA's Information Quality guidelines to ensure the objectivity of highly influential scientific information (such as IRIS assessments) disseminated by EPA. EPA, Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency (Oct. 2002), *available at* http://www.epa.gov/quality/informationguidelines/.

release reviewed by that institution's internal review process. Ultimately, that institution determined that the data could be released, with only a minor and reasonable proviso that "date of hire" information of any particular individual not be disclosed. This approach provided a simple solution to any privacy concerns. Thus, those data could easily have been made available to the public at the time that EPA issued its Draft Assessment for review.

With respect to data underlying the cancer IUR, we requested those data on February 13, 2012. On July 23, 2012, we received correspondence from the agency that ultimately handled the request (the Center for Disease Control) estimating that we would receive a final response to our request on January 31, 2014. Nonetheless, on September 4, 2012, we received the requested data, and are now awaiting response to a follow-up request for a glossary of abbreviations used in the information provided so we can begin to analyze the data. No portion of the data finally provided to us was withheld as requiring confidentiality protection, indicating that it could and should have been provided long ago.

Unavailability of these data raises a significant question concerning the process undertaken to ensure the scientific integrity of the final Report and Assessment. Without access to these data, input from the scientific community has been severely restricted. Moreover, the Panel's own review was restricted, and seemingly deficient as a result. For instance without the data, the Panel may not have been aware that duration of exposure is clearly the best measure of dose in the Rohs full data set (Rohs et al., 2008), a fact that calls into question the entire RfC analysis as explained in new expert comments (submitted to the chartered SAB by S. Moolgavkar and D. Hoel) based upon the now available data. The data are also necessary to confirm that age confounds the Rohs data set. These data issues are central to the question of whether the RfC is scientifically valid, and illustrate how the unavailability of the Rohs data prevented a identification and evaluation by the Panel of significant issues.

Because these data were unavailable until now, the chartered SAB should refer the Draft Report back to the Panel for its consideration of the data. In addition, the Panel should be advised to allow sufficient time for the public to assess and prepare comments based upon these data, which are not "new," but importantly are the data upon which the proposed RfC and IUR are based. A thorough review of these data is necessary to assess the scientific integrity of EPA's analysis.

2. THE DRAFT REPORT FAILS TO ACKNOWLEDGE A SUBSTANTIVE AREA OF DISAGREEMENT AMONG SAB PANELISTS

The Panel's deliberations evidence strong disagreement among panelists on issues that go to the heart of the scientific validity of the Assessment. Unless these disagreements were fully resolved, they should be reflected in the final Report, consistent with SAB policy. As provided

by SAB procedures for peer review of IRIS assessments, "[w]here consensus is not reached, the major substantive areas of agreement and disagreement are captured in the final report."[3]

Specifically, the Report should discuss Dr. Peto's fundamental concern that the RfC is simply not scientifically credible. To illustrate the result of the "extreme error" in the calculation of the RfC, Dr. Peto explained to the Panel that use of data provides a "reality check on the appropriateness of the modeling for pleural thickening."[4] By way of example, he explained that the modeling proposed by EPA "would imply that 50 percent of British women have pleural thickening caused by asbestos, which is not the case. And that discrepancy between this modeling and that illustrates ***how extreme the error is***. And I just ***think it's inappropriate to present these calculations***. I think they are -- ***I think they are completely divorced from reality***."[5]

Dr. Peto followed up with written comments to Panel members explaining his analysis and concluding that the RfC "analysis based on this [Michaelis-Menten] model are [sic] therefore wrong, ***and should be removed*** from the report." He then states that, "***It is not reasonable to fit a model that is clearly wrong and attempt to allow for the error in the uncertainty analysis. The model must be discarded***."[6]

The record of Panel deliberations suggests some reluctance by others on the Panel to address the complex issues raised by Dr. Peto. Dr. Peto's concerns persisted as of at least May 1, when he stated the following:

> p. 88 : "I mean I think ***the wrong models have been fitted. That's my fundamental concern with the whole document***."
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> p. 93: "But why fit the model at all when you know that it's wrong? It's just the wrong model. I mean the idea that you can just fit any old model to a graph; the graph shouldn't have been drawn in the first place."

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[3] SAB Staff Office, EPA, Advisory Committee Meetings and Report Development: Process for Public Involvement (Sept. 2004) at 6, *available at* yosemite.epa.gov/sab/SABPRODUCT...reports/.../sabso_04_001.pdf.

[4] Dr. Julian Peto, Feb. 6, 2012 Transcript at 200, *attached hereto as* **Attachment B**. This citation and subsequent citations to transcripts are to transcripts prepared by a court reporter of the Panel's February 6, 7, 8; May 1, 8; and July 25 teleconference proceedings.

[5] *Id.* (emphasis added).

[6] Email from Dr. Julian Peto to Dr. John Neuberger, Dr. Mort Lippmann, and Dr. David Kriebel (Mar. 22, 2012) (obtained via Freedom of Information Act), *attached hereto as* **Attachment C**.

> p. 95: "I mean there's nothing else I can say. ***I just think it's scientifically preposterous to carry on***."
>
> p. 116: "***It's silly to fit a model that is wrong and then modify the conclusions***. You just fit a model which is more plausible to start with."
>
> p. 117: "The specific suggestion is that the – ***a more plausible model should have been used for calculating the RfC***. . . . (interruption). . . .Not for discussion of uncertainty factors afterwards."
>
> p. 122: "***You can't choose a model which you know is wrong and then discuss how you should modify your predictions. I mean the predictions are a consequence of the model. . . . I mean it (sic) completely unreasonable. It's not the way to do science***. . ."[7]

Dr. Peto has over 30 years' experience in the epidemiology of asbestos-related diseases. Based on that experience, he has clearly and repeatedly expressed strong and fundamental concerns regarding the modeling employed by EPA to derive the proposed RfC. Aside from a mention in the Draft Report that EPA should consider "plausibility" of a model[8], we have not discerned in either the record of the Panel's deliberations or in the Report that these concerns have been fully addressed and resolved.

Notably, the Draft Report does not advise EPA to discard the model it used, but instead merely suggests that EPA consider use of another model as well, an approach that does not remedy Dr. Peto's concerns. Unless those concerns were ultimately resolved to Dr. Peto's satisfaction, the final Report should acknowledge the significant points raised by him and explain why the Panel as a whole did not consider them meritorious. Only in that way can the public have confidence that the SAB made an attempt to understand and resolve complex scientific issues presented to it. At a minimum, and as has been done with other IRIS assessments (e.g., the recent dioxin IRIS assessment), the chartered SAB should address this diversity of Panel member opinions at its teleconference and recommend to the Panel that Dr. Peto be offered the opportunity to present a dissenting opinion in the Report if his concerns persist.

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[7] Dr. Julian Peto, May 1, 2012 Transcript at 88, 93, 95, 116, 117, & 122 (emphasis added), *attached hereto as* **Attachment D**.

[8] Draft Report at 4.

3. SIGNIFICANT TECHNICAL DEFICIENCIES RAISED BY OUTSIDE EXPERTS HAVE NEVER BEEN ADDRESSED BY THE PANEL

The Panel deliberations and Draft Report do not reflect consideration of key technical comments made by highly qualified public commenters that present significant questions about the scientific integrity of EPA's Draft Assessment. Nor does the Draft Report provide EPA guidance regarding these fundamental issues. By way of illustration only, the following important public comments have not been addressed in the Draft Report, or, to our knowledge, in any meaningful way in the course of the Panel's deliberations:

(i) The calculation of the RfC should be based upon average concentration because the lifetime cumulative exposure used in the Draft Assessment: (a) yields a confusing final RfC that would be misinterpreted by risk assessors because the daily dose assumes a lifetime of exposure; and (b) contains an unnecessary adjustment divisor of 60 (or 70, as now recommended in the Draft Report).[9]

(ii) The full Rohs data base from which the RfC subcohort was derived is confounded by age, making reliance on that data base inconsistent with EPA policy and sound science.[10]

(iii) The weight of scientific evidence does not support the Draft Report's conclusion that pleural plaques are associated with pulmonary deficits, because referenced

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[9] *See* comments by Elizabeth L. Anderson, Ph.D., ATS Fellow and David G. Hoel, Ph.D., Exponent, Inc. April 9, 2012, p. 3 and 11-13, *available at* http://yosemite.epa.gov/sab/SABPRODUCT.NSF/MeetingCal/7896D6DE96BECA7F85257956006D544B?OpenDocument, stating "Because the cumulative exposure point of departure (POD) was converted to average air concentration over a 70-year lifetime (minus 10 years) to derive the RfC, the RfC will be below an effects threshold for almost all exposure scenarios used in risk assessment (e.g. a 30 year residential scenario)" and asking the SAB Panel to "Resolve the issue of lifetime averaging and real-world applications of the RfC that would result in erroneous findings of unacceptable non-cancer hazard." Dr. Anderson also stated in follow up comments for the May 1, 2012 teleconference, *available at* http://yosemite.epa.gov/sab/SABPRODUCT.NSF/MeetingCal/F41FA6AC5AF02E24852579FA006B52F6?OpenDocument, that "use of the proposed RfC including the division by 60 years (or 70 years as proposed by the SAB) leads to false positives." *See also* comments by Suresh H. Moolgavkar, M.D., Ph.D., March 27, 2012, p. 2, *available at* http://yosemite.epa.gov/sab/SABPRODUCT.NSF/MeetingCal/7896D6DE96BECA7F85257956006D544B?OpenDocument: "Since the objective is to estimate a reference concentration, why does the Agency estimate an exposure-response relationship for cumulative exposure? An alternative approach would be to use concentration directly in the statistical analysis. . . . Since the BMCL is obtained directly in terms of the concentration, it can be used as the point of departure (POD) for an RfC calculation without dividing by 60 (tantamount to adding a third uncertainty factor) . . ."

[10] *See* comments by Suresh H. Moolgavkar, M.D., Ph.D., for the February 6, 2012 SAB Panel session, p. 16 -17, *available at* http://yosemite.epa.gov/sab/SABPRODUCT.NSF/MeetingCal/7896D6DE96BECA7F85257956006D544B?OpenDocument: "I do not have access to the exact data used by the Agency, but I have analyzed full Rohs dataset as described above and there is strong evidence of confounding by age. By its own criteria, the Agency should not be using this dataset for derivation of an RfC."

studies do not support the proposition for which they were cited.[11] Although the Draft Report now provides additional citations on this issue, the Panel never directly explains how it is addressing the well-founded and specific expert public comments concerning these studies' findings, or how the Panel construes the studies to somehow support the conclusion set forth in the Draft Report.

Overall, the content of the panel deliberations and the resulting Draft Report do not reflect thoughtful consideration of key scientific deficiencies raised by highly qualified external experts in their fields. Therefore, the chartered SAB should refer the Draft Report back to the Panel to address and resolve these and other public comments in a transparent and meaningful manner.

4. THE SAB'S FINAL REPORT AND COVER LETTER TO EPA SHOULD MORE DIRECTLY ANSWER THE CHARGE QUESTIONS SO AS TO FURNISH EPA CLEAR AND USEFUL GUIDANCE

(i) The Report should state that the non-cancer endpoint is not causally related to adverse effects.

The SAB Draft Report does not fully respond to EPA's charge question with respect to the localized pleural thickening ("LPT"), the selected non-cancer endpoint. EPA's charge asks the SAB to comment upon "whether the selection of this critical effect and its characterization is **scientifically supported** and clearly described."[12] This question has not been answered,

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[11] *See* comments by Lawrence C. Mohr, M.D., F.A.C.P., F.C.C.P., Professor of Medicine, Biostatistics, and Epidemiology, Director, Environmental Biosciences Program, Attending Physician, Pulmonary Medicine Consult Service, Medical University of South Carolina, April 8, 2012, p. 4-5, *available at* http://yosemite.epa.gov/sab/SABPRODUCT.NSF/MeetingCal/F41FA6AC5AF02E24852579FA006B52F6?OpenDocument, stating that "It is true that the preponderance of a large body of literature demonstrates that there is no statistically significant or clinically significant correlation between pleural plaques and decreased pulmonary function." *See also* pp. 22-25 and Appendix reviewing four recent publications.

See also comments by Elizabeth L. Anderson, Ph.D., ATS Fellow and David G. Hoel, Ph.D., Exponent, Inc., April 9, 2012, p.4, *available at* http://yosemite.epa.gov/sab/SABPRODUCT.NSF/MeetingCal/7896D6DE96BECA7F85257956006D544B?OpenDocument, explaining that "the Rohs et al team has lung function data" [per a letter from Dr. Lockey to Dr. Wong of January 1, 2012] and that in a previous study Dr. Lockey "actually did not find a statistically significant relationship between 'restrictive lung defect' . . . . and cumulative exposure." They further review limitations of cited studies and conclude (p. 8) that "if the quantitative relationship between LPT (pleural plaques) is not confirmed to be associated with an adverse effect such as decreased lung function, and the mechanism for such a relationship is unknown, it can be viewed only as a marker of exposure that is not verifiably causative of an adverse effect."

[12] Charge Question II.A. 2, Charge for IRIS Assessment for Libby Amphibole Asbestos, attached to December 21, 2011 Memorandum from B.Clark, NCEA to V. Vu, EPA SAB ("Charge Question"), *available at* http://yosemite.epa.gov/sab/sabproduct.nsf/MeetingCal/7896D6DE96BECA7F85257956006D544B?OpenDocument (emphasis added).

particularly with respect to the issue of whether there is any proven *causal* association between LPT and a functional impairment based upon the weight of scientific evidence. To be thorough and clear, the SAB Report should clearly state, for the reasons summarized below, that portions of EPA's characterization are not scientifically supported.

For example, the first two symptoms that EPA's Draft Assessment references as possibly associated with LPT are "breathlessness during exercise and chronic chest pain." As expert public comments have made clear, credible scientific support for that portion of EPA's Draft Assessment is lacking. Furthermore, to our knowledge, the Panel has not even addressed that portion of EPA's Draft Assessment. The final Report should explicitly state that this portion of EPA's Draft Assessment is not supported by available scientific evidence.

For the third and last symptom that EPA's Draft Assessment suggests is associated with LPT, "restrictive lung function," the Draft Report provides a vague and unclear conclusion whose meaning and underlying reasoning is virtually unascertainable from the Report. As background, the Panel's April 11 draft report stated that LPT has a "measurable relationship to altered lung function." After the significance of the study upon which this statement was based was questioned, the Panel revised this language in its July 11, 2012 draft to state that LPT is "predictive of risk for other asbestos-related diseases." Unfortunately, this language further confused the issue, because the term "predictive" suggested (but did not find) an unproven disease pathway or a causal connection. EPA itself sought clearer guidance on exactly what the Panel had concluded based upon the literature[13], and the panelists made a number of statements that evidenced that they were struggling to find any clear scientific causal association between LPT and adverse symptoms.[14]

The current Draft Report sidesteps the issue of whether LPT causes any symptoms by concluding that LPT is "**generally associated** with reduced lung function."[15] There are two fundamental problems with this language. First, it fails to provide clear guidance to EPA and the public. What precisely does the Panel mean by "generally associated"? If the panel is suggesting a causal relationship between LPT and reduced lung function, then it should state that

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[13] July 24, 2012 Memorandum from David Bussard, NCEA to Dr. Agnes Kane, EPA SAB re Questions and Clarifications related to SAB July Draft Report at 2, *available at* http://yosemite.epa.gov/sab/SABPRODUCT.NSF/MeetingCal/DE16F40DF2BE9271852579FB0054C2BF?OpenDocument ("EPA would appreciate if the Panel could clarify what is meant by 'predictive' and how that might differ from 'associated'?)"

[14] See, for example, Dr. John Balmes, Feb. 6, 2012 Transcript at 208, *attached hereto as* **Attachment B** ("where localized or pleural thickening has been brought up **isn't necessarily associated with decreased lung function**") (emphasis added); Dr. Salmon, May 1, 2012 Transcript at 56, *attached hereto as* **Attachment D** ("we are looking at these radiographic changes as an adverse effect in their own right. **We are not necessarily arguing whether or not they progress to some other disease entity**") (emphasis added).

[15] Draft Report at 1.

conclusion clearly and furnish the scientific basis for it. By using the vague and unexplained term "generally associated," however, the Draft Report leaves EPA and the public to guess at the Panel's meaning. For example, perhaps the Panel is referring to a weak correlation between LPT and pleural plaques that is only seen at high levels of exposure to asbestos. If so, this finding should be stated so EPA can assess whether it has selected an appropriate endpoint that is consistent with agency policy for doing so.[16]

A second problem with the Draft Report's conclusion is that it does not discuss how cited specific scientific studies support its findings. As expert public commenters have pointed out to the Panel, these studies do not support the proposition for which they are cited. Thus, on this issue of symptoms caused by LPT and whether the Assessment's characterization is "scientifically supported," the Draft Report falls well short of providing clear and useful guidance to EPA.

It is the responsibility of the chartered SAB to ensure that its final Report provides clear and useful guidance to EPA and that the bases for the Report's conclusions are transparent and reflect thorough consideration of the best available science. Because this Draft Report's discussion of the relationship between LPT and potential adverse health effects meets none of these objectives, the chartered SAB should refer the Draft Report back to the panel with instructions that it revisit and clarify its discussion and conclusions regarding this issue.

(ii) To respond properly to EPA's charge questions, the SAB Report should clearly and succinctly state that the RfC modeling was inadequate and should be discarded.

For the RfC calculation, EPA's charge question asks if "the selection of the [Michaelis-Menten] model [is] scientifically justified and clearly described."[17] This question has not been answered in the Draft Report. In light of Dr. Peto's strongly worded conclusion that the model is "wrong," and the Draft Report recommendations that seem to suggest that EPA should choose a different model, the Panel appears to have concluded the model is not scientifically justified. However, the Draft Report does not say this. Instead, the Panel's conclusion is lost in nuanced

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[16] *See* Environmental Criteria and Assessment Office, EPA, Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (Oct. 1994) at 2-7, *available at* http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=71993 ("Although the development and use of biologic markers is increasing at a rapid rate, the validity and meaning of the markers need to be established before they can be used as analogous to 'exposure' or 'disease' in classical epidemiologic research and prior to their use in quantitative dose-response assessment."); EPA. A Review of the Reference Dose and Reference Concentration Process (Dec. 2002) at 4-11, *available at* http://www.epa.gov/raf/publications/review-reference-dose.htm ("a statistically significant change that lacks biological significance is not considered an adverse response").

[17] Charge Question III.A.2.

and contradictory language.[18] The most recent Draft Report eliminates the clearest statement on this issue from the prior draft, i.e., that the Michaelis-Menten model should be "replaced." To provide clarity on this issue, the chartered SAB should ask the Panel to respond more clearly and directly to the charge question.

5. THE SAB REVIEW PROCESS HAS BEEN TOO RUSHED, AND THE PANEL AND THE PUBLIC SHOULD BE PROVIDED WITH ADDITIONAL TIME TO CONDUCT A MORE THOROUGH SCIENTIFIC REVIEW

The Draft Assessment peer review process has been rushed, and has failed to provide adequate time for the Panel and chartered SAB to understand the Draft Assessment and the public comments on it, and to address the key underlying issues in a thoughtful and independent way. Similarly, inadequate time frames have been furnished to allow the public to provide oral and written comments on the Draft Assessment. As an example, the Draft Report was not provided to the chartered SAB and the public until the last day in August, allowing little more than two weeks for preparation of public comments, and little time for the chartered SAB's own review before the September 25 teleconference. We are concerned that such an abbreviated period precludes an adequate opportunity for thorough and thoughtful public comment and chartered SAB consideration of the complex and controversial scientific questions posed by the Assessment.

Panel deliberations were also rushed, allowing little time for busy panelists to focus on these difficult issues. As one panelist observed:

> "This has been very challenging. This group is coming from very different perspectives and degree of familiarity both with the details of the Libby cohort data, with the risk analysis process, and with the Libby AA risk assessment itself. ***I would have preferred that we back up, start with the Risk Assessment document again, and make sure everyone was really grounded in what had been done***."[19]

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[18] The Draft Report initially asserts that "[f]rom a statistical standpoint, this methodology is scientifically justified." Draft Report at 26. Then, however, the Draft Report "recommends that a thoughtful approach to model selection be used, including consideration of biological/epidemiological plausibility, combined with careful examination of the data and application of the AIC [Akaike Information Criteria]" and "that model features should also be considered in choosing a model." *Id*. at 26-27. Although the Draft Report does not state that an alternative model should be selected, it states that "a thoughtful approach may lead to selecting the dichotomous Hill model." *Id.* at 27.

[19] Email from Dr. Katherine Walker to Dr. Diana Wong (May 7, 2012) and related email chain providing background information (May 3, 2012) (obtained via Freedom of Information Act), *attached hereto as* **Attachment E**.

Clearly, this rushed schedule placed a hardship on panelists and likely limited their ability to complete a carefully considered evaluation.

The accelerated review also limited opportunities for public input. For example, and as discussed above, the entire review was completed before access to key underlying raw data could be obtained for scientific scrutiny. Also, despite repeated requests for more time given the complexity of the issues and the limited number of presenters involved, the public presentations before the Panel were limited to three minutes, which was way too short by any reasonable yardstick to address the multiple complex issues at stake.

In an effort to enhance the opportunity for, and value of, public comment on draft IRIS assessments, the SAB Staff Office recently concluded that members of the public should typically be afforded some meaningful dialogue with SAB IRIS panels (and presumably the chartered SAB) during public meetings and teleconferences to ensure an appropriate exchange of expert technical views and recommendations. During the process to date for this Draft Assessment, that opportunity was only offered to public commenters at the first Panel session in February, 2012. The May and July Panel sessions offered merely three minutes for commenters at the beginning of each session, but no follow-up opportunity to engage on the commentary provided at those sessions. Similarly, no such opportunity has been afforded for the September 25 teleconference. These shortcomings hardly comport with a process truly designed to seek and utilize the benefit of external expert opinion.

As we believe the discussion in this letter amply demonstrates, the course of the proceedings for the critical peer review of the Draft Assessment has been procedurally deficient, and the Report prepared by the Panel does not reflect clearly stated and substantiated findings of the Panel with respect to several key issues addressed by the Draft Assessment or what appear to be strong dissenting views regarding Panel conclusions. Accordingly, we respectfully request the following:

- All commenters at the September 25 teleconference be afforded up to 10 minutes to make their oral presentations;

- Prior to a decision by the chartered SAB at that teleconference as to a path forward on the Draft Report, a meaningful opportunity be provided for commenters to engage the chartered SAB and any Panel members participating in the teleconference on issues discussed during the teleconference or in the Draft Report;

- Based on the fundamental shortcomings in the Draft Report expressed in this letter and other public comments, the chartered SAB should refer that draft back to the Panel to address those deficiencies that have resulted in a failure to provide clear – and well founded and explained – technical conclusions that comport with

the weight of best available science. Among other things identified herein, that referral should request that the Panel consider, and provide an adequate opportunity for public comment on, data underlying the Draft Assessment that has only very recently been made publicly available and for which a meaningful opportunity for comment has not been heretofore provided;

- Panel members who continue to hold dissenting views be expressly offered the opportunity, consistent with SAB policy, to present "dissenting opinions" to be included as part of the final Report, together with an explanation in the Report as to why the remainder of the SAB did not consider any such opinions meritorious; and

- A written response from the SAB Staff Office to these requests prior to the September 25 teleconference.

Thank you for your timely consideration of, and attention to, these requests.

Sincerely yours,

/s/

Karl S. Bourdeau

Attachments

ATTACHMENT A

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June 25, 2012

VIA E-MAIL

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Re: SAB Panel Report on Draft Libby Amphibole Asbestos IRIS Assessment

Dear Dr. Wong:

On behalf of an interested party, we have closely reviewed the draft Science Advisory Board ("SAB") Panel peer review report on the proposed Libby Amphibole Asbestos ("LAA") IRIS assessment and observed the Panel's public deliberations. In order to assist the Panel as it further deliberates, this letter provides the following brief comments. In particular, this letter points out a few significant instances in which the draft report does not appear consistent with statements of Panel members during the Panel's May, 2012 teleconferences, and where the Panel's draft letter to EPA Administrator Jackson regarding that report does not reflect principal conclusions the Panel appears to have reached in its report and/or deliberations. I request that you forward these comments to the Panel for its consideration as it finalizes its draft report and letter, and confirm to me when you have done so.

1. **The Panel's Report and Letter Should Address Clearly and Thoroughly Significant Scientific Concerns Expressed by the Panelists.**

   a. **The Panel's Final Report Should Clarify That the Non-Cancer Endpoint Is Not Known to Be on a Disease Pathway.**

The cover letter and draft report both indicate, without support, that localized pleural thickening ("LPT") has a measurable relationship to altered lung function, i.e., that LPT is on the disease pathway. However, the Panel has not reached any such determination. During the May 1, 2012 telephone conference, Dr. Salmon clarified that the Panel is *not* determining that LPT is on a disease pathway. Dr. Salmon said that "we are looking at these radiographic changes as an adverse effect in their own right. We are not necessarily arguing whether or not

they progress to some other disease entity. And that it needs to be considered as an adverse effect in its own right." Dr. Salmon went even further, asserting that expert commenters' testimony explaining the absence of any relationship between LPT and disease is therefore not pertinent. No one on the Panel challenged Dr. Salmon's comment.

Despite Dr. Salmon's clarification that the Panel is not finding a relationship between LPT and disease, the Panel's draft report inaccurately conveys the opposite message: that LPT itself leads to adverse lung function. Such a finding conflicts with the weight of scientific evidence. For instance, Dr. Lawrence Mohr, Professor of Medicine, Biostatistics and Epidemiology and the Director, Environmental Biosciences Program at the Medical University of South Carolina, with particular expertise in pulmonary medicine and lung disease, observed that the large body of literature pertaining to LPT demonstrates that there is no statistically significant or clinically significant reduction in lung function associated with LPT per se. Also, Dr. John DeSesso, Adjunct Professor of Biochemistry and Molecular & Cellular Biology at Georgetown University School of Medicine, testified on how LPT differs structurally from those asbestos-related diseases that are symptomatic. The Panel did not disagree with, or otherwise address, these comments or that substantial body of scientific opinion during the teleconference.

In its draft final report and letter to the EPA Administrator, the Panel should clearly state that it has not concluded that LPT causes, or progresses to, reduced lung function, if that is the case. If, on the other hand, the Panel actually disagrees with Dr. Mohr, Dr. DeSesso, and the considerable body of scientific evidence that supports their conclusions, then the Panel should explain clearly the basis for its view, rather than simply disregard the testimony of these experts. The upcoming July 25 teleconference would provide a timely and transparent forum in which to do so, and we request that you put this item on the Panel's agenda for that teleconference.

b. The Panel's Draft Letter to EPA Administrator Jackson Fails to Reflect the Panel's Rejection of the Michaelis-Menten Model.

Panel deliberations have been highly critical of EPA's choice of the Michaelis-Menten model, one of EPA's key modeling tools used to support its conclusions. For example, in the May 1 teleconference, Dr. Peto reinforced the deficiencies of the model selection for deriving the proposed Reference Concentration ("RfC"), noting repeatedly that that model is simply "wrong," and a "scientifically preposterous" basis upon which to base the RfC. The Panel's draft report embraces this concern, noting that this model should be "replaced." Despite the fundamental importance of that recommendation, the draft letter to Administrator Jackson fails to even acknowledge this issue. Given the model's critical role in the derivation of the RfC, this recommendation should be set forth clearly in the Panel's cover letter.

c. The Panel's Report and Letter to the Administrator Should Advise That EPA's Data Sets Are Too Small to Serve As a Defensible Basis for the RfC and IUR Proposed.

During the teleconference, several members of the Panel acknowledged the severe limitations of the data sets chosen, noting that "there's not much data support" (Dr. Sheppard), "we know these data sets are limited" (Dr. Walker), and "you can't develop a model for mesothelioma based on seven cases or whatever it is [as to do so is "completely disreputable"] (Dr. Peto). Also, expert commenters have explained why the data sets selected by EPA for deriving the RfC and Inhalation Unit Risk ("IUR") are too small to serve as a scientifically defensible basis for the RfC or the IUR.

The Panel's draft report does not address this fundamental shortcoming. Instead, the current draft only obliquely recognizes the importance of using a larger data set, e.g., by noting that a "larger population over a lifetime should be considered when selecting the models with which to characterize exposure-response relationships" and that because there are "285 [additional] workers with at least some information [, p]ossibly some additional analysis could be done on that group" to derive the IUR. The draft report fails, however, to convey clearly Panel members' concern over the inadequacy of the data sets chosen by EPA. Moreover, the draft cover letter to the Administrator fails to even acknowledge this significant issue and the resulting weakness and uncertainty of both the RfC and IUR if derived from the extraordinarily small amount of data employed by EPA. The Panel's report and letter should directly address these data limitations.

2. The Panel Should Recommend Consideration of Toxicology Data From a Range of Other Amphiboles.

During its deliberations, Panel members discussed that Libby amphibole likely acts in ways comparable to other amphiboles. As observed by panelists, the results of modeling the exposure-response relationship of a full range of other amphiboles should be taken into account by EPA in its final assessment. This recommendation should be stated in the Panel's report and cover letter.

The current draft report only touches upon this issue, finding that in light of the similarity between amphiboles in composition, physical properties, and biological effects, "it appears reasonable, and indeed necessary, to at least debate the question of whether the available data on non-cancer health effects of amphiboles are sufficient to mitigate the acknowledged data shortage for Libby amphibole itself." (p. 31). To the extent the Panel has determined that EPA should rely upon, or at least consider, data regarding other amphiboles, e.g., to address in part the data set shortcomings identified above, the Panel should clearly say so.

We understand that there is credible scientific evidence that the carcinogenic potency of LAA lies somewhere in the middle of the range of carcinogenic potencies of amphiboles. For example, at least one expert commenter referenced evidence that Libby amphibole is less reactive and therefore less toxic than some other amphiboles. The Panel should recommend explicitly that EPA acknowledge and consider, as scientifically appropriate, this available toxicity information in any final LAA toxicity assessment.

3. The Panel Should Avoid Policy Recommendations.

The Panel's discussion at the May 8 teleconference demonstrated that certain proposed revisions to the Panel's draft report were informed by policy preferences rather than science. For example, both Dr. Balmes and Chairwoman Kane seemed to suggest that the Panel's report should advocate a "more conservative approach" that was "more protective of public health." The questions before the Panel concern which hypotheses or findings are supported by the weight of scientific evidence. Policy choices regarding the level of human health protection EPA should provide for are beyond the purview of the SAB, as noted by the SAB Staff Office itself in its recent enunciation of additional practices designed to enhance SAB panel activities.

Another example of a public policy question that the Panel should decline to address is whether a biological marker should serve as an endpoint for purposes of a toxicological assessment. The scientific question for the Panel is whether EPA's draft findings as to symptoms associated with LPT are supported by the weight of the scientific evidence, not whether from a policy perspective this particular biological marker is an appropriate endpoint even without symptoms. Accordingly, the SAB Panel should omit policy recommendations, and in its report and cover letter limit itself to the scientific evaluation of EPA's draft document.

4. The SAB Panel Should Consider and Respond to the Important Scientific Points Raised by Expert Commenters.

The Panel has yet to openly and thoroughly discuss the informed public comments offered by highly qualified experts, even though these experts raised legitimate and important questions about the Panel's draft conclusions and recommendations. We urge the Panel to discuss these important scientific issues and opinions. Unless the Panel does so, it will not have demonstrated thoughtful and transparent consideration of external expert scientific opinion being offered to enhance the Panel's deliberations. Moreover, in the absence of such a discussion, interested members of the public will be left without an understanding as to the Panel's reaction to fundamental comments regarding, among other things, the data sets and models chosen. We request that at its July teleconference the Panel discuss the points addressed in this letter, and the expert comments related to them, to provide the public with a clear explanation of the Panel's analysis of them.

In closing, we ask that the SAB Panel address the above-described inconsistencies between panelist and/or expert comments and the Panel's draft report and cover letter. We also encourage the Panel to supplement and clarify its draft report and cover letter with clear, specific, and objective advice to EPA, with the goal of EPA issuing a final assessment that more fully reflects the weight of scientific knowledge and accepted scientific methods.

Sincerely yours,

Karl S. Bourdeau

cc: Dr. Vanessa Vu

ATTACHMENT B

In The Matter Of :

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
SCIENCE ADVISORY BOARD

LIBBY AMPHIBOLE ASBESTOS REVIEW PANEL
MEETING - DAY 1
February 6, 2012

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1325 G Street NW, Suite 200, Washington, DC
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Page 197

1 in the morning. I can also give them to Dr. Wong to
2 provide to you. Whether she does that via the web
3 site or some other mechanism, I don't know.
4 With exception of the Marshand paper
5 unless, Dr. Winn, do you have that?
6 FEMALE SPEAKER: I don't have it with me
7 but I can get it.
8 DR. DeVONEY: Okay. So I think we are
9 covered on that. Would a CD in the morning work for
10 you or do you want hard copies? Just let me know.
11 DR. WALKER: If you can get it on the web
12 site, we can just download it directly.
13 DR. DeVONEY: Okay. I'll coordinate with
14 Diana either at break or after lunch. And, Dr. Kane,
15 just let us know in what format you would like it
16 provided. We have electronic copies of it all.
17 DR. KANE: What would everyone like?
18 Electronic copies? Is that okay? Okay. Thank you
19 very much.
20 I didn't mean to exclude the rest of the
21 committee from reviewing those papers. I was
22 deferring to your expertise of the subgroup for the

Page 198

1 really careful analysis. Everyone is actually invited
2 to weigh in.
3 DR. VU: I just want to clarify my points
4 earlier is that this draft the agency has not
5 considered those studies. So one of the things that
6 you could recommend to the agency whether they should
7 consider or not, certainly the draft assessment should
8 have the current information, but whether you would
9 recommend the agency to initially consider this.
10 You are not asked to analyze and come up
11 with a reference concentration. You advise the agency
12 what needs to be done. Thank you.
13 DR. NEWMAN: That's good news.
14 (Laughter)
15 DR. KANE: All right. This is a large
16 subgroup, so I would like to invite Dr. Kriebel.
17 Comments?
18 DR. KRIEBEL: Thank you. Yeah, I actually
19 don't think I have much to say at this point. Because
20 I really need to hear a little bit more.
21 I think specifically one of the things
22 that's happening here that for me is useful is trying

Page 199

1 to think about how -- one of the things I'm hearing
2 here is a concern of the committee to try and find
3 ways to bring in -- to suggest to EPA how to bring in
4 additional information that may be supportive of an
5 RfC without necessarily completely changing the
6 original strategy.
7 So, for example, these community exposure
8 studies, there's this concern that by focusing only on
9 the subgroup that's got the really good exposure data,
10 we lose a lot of the larger cohort. And of course
11 that is a concern. Doesn't mean that we should -- I
12 wouldn't necessarily recommend that they throw out
13 what they have done and start over, but I'm looking
14 for ways to suggest that the approach can be
15 strengthened.
16 And I really don't have anything specific
17 yet because I need to hear a little bit more about
18 this issue of the non-cancer endpoint. So nothing
19 more for now.
20 DR. KANE: Would anyone else like to add
21 something along those lines? Yes, Julian.
22 DR. PETO: At the risk of repeating myself,

Page 200

1 I mean a reality check on the appropriateness of the
2 modeling for pleural thickening is as I said this
3 morning, there's a 500-fold difference in the
4 predicted prevalence of pleural thickening compared
5 with the mesothelioma. And in Britain we've actually
6 got data on this but, I mean, roughly one in a
7 thousand British women die of mesothelioma.
8 There are 300,000 deaths a year, and
9 there's the order of 300,000 deaths in Britain. So
10 one in a thousand British women die of mesothelioma.
11 And there's quite strong evidence that more than half
12 of those are caused by environmental exposure. So
13 this is actually the result of very long-term,
14 low-level asbestos exposure.
15 And if you multiply 1 in a 1,000 by 500, it
16 would imply that 50 percent of British women have
17 pleural thickening caused by asbestos, which is not
18 the case. And that discrepancy between this modeling
19 and that illustrates how extreme the error is. And I
20 just think it's inappropriate to present these
21 calculations. I think they are -- I think they are
22 completely divorced from reality.

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Page 201

1 DR. KANE: All right. So we have that
2 viewpoint on the table. Let's leave it on the table
3 for further discussion.
4 Lianne Sheppard? You also were involved in
5 this subgroup.
6 DR. SHEPPARD: Yeah. I don't know that I
7 have too much more to add. I thought that the -- it
8 was the Marysville cohort was well chosen based on the
9 criteria that were used. It would be nice to be able
10 to focus on environmental exposures, but I recognize
11 there really aren't the exposure data except for maybe
12 in this new Minneapolis cohort.
13 So that would be really great to get the
14 perspective of that. And having more than one study
15 because there's always heterogeneity in estimates,
16 having more than one study so we can get more
17 perspective on these estimates would be great. But
18 given what the EPA had to work with, I think they made
19 very appropriate choices.
20 DR. KANE: Now, do other members of the
21 panel have any other comments about this, the choice
22 of the study populations particularly? Dr. Salmon?

Page 202

1 DR. SALMON: I think obviously the choice
2 in the reports as we have it is very much driven by
3 what's available. And I think the, you know, now that
4 it appears we do have some additional data on
5 additional endpoints and additional study populations,
6 I think it's very important to take a look at those.
7 I mean the agency will have to decide what they can do
8 with them and whether they can be actually used as the
9 basis of the RfC.
10 Clearly I think at this -- for this
11 particular charge question, I think we are talking
12 about hazard identification. And I don't think that
13 there's any question that these studies would
14 contribute to that. I think we can probably afford to
15 defer discussion about those response to the related
16 charge question.
17 And I think specifically as far as hazard
18 identification is concerned, it's easy to say that the
19 new information should be at least reviewed for
20 relevance and to the extent to which it supports the
21 existing conclusions which I believe it does from what
22 I'm -- what little I know about it at this point. So

Page 203

1 that's it.
2 DR. KANE: All right. Some of you were
3 having discussions about whether PFTs, pulmonary
4 function tests, were available on any of these
5 populations. Is that to say that you would -- you are
6 looking at the possibility of something other than
7 pleural plaques for this kind of non-cancer endpoint?
8 DR. NEWMAN: I think that's going to go
9 maybe to the next charge question. Yes.
10 DR. KANE: Are you ready to go there yet?
11 DR. NEWMAN: Yeah, but I think I came up
12 with it in the context of using that as a way of
13 corroborating whether pleural plaques are an adverse
14 effect.
15 DR. KANE: You stated that very clearly.
16 So we are ready to move on to the next charge
17 question, that would be number 2 on the screen related
18 to the radiographic evidence for localized pleural
19 thickening or pleural plaques.
20 All right. Since, Dr. Newman, you got us
21 in that transition, you go.
22 DR. NEWMAN: Okay. Will do. In my view

Page 204

1 the selection of radiographic evidence of localized
2 pleural thickening in humans is an appropriate
3 critical effect for the derivation of the RfC. I
4 think it's well supported by the lines of evidence
5 that we find in Section 4.1.1.4.2.
6 (Laughter)
7 DR. NEWMAN: And the section is clearly
8 described. Additionally, I think the Larsen data from
9 2010 paper helps reinforce the point that pleural
10 changes would be more suitable than, say, using the
11 presence of small opacity profusion scores.
12 You know given that the time from hire to
13 date of radiographic appearance of a pleural change
14 comes earlier than the -- than the appearance of small
15 opacities. I think that we are all very eager to see
16 Dr. Larsen's abstract in paper to help, you know,
17 further for the EPA the lines of evidence relating
18 pleural changes to spirometric abnormalities. So I
19 think that's going to be a welcome addition for the
20 EPA to consider.
21 One of the -- one of the things that I
22 don't want to have missed in this conversation is that

Page 205

1 if for some reason we as a group would say to the EPA
2 that localized pleural thickening is not a reasonable
3 basis for an RfC, if we were to say that, I think that
4 then we have to think, well, what's the next best
5 thing in terms of a non-cancer endpoint.
6 And in my point of view that would be the
7 presence of asbestosis as reflected by small opacities
8 on chest radiographs. It's not like if not pleural,
9 then nothing. It's if not pleural, then it's
10 asbestosis, in my view.
11 So, you know, while there are other
12 endpoints health endpoints that might be considered
13 candidates for the critical effect for deriving the
14 RfC, none of them in my view is superior to localized
15 pleural thickening. But the ones that I think we all
16 know one to consider would be things like diffuse
17 pleural thickening and small opacity profusion.
18 Just to sum up, localized pleural
19 thickening I think has the appropriate specificity and
20 is not confounded by cigarette smoking, and I think is
21 a suitable basis for deriving the RfC.
22 DR. KANE: Dr. Woskie.

Page 206

1 DR. WOSKIE: I have to remind you that my
2 training is as an industrial hygienist, not a
3 respiratory physician. So I have to defer to my
4 colleagues' knowledge about the physiology. But the
5 argument I thought was well made in the document and
6 made sense to me and also was supported by the
7 reported latency results that the localized pleural
8 thickening occurs in, you know, 8, 10 years compared
9 to the diffuse as far as follow-up, you know, having a
10 cohort with sufficient follow-up to actually see
11 disease.
12 So that was the other piece of the argument
13 that made sense to me.
14 DR. KANE: Dr. Sheppard?
15 DR. SHEPPARD: Yeah, I generally also
16 agreed. I brought up a question this morning and I
17 want to revisit it and engage our physician colleagues
18 on the panel with a little bit more discussion.
19 I think I've been convinced, but the basis
20 in this data set is x-ray findings. And there are
21 other changes on x-rays besides localized pleural
22 thickening which are also caused by asbestos. And so

Page 207

1 as a statistician why not just look at all of them,
2 any change on x-ray that might be caused -- that's
3 considered caused by x-ray, I mean, by asbestos,
4 particularly since these are prevalent x-rays.
5 And the changes most likely happened way
6 back in time. So we are not looking at any time to
7 event in this analysis at all. So I just wanted to
8 revisit that question one more time before we put it
9 to bed. Why -- and in fact in the primary analysis
10 cohort it makes almost no difference because there's
11 one case that's excluded that has another outcome.
12 But in the bigger cohort there are more cases.
13 So why not help me understand a little bit
14 better why wouldn't we look at more -- more changes on
15 x-rays than just that one?
16 DR. KANE: Can anyone answer that question?
17 Dr. Newman.
18 DR. NEWMAN: Well, I may not answer it, but
19 I'll try. And I'll welcome input from some of my
20 colleague pulmonologists. I think that's a really
21 interesting idea.
22 As a general observation, the pleural

Page 208

1 findings will appear before the other findings. And
2 so I think that's why the thinking has tended to focus
3 on the pleural abnormalities.
4 DR. SHEPPARD: But my understanding is that
5 sometimes you see the one outcome and not the other,
6 right?
7 DR. NEWMAN: That's true. One can see, for
8 example, asbestosis, the fibrotic lung disease, you
9 can that on x-ray and in an individual who never
10 develops any pleural abnormalities. So that
11 definitely does occur.
12 DR. BALMES: I guess I'll just chime in as
13 another pulmonary physician that again I think it's an
14 interesting idea. I agree with Lee that usually
15 you'll see localized pleural thickening before you
16 would see asbestosis or diffuse pleural thickening.
17 The advantage of diffuse pleural thickening
18 or asbestos is those are clearly linked to decreased
19 lung function where localized or pleural thickening
20 has been brought up isn't necessarily associated with
21 decreased lung function. I don't know how much
22 difference it would make with the Marysville cohort,

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Page 209

1 but it's certainly a reasonable suggestion.
2 DR. KANE: Dr. Redlich, I would like to ask
3 another pulmonologist.
4 DR. REDLICH: I think we would all sort of
5 feel more comfortable because of this question of how
6 significant our pleural plaques is if there was enough
7 data to do a risk estimate on other outcomes, but in
8 that same paper there were only 12 participants, I
9 believe, or 8 with interstitial changes.
10 So it ends unbeing a much smaller number.
11 And of the 80 with pleural changes, only 12 had
12 diffuse pleural thickening. So -- what number was it?
13 Did I have it wrong?
14 I am sorry. Even less. So I think the
15 problem is there haven't been enough of those other
16 endpoints.
17 DR. SHEPPARD: Yeah, but I'm talking about
18 adding them all together, not looking at one outcome
19 versus another.
20 DR. WOSKIE: So you are saying any --
21 DR. SHEPPARD: Yeah, any change.
22 DR. KANE: Yes, Dr. Salmon.

Page 210

1 DR. SALMON: I just wanted to put in a
2 comment here from the risk assessment point of view as
3 opposed to lung, lung physiology. One of the things
4 which we actually saw earlier about the National
5 Academy's recommendations was the importance of
6 comparability between different risk assessments.
7 And this is important for a whole variety
8 of reasons, but certainly it's from a practical point
9 of view it's a very useful attribute for the agency if
10 the different risk assessments are comparable at some
11 level. And in order to assure that at least for the
12 simple case of laboratory studies in animals, the
13 EPA's gone to quite some lengths to define degrees of
14 severity of the effects and what they would regard as
15 a suitable effect to use as basis of an RfC or some
16 other guidance level.
17 There's a considerable problem arises when
18 we move away from the well-trodden paths of analyzing
19 animal studies and getting into epidemiology which as
20 always is a lot more complicated. And I think one of
21 the things to bear in mind is I think the agency made
22 a good choice here, certainly with the data that they

Page 211

1 had at the point of writing the report, I think they
2 made an excellent choice of endpoint.
3 And I think it's interesting that they made
4 a -- what I should probably say a good effort at
5 defending that as being not only an observation but an
6 observation in adverse effect. But I think one of the
7 things to bear in mind is that if this was an animal
8 study, then the simple pathological observation, which
9 of course would have been obtained by slicing up the
10 rat rather than just looking at x-rays, so it would be
11 a bit easier in some respects, but nevertheless we are
12 looking here at an actual structural change which we
13 regard as being a deviation from normality in tissue
14 structure which was associated with the exposure, that
15 in itself would be regarded as a relatively severe
16 endpoint in an animal study.
17 It wouldn't have to be associated with the,
18 you know, detriments in lung function which you can
19 measure in rats but it's not usually done because it's
20 difficult and the blighters bite when you are trying
21 to do it. But the fact of the matter is that in, you
22 know, in the spectrum of endpoints which are typically

Page 212

1 taken up for use in risk assessment, just the
2 observation of a structural change of this sort in
3 response to exposure would in itself be regarded as
4 quite a severe endpoint.
5 It's not -- it's not as minimal as you --
6 as you sometimes would be tempted to regard it from
7 the way it's described in x-rays. And I think this is
8 a not uncommon problem with epidemiological studies
9 that we often don't have access to the sort of minimal
10 type responses which are typically regarded as if you
11 write the entry point for adversity in the animal
12 studies.
13 And I think that's something that needs to
14 be borne in mind when we are debating things like, you
15 know, is this a sufficient -- is this a truly adverse
16 effect. There's absolutely no question whatsoever
17 that it would be regarded as not merely adverse but
18 quite substantially adverse if this was an animal
19 study.
20 DR. KANE: Let me ask Mort Lippmann first,
21 and then we'll come back to you, Jeff, and other
22 person here. Mort, do you have something to add?

Page 213

1 DR. LIPPMANN: Well, the x-ray evidence can
2 be misleading. I mean just because you have
3 radiographs of coal, you can -- (inaudible) -- some of
4 them really look terrible by x-ray but they have no
5 functional deficit. There's no evidence of life
6 shortening for many of them.
7 And so the observation that something can
8 be measured doesn't prove adversity. In fact the coal
9 miners are more often compensated for black lung by
10 x-ray but not for substantial pulmonary function loss
11 which they, you know, which isn't part of the
12 definition legally.
13 You can get siderosis from iron oxide with
14 little evidence of serious consequences. So I'm
15 reluctant to, you know, set a standard or reference
16 concentration on simply something that can be
17 measured. I think we need more.
18 DR. KANE: All right. Let's keep all these
19 thoughts on the table. Jeff?
20 DR. EVERITT: Well, just approaching it
21 from the way we do animal data with, you know,
22 pathology endpoints, which is an art and a science to

Page 214

1 itself, but we often combine endpoints. So you might
2 look at a lung and say, okay, you have got
3 fibroproliferative disease. You might combine the
4 lung and pleura.
5 You know you might not separate if you
6 don't know they are different pathogenic mechanisms
7 that underpin it. So then the question would be why
8 not go back to a situation where you just did multiple
9 radiographic abnormalities as that assessment. And
10 certainly if you have parenchymal lung fibrotic
11 lesions by radiograph and you had pleural
12 fibroproliferate disease, it would give you more
13 assurance on a radiograph like that that you were
14 probably dealing with something that you'd have a
15 little more assurance that you were getting into an
16 adverse health effect as opposed to a bio marker.
17 DR. SALMON: I can't think of any risk
18 assessment which has been undertaken with the
19 assumption that an observable structural
20 histopathological change would be regarded as a
21 biomarker. There is no such risk assessment.
22 DR. KANE: Dr. Kriebel.

Page 215

1 DR. KRIEBEL: Yeah. So I think we were
2 discussing this question of whether these x-ray
3 changes are a useful, suitable non-cancer endpoint.
4 And I think here's a place where I am wondering about
5 drawing on other asbestos literature.
6 And I'm sorry that I haven't done my
7 homework here and gone and done this myself, but the
8 question I have, and maybe the occupational physicians
9 can help me with this, are there not other asbestos
10 cohorts in which we have studied the relationship
11 between x-ray changes and pulmonary function so that
12 we can talk more meaningfully about that link by
13 drawing on other cohorts?
14 This is a place where I would think it is
15 very appropriate to use other kinds of asbestos
16 literature. Doesn't have to be Libby asbestos because
17 we are simply trying to build the case for the meaning
18 of diffuse pleural thickening or localized pleural
19 thickening and so on.
20 And I would suggest that this document
21 perhaps could have been strengthened by appealing to
22 that literature.

Page 216

1 DR. NEWMAN: If I can respond to that, I
2 think this is one of those places where looking at the
3 other literature, specifically on the question of
4 what's the relationship between pleural thickening and
5 physiology, in this case spirometry it is very
6 appropriate. And some of that is referenced in this
7 document, so you see for example a fairly old now but
8 landmarked paper that David Schwartz did quantifying
9 on CAT scan the amount of pleural plaque and relating
10 it to spirometric abnormalities.
11 So there are studies like that. And that
12 is one that is cited in this document. And in a way,
13 Dr. Kriebel, it's to me as a pulmonary physician, it
14 doesn't matter what put those pleural plaques there.
15 If you are just asking me are pleural plaques related
16 to abnormal spirometry, that entire literature could
17 be brought to bear.
18 DR. KANE: Oh, good. I would like the
19 other pulmonologists to weigh in on this.
20 DR. BALMES: Well, one of the comments that
21 Mort made caused me to put this into perspective with
22 regard to ozone and lung function changes. And Mort

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Page 217

1 was saying just because we can measure pleural plaques
2 by radiography doesn't mean it's an adverse effect.
3 Well, Mort was a fellow panelist on the
4 Cleaner Scientific Advisory Committee Ozone Review
5 back in 2006 to '8, and the driver for the
6 recommendation from that panel with regard to the
7 national ambient air quality standard for ozone was
8 were changes in lung function, spirometry that were
9 pretty small.
10 I mean with a lot of ozone exposure you get
11 a lot of lung function change, but with a little bit
12 you ozone exposure you get less lung function change.
13 And there was -- the question of whether that -- an
14 adverse effect or not was discussed by that panel, and
15 it was also discussed by the American Thoracic
16 Society. And the determination was made that a
17 decrease in lung function of ten percent, spirometry,
18 FEV-1 of 10 percent was an adverse effect.
19 And the levels of change with lower levels
20 of ozone exposure are even less than ten percent but
21 they were statistically significant. And that's, you
22 know, that's -- and then there were individuals in the

Page 218

1 groups of subjects exposed to ozone experimentally
2 that had -- even though the group mean effect was less
3 than ten percent, there were individuals with less
4 than ten percent change.
5 I think that we are not too for away from
6 that with that same kind of approach with pleural
7 plaques. I would agree that most people with
8 localized pleural thickening don't have physiologic
9 changes of clinical significance. You can find as
10 David Schwartz did, if you look hard enough, some
11 evidence of decreased lung function in people with
12 pleural plaques.
13 On the other hand, it's a structural
14 difference. I am not sure I'd want my kids to have
15 pleural plaques even if there's no lung function
16 change. So I guess I'm torn between sort of the lack
17 of physiologic impact of most people with localized
18 pleural thickening versus the fact that it's -- it is
19 a structural abnormality that deviates from normal.
20 So I guess what I'm trying to say is I am
21 still unsure.
22 DR. KANE: Dr. Redlich, and then we'll go

Page 219

1 to some other comments.
2 DR. REDLICH: Well, I mean I think there is
3 a literature that does support -- I'm sorry. You know
4 the Wylie paper which was the APSDR analysis of lung
5 function and radiographic changes did see an
6 association with pleural plaques and the reduced FEC.
7 So I think the sort of general summary or
8 conclusion that pleural plaques are not associated
9 with any change in lung function is actually not
10 supported, you know, consistently by the literature.
11 And one can also argue that for various reasons
12 cross-sectional studies and design, there are a number
13 of issues in that analysis. But I think the -- the
14 data from the Wylie paper does support, and that's
15 actually with the Libby asbestos.
16 But I also agree that I -- given that
17 obviously the question has come up how significant are
18 pleural plaques, and if the whole risk assessment is
19 based on that, then it would make sense to as best as
20 possible justify using that endpoint, which I think
21 the document does a reasonably good job of doing. It
22 would be nice, I think we would all feel more

Page 220

1 comfortable -- the suggestion of using other endpoints
2 or combining, if you look at the papers and the
3 numbers, there just aren't enough of the other
4 endpoints.
5 The other changes on x-rays, there were
6 eight additional people. And those eight, a lot of
7 them already had the pleural changes. So in terms of
8 -- I don't think it would substantively change the
9 risk assessment unless some of the papers that have
10 been mentioned that are appending may, I mean, I'm
11 normally a believer that one more paper isn't going to
12 change your bottom line. And you also don't go nuts,
13 but in this case if the paper, those additional
14 pending papers are also looking at, you know,
15 asbestosis or lung function, it would provide
16 additional support potentially.
17 DR. KANE: Dr. Kriebel.
18 DR. KRIEBEL: Just one more comment on
19 this. I just want to remind the committee, you know,
20 because you can x-ray -- and a physician x-rays a
21 single human being and can give a pulmonary function
22 test to a single human being, you can observe that

Page 221

1 someone can have fantastic ugly-looking things on
2 their x-ray and their lung function looks fine. But
3 that's not really relevant evidence.
4 This is a population level question. This
5 is an epidemiologic question. And the question is
6 whether populations in which there is a prevalence of
7 radiographic changes are at increased risk of some
8 loss of function or ill health. So I think we have to
9 be very clear to ask the question that way.
10 And I think that the document could be a
11 little bit stronger. I can try and be more specific
12 in my comments, but I think it could be a bit stronger
13 in trying to make that case that it's reasonable to
14 presume that if you see pleural changes that it means
15 one of two things: Either it means direct
16 pathophysiologic effects of pleural changes on the
17 healthy functioning of the lungs, or it means it's a
18 biomarker on the pathway.
19 And if you see pleural changes, it's very
20 likely that on average the population will be losing
21 lung function. And I think that that argument could
22 be made stronger.

Page 222

1 DR. KANE: Dr. Balmes.
2 DR. BALMES: Well, I totally -- as a
3 clinician who may have been guilty of being too
4 anecdotal there, I appreciate this epidemiologic
5 question. I think you could make the case with
6 certain papers that pleural plaques may be associated
7 with decreased lung function. There are a few papers,
8 but there are a number of epidemiological papers where
9 you could use to make the counter argument. So it's a
10 bit tricky.
11 DR. KANE: Dr. Newman?
12 DR. NEWMAN: Yeah. I think, Dr. Kriebel,
13 you raised kind of an interesting concept here. I
14 actually agree with Dr. Salmon that the notion of
15 calling pleural plaques merely a biomarker is probably
16 not what I would like to see us suggest here. But I
17 think in terms of thinking about this pathway, this
18 natural history of the asbestos-related non-malignant
19 disease is an interesting one.
20 And that pathway which we've sort of
21 inferred and assumed that people know, is that for
22 many of our patients the first thing, and the epi

Page 223

1 studies will bear this out, the first thing you see
2 are the pleural abnormalities. But that in itself,
3 the development of those pleural abnormalities is
4 indicative of an increased risk of developing other
5 more severe consequences including asbestosis, the
6 lung disease.
7 If -- now I'll revert to being anecdotal,
8 which is that I wish that we had in our public
9 comments patients from Libby who have pleural plaques,
10 because I suspect that what they would say to us is
11 the presence of pleural plaques, even if my lungs are
12 working fine on spirometry is a bad thing for me. And
13 if you could ask your animals in your research
14 studies, they probably would say the same thing.
15 And I don't mean to be facetious but, you
16 know, I mean this quite sincerely that when I have
17 told patients that they have pleural plaques
18 indicative of past asbestos exposure, and I told them
19 what the implications of that is for them today and
20 the future, the psychological impact of that itself is
21 something of significant note. And that's speaking
22 now anecdotally from a clinician standpoint.

Page 224

1 DR. KANE: One population that has been
2 very, very well studied that was exposed to amphiboles
3 only is Wittenoom. And I would like to ask EPA to
4 review the epidemiologic literature on Wittenoom.
5 DR. BALMES: Just one more comment that
6 that hopefully will be helpful to EPA. I think it's
7 referenced already in the document, but there was an
8 American Thoracic Society statement on the diagnosis
9 and treatment of non-malignant asbestos-related
10 disease. I happen to be a coauthor of that document.
11 And I just brought it up. It took me
12 forever to find it, but I finally did,
13 UNIDENTIFIED FEMALE SPEAKER: Do you
14 remember what you wrote?
15 DR. BALMES: But, anyway, it has a nice
16 summary of the data as of early, you know, that came
17 out in 2004, but has a nice summary of the data with
18 regard to the consequences of pleural plaques. I
19 think you have already referenced it, but it might
20 help to elaborate are what Dr. Kriebel was seeking.
21 DR. KANE: Dr. Salmon.
22 DR. SALMON: Just one very last brief

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Page 225

1 comment. Because I think the x-ray endpoint is a good
2 one doesn't in any sense mean that I don't think it
3 would be a good idea to take a look at the new lung
4 function data and see what that has to say as well. I
5 just wanted to make that clear.
6 DR. KANE: All right. So we have a broad
7 spectrum of view points on this point. And this is a
8 very, very important point of course for this EPA
9 document. I think it would be premature to draw a
10 final conclusion at this point because we have some
11 outstanding papers that we are going to get electronic
12 access to, I hope by tomorrow morning.
13 And I think we are going to have to revisit
14 this although Vanessa is not going to want to hear
15 that. We are going to have to revisit this discussion
16 again.
17 MR. BUSSARD: Just to note, we'll see what
18 we can do, but there may be copyright issues with
19 getting them to you tomorrow morning. So we will get
20 them to you as soon as we can. If that's tonight or
21 tomorrow that's what we'll do. But there's some
22 issues with providing copyright that we have to look

Page 226

1 into.
2 DR. KANE: From my own perspective I've
3 heard a diverse range of viewpoints. And, Julian, I
4 haven't forgotten yours. Yours is also on the table
5 here. It's a very broad range of opinions with this.
6 And this is a very, very important point for the
7 document.
8 And I do not really want to push the
9 committee to reach a consensus or put out a very wide
10 range of viewpoints until we have a chance to look at
11 additional information.
12 Does everyone agree with that?
13 DR. WOSKIE: I agree, but I just want a
14 clarification from Julian, from you about my
15 impression was your concern was about the results of
16 the modeling of this, the outcome of the modeling.
17 Were you also expressing doubts about the
18 use of pleural thickening as a reasonable outcome to
19 look at? Separate.
20 DR. PETO: I was just making the point that
21 the rationale for the EPA ignoring non-malignant
22 effects in 1988 as I understand it was the evidence

Page 227

1 that the ratio between the severity of non-malignant
2 effects to cancer, not the actual Libby, the ratio has
3 declined as exposure levels had fallen, and that the
4 sort of exposure levels that you are concerned about.
5 The impression was not only that they be
6 rarer but that they would also be less severe and the
7 cancer was simply of comparable frequency and
8 obviously more important. And so rational focus on
9 that and not to attempt to use non-malignant effects
10 in relation to the evaluation of the effects of
11 exposures. That was one point.
12 The modeling point is a separate one which
13 we'll come back to. And the question of whether or
14 not there would be any significant deficits, as a
15 result in very low-level asbestos exposure, I mean, in
16 a sense it's a modeling question but it's a different
17 modeling question.
18 DR. SHEPPARD: So just to push you a little
19 bit, are you suggesting that there's no need for an
20 RfC because any cancer --
21 DR. PETO: Not based on -- yes. Yes, I am.
22 I mean I think the effects of asbestos, the

Page 228

1 carcinogenic effects of asbestos are severe and fairly
2 well established. And I don't think that it's
3 generally thought that the effect of chronic, very
4 low-level exposure is going to be appreciable compared
5 with the cancer risk.
6 DR. KANE: Yes. Dr. Neuberger.
7 DR. NEUBERGER: My understanding is that
8 there was quite a bit of exposure in the Libby
9 population leading to non-cancer health outcomes. So
10 we are now dealing with a non-occupational high
11 exposure situation is my understanding.
12 So in that case what Bill Nicholson was
13 thinking I imagine was that this was mainly an
14 occupational issue, and that the environmental issue
15 is more the cancer because it's at a lower level of
16 exposure that you are dealing with.
17 Is that your understanding or do you differ
18 with that?
19 DR. PETO: I don't know in the Marysville
20 cohort was an occupational cohort. I don't know what
21 the evidence is in relation to the prevalence of
22 pleural thickening as a result of environmental

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Page 229

1 asbestos exposure. I mean there aren't -- are there
2 substantial data in Libby on the prevalence of pleural
3 thickening on people who simply had environmental
4 exposure?
5 FEMALE SPEAKER: Yes.
6 DR. KANE: Dr. Newman?
7 DR. NEWMAN: Dr. Peto, I just want to
8 pursue this a little bit more if I may, since I think
9 some of us are going to try to summarize the divergent
10 viewpoints. And tell me if I have this right. Are
11 you saying that because the modeling doesn't make
12 sense, we therefore should throw out the RfC concept
13 entirely and just stick with cancer? Is that what you
14 are saying?
15 DR. PETO: I am not quite sure what the
16 implications are, but I don't think it's a good idea
17 to put out a document in which the modeling is
18 completely inconsistent with the epidemiologic
19 evidence, particularly when the models have been
20 developed so in complete isolation from the
21 epidemiological evidence.
22 I mean we are going to come back to this in

Page 230

1 relation to mesothelioma as well, I mean, some of the
2 predictions in relation to mesothelioma are completely
3 inconsistent with the epidemiological evidence. And
4 in particular the prediction that the ratio of pleural
5 thickening to mesothelioma is going to be 500 to one
6 as a result of an environmental exposure is certainly
7 consistent with the epidemiological evidence.
8 But that's a different point from the, I
9 mean, I'm not quite sure what it means to say that you
10 choose something as a basis for an RfC but then apply
11 methodology to it which produces results which are
12 inconsistent with the data. I mean I don't -- you
13 can't partition these questions in this way. Is this
14 an appropriate measure, yes or no, if you decide it
15 is. But you don't know how to extrapolate it to the
16 effective chronic low-dose exposure, then it isn't.
17 I mean it isn't a completely theoretical
18 issue.
19 DR. KANE: I think Mort has a comment here,
20 Mort?
21 DR. LIPPMANN: I was saying that you can't
22 relate the RfC to real information because the RfC in

Page 231

1 this case and in every other one will have at least
2 two orders of magnitude safety factor.
3 DR. KANE: Yes. Dr. Kriebel.
4 DR. KRIEBEL: Yeah. I was just going to
5 add to that, Dr. Peto, you mentioned earlier your sort
6 of back-of-envelope calculation about the implications
7 in Britain would be that 50 percent of women would
8 have -- but actually that's not so bad because if you
9 take an order of magnitude below that, there's
10 supposed to be a safety factor, five percent of
11 British women will have those changes. So it's not
12 necessarily that far off. That's the logic.
13 DR. PETO: But I don't think it is. I mean
14 the safety factor of 100 comes from a vague factor of
15 100 in relation to general uncertainties and
16 measurements in the cohort. And there's a factor of
17 ten and then a further factor of ten to do a variation
18 individual susceptibility, so it isn't true that there
19 would be a hundred-fold difference in the prevalence
20 in the population.
21 There's a possibility that the effect might
22 be concentrated in ten percent of the population.

Page 232

1 That's half of the factor of 10. I mean there's 100,
2 there's 10, a general sort of measurement uncertainty,
3 and 10 for lack of knowledge about individual
4 susceptibility. Isn't that add up to 100?
5 That would be five percent prevalence. So
6 five percent of women would have pleural thickening
7 caused by environmental asbestos exposure. That's
8 possible, is it? Okay.
9 DR. KANE: Dr. Balmes, perhaps five percent
10 in Libby.
11 DR. BALMES: Yeah. I was just going to
12 address Julian's question about have community studies
13 shown increased prevalence of pleural thickening in
14 Libby. And it's my understanding that several studies
15 have shown that, so that the reason that EPA isn't
16 using those studies for RfC calculation is that the
17 exposure data aren't very clear in terms of what
18 exposures, what level of exposure actually occurred
19 from the various activities of playing on the tailings
20 from the mine and popping vermiculite as a kid on a
21 frying pan, et cetera.
22 But I think there's very little question

Page 233

1 that there's a high prevalence of pleural thickening
2 among the community members not exposed at work. So I
3 think it's a real issue, the localized pleural
4 thickening. Whether it should be the basis of an RfC
5 is another story, which we are discussing.
6 DR. KANE: Dr. Neuberger.
7 DR. NEUBERGER: Yeah, I was just going to
8 say that the mortality study in Libby that ATSDR did
9 showed an elevated asbestosis rate of somewhere I
10 think 40 to 60 times, either the state or the federal,
11 I can't remember which is which. And just glancing
12 here at some of the information in here, they did have
13 some information from their clinical study.
14 I guess this is an ATSDR study also for
15 people who had not worked -- they were community
16 members that did show some effects from pleural
17 thickening. So getting back to our earlier point
18 where you asked about it, it looks to me like there is
19 some data. The mortality data could have been better
20 done if it had tried to screen out the workers and
21 just done both workers and community members
22 separately.

Page 234

1 And they would have had to go into the
2 database and, you know, the death certificates and
3 pull the records and find out. That wasn't done. And
4 maybe that's something that we could recommend that
5 they try to do that.
6 But I -- to me, there does seem to be
7 something going on, you know, in the community.
8 DR. KANE: Dr. Sheppard?
9 DR. SHEPPARD: So right now I think we are
10 really trying to sort out the choice of this outcome
11 measure for the RfC, but I think it's -- we'll need to
12 come back to the question about aligning the two
13 approaches and what they say about each other, but
14 this kind of inconsistency that you are uncomfortable
15 with, Dr. Peto, is not -- is present in other places
16 like in the effects of air pollution on health with
17 acute effects versus chronic effects, and people for
18 years have tried to sort out how to align those. And
19 it's a very difficult question.
20 So I'm fairly comfortable actually with
21 dealing with each of these separately, although I do
22 think there's reason for the committee to try to

Page 235

1 reconcile our understanding of them both, but we may
2 end up not being able to get to the bottom of that.
3 DR. KANE: All right. So maybe it's not an
4 irreconcilable issue at this point. And maybe we
5 should be a little more conservative. Anyone object
6 we move forward? Forward.
7 So the next topic to be discussed should be
8 less controversial. It would be Section 4.2., 4.3,
9 4.4, animal and mechanistic studies. This will be the
10 subgroup we'll start with Jeff Everitt then Tom Hei
11 and then Jamie Bonner.
12 DR. EVERITT: Okay. I thought this section
13 was fairly well written, with perhaps the exception of
14 I agree with some earlier comments that Dr. Lippmann
15 made that it would be nice if somewhere in the
16 document it just had a little bit of a summary of
17 what's known about amphibole asbestos inhalation in
18 general without reinvesting in the whole asbestos
19 question.
20 But the issue of in animal studies to date
21 there is a lot known about dimensionality, durability,
22 some of the important issues that lead to effects in

Page 236

1 animals, but I do think that the big challenge, you
2 know, for this report is that there really are no
3 long-term studies of Libby amphibole in animal models
4 for -- by the inhalation route of exposure.
5 And so it's very, very difficult from the
6 literature that's there to get an assessment of sort
7 of the potency of Libby amphibole against other types
8 of amphiboles from the animal data. But I do think
9 the way it's written is appropriate.
10 I think that the fact that tremolite
11 studies are quoted is fine. I think it certainly
12 discusses the role of what's known about Libby
13 amphibole versus the tremolite inhalations and
14 instillations that have been done. I do think that
15 the -- it does properly put into perspective that what
16 is known in the very limited data we have on Libby
17 amphibole in animals, it does support the -- the
18 lesions that have been noted in the epidemiologic
19 studies with what's known about other amphibole
20 exposures.
21 I think that the non-animal, the other
22 mechanistic studies that are listed are very difficult

ATTACHMENT C

From:	Julian.Peto@lshtm.ac.uk
To:	John Neuberger; Mort Lippmann; David_Kriebel@uml.edu
Cc:	Diana-M Wong/DC/USEPA/US@EPA
Subject:	Re: Libby: Draft Responses to Charge Question III.A.4 and III.B.4
Date:	03/22/2012 04:30 AM
Attachments:	Revised+Panel+Comments+Feb+29+2012.pdf

Dear Diana

Libby amphibole review

I have not contributed as much as I would have liked to the post-meeting discussions. (b) (6) [redacted] owever, I also have a fundamental problem with the EPA review process. By dividing comments between separate charge questions we cannot see the wood for the trees. My central concern with the Libby draft review is the adoption of models which are fundamentally wrong epidemiologically for both mesothelioma and pleural thickening, and until this is addressed the other charge questions (apart from the choice of studies, which we all agree is appropriate) are of secondary importance. The core issue is the effect of time since beginning exposure. To abandon widely accepted and (in my opinion) better models for the purpose of risk prediction is exactly analogous to choosing the Ptolemaic over the Galilean model of the Solar System to predict where the planets will be next year.

The effect of time since beginning exposure is buried in a list of "potential confounders and covariates" under charge question III.A.4, and the draft response doesn't even mention it. In relation to LPT, I would simply insert what I wrote in my overall comment, i.e.:

It is well-known that local pleural thickening continues to develop for many years after asbestos exposure has ceased. In contrast, the fitted Michaelis-Menten model predicts that within 10 years of stopping asbestos exposure the prevalence reaches a plateau. The analysis of the prevalence of pleural thickening as a function of cumulative exposure with a lag of 10 years cannot be correct if pleural thickening continues to appear more than 10 years after exposure has ceased, as the lagged cumulative dose would remain constant while the prevalence continues to rise. The analyses based on this model are therefore wrong, and should be removed from the report. In sections 5-2-3 and 5-2-4 the Michaelis-Menten model is selected and fitted, including the uncertainty factor analysis and calculation of the RfC. The fact that the prevalence of LPT continues to increase with increasing time since first exposure is then belatedly acknowledged in section 5.2.5. Section 5-3-3 justifies this contradiction by the following statement: "Note that the likelihood that prevalence of localized pleural thickening may further increase beyond 30 years after first exposure is a principal rationale cited for the selection of a database UF of 10 in this current assessment". It is not reasonable to fit a model that is clearly wrong and attempt to allow for the error in the uncertainty analysis. The model must be discarded.

As I said at the meeting, I have similar fundamental reservations about the mesothelioma model. The response to III.B.4 says "The mesothelioma undercount is adjusted for the entire lifespan (70 ÷54) and for the undercount in death certificates. These approaches seem logical and generally well described...." This is obviously incompatible with my comments, which included: "The effect of exposure from birth to age 70 rather than from age 16 to 70 (54 years) is then calculated by simply multiplying these predicted lifetime risks by 70/54. A factor of about 3 would be more appropriate. These models are inferior to the epidemiologically and biologically more plausible model for mesothelioma that the EPA adopted more than 20 years ago..."

If I couldn't persuade other panel members to agree at the meeting I can't expect to do so by email, and I don't know how to proceed. My personal view is that the EPA should reconsider the core issue of model selection and redraft the review accordingly. I've attached the latest online pdf of panel members' comments - mine are on p57.

Best wishes

Julian

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julian.peto@lshtm.ac.uk>>> "John Neuberger" <JNEUBERG@kumc.edu> 21/03/2012 20:13 >>>
Dave,

See attachment.

This is a highly statistical area and I would be more comfortable after Dr. Peto responds; he is currently unavailable. I'm open to discussing any changes or corrections to my comments. Let me know if you want to discuss this further.

John

>>> Diana-M Wong <Wong.Diana-M@epamail.epa.gov> 3/19/2012 10:26 AM >>>

Attached please find comments on draft response to charge question III.A.4. Draft response to charge question III.A.7 is also attached for your information.

Please revise and send the revised draft back to me by March 22. Thank you very much.

(See attached file: Group Response to Charge Question IIIA4dw.docx)
(See attached file: IIIA7LS.docx)

Diana

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ATTACHMENT D

In the Matter of:

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY SCIENCE ADVISORY BOARD

LIBBY AMPHIBOLE ASBESTOS REVIEW PANEL MEETING
May 1, 2012

MERRILL LAD
1325 G Street NW, Suite 200, Washington, DC
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Page 81

1 it pertains directly to this response, but I think
2 it -- I think if I remember correctly that has been
3 incorporated in this full section somewhere.
4 DR. SALMON: Yeah. We need to have that
5 somehow -- maybe it's sufficiently explained
6 elsewhere. I just feel we need to have that in mind
7 in any comments we make about using external data to
8 inform parameters. Having said that, of course for
9 some models that's an essential feature. You can't
10 use some of the possible models without relying on
11 external data.
12 DR. KANE: Well, Lianne and Andrew and
13 Julian, what do you think specifically about the
14 comments in the draft report on pages 25 and 26 with
15 respect to charge question 2?
16 Do you have specific changes to recommend
17 here?
18 DR. SHEPPARD: No, I think it's good.
19 DR. PETO: I think as stated it covers the
20 issues we had, myself.
21 DR. KANE: All right. So pages 25 and 26
22 are okay.

Page 82

1 DR. PETO: This is Julian. My concern is
2 with the choice of the model. I mean the way the
3 modeling was done was the issue, the continuing
4 increase after exposure had ceased wasn't discussed, I
5 mean, in the report. I mean the RfC is finally -- is
6 derived. And then followed by in -- I am referring to
7 the report, I mean Section 5.2.5, alternative analysis
8 of the cohort followed by 5.3, 5.3 uncertainties in
9 reference concentration and, I mean, in that Section
10 5.3.3 uncertainty due to time from first exposure, I
11 mean --
12 DR. SALMON: But, Julian, you have to
13 remember that the model, you know, the model which was
14 being applied here was used exclusively to fit the
15 data within the period of observation. It actually
16 wasn't used to handle --
17 DR. PETO: It's going to be used to
18 instruct the low-dose long-term exposure. I mean
19 you've got --
20 DR. SALMON: Oh, no. No. Read the report.
21 It isn't.
22 DR. PETO: Yes. That's what's complicated.

Page 83

1 DR. SHEPPARD: And, actually, the time
2 since first exposure is much more relevant to the full
3 Marysville cohort, and this question is addressing the
4 subcohort analysis.
5 DR. PETO: The RfC was calculated without
6 discussing this issue at all. I mean it -- the last
7 sentence in that 5.3.3 is uncertainty due to time from
8 first exposure, there's just a sentence that says,
9 that one I quoted, the likelihood of the prevalence of
10 LTP may further increase beyond 30 years after first
11 exposure is a principal rationale cited in the
12 selection of a database uncertainty factor of ten in
13 the current assessment.
14 So the calculation is done. And then you
15 say, well, the model is just completely wrong and
16 completely fails to take account of this enormous
17 effect, this huge effect, the continued increase after
18 exposure is ceased. And you have an uncertainty
19 factor of 10 to take account of those. Why not 100?
20 Why not 2?
21 I mean it's -- I mean the model is simply
22 wrong. If you're modeling a disease response then, I

Page 84

1 mean, to choose the model prevalence --
2 DR. SALMON: One of the key issues here is
3 we are doing a benchmark dose analysis. We are not
4 trying to do a research study which examines --
5 DR. PETO: No. We are trying to predict
6 lifetime risk to people at low dose exposure. That's
7 what you are trying to calculate.
8 DR. SALMON: For the non-cancer effect you
9 are not trying to use that model to examine the entire
10 lifetime cause of the disease, nor are you trying to
11 examine the biological basis of the response.
12 DR. PETO: It's got nothing to do with the
13 biological basis. It's the epidemiological basis.
14 What's the pathogen you see in cohorts of people
15 exposed at different levels for different durations
16 and followed up for different periods of time.
17 DR. SALMON: This is a risk assessment, not
18 a research project.
19 DR. SHEPPARD: This is a very small cohort
20 with a very small number of cases. The advantage of
21 it is that there's a lot of data down in the low end
22 of the exposure range so that that helps to inform the

Page 85

1 BMCL.
2 DR. PETO: Yeah.
3 DR. SHEPPARD: And this model in my mind is
4 a descriptive model. It's not a mechanistic model.
5 DR. PETO: Absolutely. Absolutely.
6 DR. PETO: It's not a question of being
7 mechanistic, it's a question of whether or not you
8 separate whether the variables which are the level of
9 exposure and duration of exposure and how long you
10 follow it up for. Those are the three variables.
11 DR. SHEPPARD: But the subcohort doesn't
12 have much variability in time since first exposure, so
13 there's not much information there with which to do
14 anything about it, so that's just a feature of this
15 data set. The full cohort there's more information,
16 and we made some very explicit recommendations about
17 how to address it, which we can discuss when we get to
18 that question.
19 DR. KANE: But, Julian, I think the point
20 is that your comments are relevant but they are not
21 relevant to this particular charge question.
22 DR. PETO: You can partition the analysis.

Page 86

1 You can do a model -- the Fischer model which is
2 completely inconsistent with the epidemiology, then
3 you have satisfied that requirement by according to
4 risk assessment conventions just seems to be
5 scientifically extraordinary. I mean I said it
6 really --
7 DR. SHEPPARD: What model do you suggest
8 then, Julian, with this data set --
9 DR. PETO: Well, considering different
10 models, seeing which one is most plausible in terms of
11 the epidemiology of pleural changes in asbestos
12 exposure, and then fitting a model which is consistent
13 with the, you know, the best description how does the
14 human body react when it's exposed in this way.
15 It's not a biological model, it's an
16 epidemiological question. You are trying to link
17 disease prevalence at different points in life to
18 duration and level of exposure. That's what you are
19 doing. That's all you are doing.
20 And the model is completely arbitrary. I
21 mean the justification of the model isn't scientific
22 in any sense. And the model that's chosen is --

Page 87

1 completely fails to affect the most elementary
2 striking factor, prevalence of LPT which goes on
3 dramatically with the passage of time after exposure
4 has ceased.
5 DR. SHEPPARD: But there's no date on that
6 in this data set. How are we going to address it in
7 this data set?
8 DR. PETO: Well, that's a fundamental
9 point. When you choose a model, I mean, that's why
10 the document should begin by saying this is an
11 amphibole. I mean what amphiboles do to LPT and
12 cancer. You don't choose a model on the basis of some
13 -- just out of the air.
14 You choose a model that fits the data, the
15 data -- the data on similar exposures in other larger
16 studies. They are already --
17 (unintelligible, multiple voices)
18 DR. PETO: You don't develop a model on the
19 basis of data set like this. A model is simply -- you
20 choose a model, I mean, scientifically on the basis of
21 the information.
22 DR. WALKER: Julian, this is Katie Walker.

Page 88

1 I mean this does seem to be the fundamental question
2 though as to whether or not there is another data set
3 of Libby amphibole asbestos that is relevant.
4 DR. PETO: It doesn't have to be Libby
5 amphibole asbestos. Libby --
6 DR. WALKER: Well, that's a fundamental --
7 DR. PETO: -- amphibole asbestos differs
8 magically from some other form. It's not -- it isn't
9 true anyway. I mean the risk does go up going up with
10 the longer follow-up.
11 DR. SALMON: I believe what you have just
12 said, but you have to prove it before you can make
13 that assertion. That's the problem.
14 DR. PETO: Goodness me, I mean, if the EPA
15 has chosen a model that's completely inconsistent,
16 both the general epidemiology and with this study, I
17 mean the longer follow-up prevalence LPT went up
18 dramatically. I mean we won't -- any reason for
19 assuming that Libby amphibole asbestos behaves like
20 other amphiboles.
21 They only ostensible thing to do is to fit
22 models which have been developed in relation to Libby

Page 89

1 amphiboles.
2 DR. SHEPPARD: But, Julian, we'll be
3 sending the plateau be increased to 85 percent because
4 that's what the evidence in the literature suggests
5 completely consistent with your comment.
6 DR. PETO: But what plateau? I mean I
7 don't understand what the plateau means. The plateau
8 is just a plateau which then shoots up. There's an
9 increasing curve. I mean the idea that you can
10 partition an analysis in this way is I think just odd.
11 I mean I think the wrong models have been
12 fitted. That's my fundamental concern with the whole
13 document.
14 DR. WALKER: What model are you suggesting,
15 Julian?
16 DR. PETO: That the incidence rather than
17 the prevalence is model as a function of cumulative
18 dose, for a start. I mean the incidence rate is the
19 rate of new appearance of LPT in somebody who didn't
20 have it last year. I mean the prevalence --
21 DR. WALKER: And so where do you get the
22 data set from?

Page 90

1 DR. PETO: I mean you can get some estimate
2 from the extent to which it happens in these data by
3 the gross increase in LPT between the two follow-ups.
4 I mean as I said probably 35 years ago criticizing the
5 derivation of the high dual standard for asbestos
6 based on early signs of asbestosis in relation to
7 prevalence plotted against cumulative dose and pointed
8 out in that paper in the Lancet in 1978 that you can
9 underestimate the risk by order of magnitude.
10 I mean to simply draw the graph is a
11 mistake. Say you draw a graph which has cumulative
12 dose on the bottom axis and prevalence on the vertical
13 axis, you've assumed that the incidence is zero when
14 exposed to CC's. When exposed to CC's, you don't move
15 along the cumulative dose axis but you do move up the
16 prevalence axis.
17 Prevalence is the integral incidence. You
18 add incidence up to your life and that's your
19 prevalence. You shouldn't plot a graph let alone
20 discuss what model to fit to that graph of cumulative
21 dose against prevalence. It's just a fundamental
22 scientific mistake. This is entailed in the very

Page 91

1 strong assumption that symptoms can't develop after
2 exposure ceased, which you know is false.
3 I don't know how else to express it. You
4 see the point. I mean you have got a graph of
5 cumulative dose against prevalence, and you know that
6 if cases go on developing after exposure has ceased,
7 you come back ten years later, nobody has moved along
8 the cumulative dose axis because they haven't gotten
9 any more exposure, but the graph has gone up.
10 So to fit in any line to that graph, to
11 even look at the graph, to even plot the graph is a
12 fundamental mistake.
13 DR. WALKER: So an interesting exercise
14 that could be done would be some sort of extended
15 sensitivity analysis where one would stimulate changes
16 in response for the people that don't have LPT in this
17 data set and just randomly choose the individuals that
18 have that or potentially do it as a function of
19 exposure, and then show how that would affect the BMCL
20 as in that kind of "what-if" analysis.
21 That would be completely consistent with
22 using this data set in your suggestion and --

Page 92

1 DR. PETO: It's not the data set. I don't
2 understand why the model was chosen. I mean the model
3 is just the wrong model.
4 DR. WALKER(?): Julian, stop a minute. It
5 seems to me sort of somewhat inappropriate to suggest
6 that we know with absolute certainty which model is
7 correct. I mean every model --
8 DR. PETO: What we know with absolute
9 certainty is that to even plot a graph of cumulative
10 dose against prevalence is a mistake because you know
11 that when exposure stops, the prevalence goes on going
12 up. You don't move along the axis. The graph is
13 wrong. It doesn't matter what values you fit to it.
14 DR. WALKER (?): Well, isn't that based on
15 a certain data set that you have explored in detail
16 some time ago and then --
17 DR. PETO: What data set? What data set?
18 The huge increase with the further passage of time
19 shows that that happens. I mean there's studies that
20 were done 35 years ago on asbestos workers that showed
21 that happens. You have to model incidence, not
22 prevalence.

Page 93

1 Incidence is what happens to you now as a
2 result of what's already happened to you. Prevalence
3 is all the things that have happened to you over your
4 life added up.
5 I mean when you write down an incidence
6 model, it implies prevalence. You can drive an
7 incidence model from a prevalence model, and you can
8 derive vice versa. But as soon as you write down a
9 model where cumulative -- where prevalence is a
10 function of cumulative dose, that implies the very
11 strong assumption that incidence is zero after
12 exposure's ceased.
13 DR. SALMON: But we are not using the model
14 that we are talking about to make that extrapolation.
15 DR. PETO: But why fit the model at all
16 when you know that it's wrong? It's just the wrong
17 model. I mean the idea that you can just fit any old
18 model to a graph; the graph shouldn't have been drawn
19 in the first place.
20 DR. SALMON: I think the short answer is
21 the technique of benchmark dose analysis relies on the
22 concept of fitting what you described as any old model

Page 94

1 to the actual data. And the fact of the matter is
2 that this is a relatively arbitrary model which fits
3 the observed data of the subcohort at some level,
4 whereas in fact the models which you are arguing for
5 which have an external justification and biological
6 mechanism and/or in --
7 DR. PETO: It's not the mechanism.
8 DR. SALMON: -- on other cohorts in fact
9 don't fit that particular segment of data as well, for
10 reasons which are numerous but not necessarily very
11 substantial in terms of what their indications are,
12 but nevertheless they say that those models don't fit
13 the data very well.
14 DR. PETO: The --
15 DR. SALMON: All very well arguing that you
16 should use a model which is informed by other
17 epidemiological cohorts or biological rationality or
18 whatever, but the fact of the matter is that those
19 models don't actually fit the data particularly well
20 due to the peculiarities of the data.
21 DR. PETO: That isn't true. That isn't --
22 DR. SALMON: It's what it says in the

Page 95

1 report.
2 DR. PETO: This one does. They account,
3 the dose increase --
4 (inaudible, multiple speakers)
5 DR. SALMON: They are not trying to account
6 for anything with this model. We are trying to fit
7 the data --
8 DR. PETO: Well, you are not trying to
9 account, the observation there's an order of magnitude
10 increase in the prevalence of LPT when exposure --
11 DR. SALMON: -- can't do anything. That's
12 the whole point. This is not the model to account for
13 anything. This is a model to fit the data.
14 DR. PETO: You don't think that's part of
15 the data, the fact that you know there was no
16 magnitude of increase in LPT between the two follow-up
17 periods. Isn't that part of the information that you
18 have?
19 DR. SALMON: Well, it's not part of the
20 information that we are trying to fit with this model.
21 DR. PETO: I mean there's nothing else I
22 can say. I just think it's scientifically

Page 96

1 preposterous but, I mean, carry on.
2 DR. SALMON: Yes, the sense in which it's
3 deliberately scientifically preposterous because it's
4 attempting not to prejudge the numerous important
5 issues which you have raised.
6 DR. KANE: May I make a suggestion? We are
7 not going to resolve this particular question
8 immediately, but some of the issues that have been
9 brought on the table for discussion, namely
10 consideration of some alternate models are discussed
11 in our draft document on pages 26 and 27. And there
12 are specific recommendations listed there.
13 So can we turn to that. This is under the
14 charge question number 3, alternative modeling
15 approaches. I think, Lianne, you were referring to
16 these suggestions earlier. And here there are some
17 specific recommendations made that I don't think, but
18 I'm a little bit naive about this, would represent too
19 much additional effort on the part of the EPA.
20 DR. PETO: But, I mean, the time since
21 first exposure is, I mean, the way the analysis is
22 done is the cumulative dosage related to prevalence,

Page 97

1 and then the RfC is calculated. And then it's
2 followed by discussion of alternative analyses.
3 I mean the idea that you choose the model,
4 do an analysis, calculate the key results on the basis
5 of that model and then consider other alternative
6 models seems completely backwards. I mean surely you
7 choose the model, the range of models that you want to
8 fit, and you fit the data and see how they affect the
9 conclusions.
10 I mean to simply add an uncertainty factor
11 of ten because you know the model is grossly wrong in
12 failing to allow for this huge effect just seems
13 completely peculiar. It's not the uncertainty factor,
14 it's the result of fitting the wrong model. You can
15 always do it in the ozone as well.
16 DR. KANE: Lianne or Andrew? Anyone else
17 have any suggestions about this point? Michael?
18 DR. PETO: My suggestion is that the EPA
19 should consider looking at models which relate
20 incidence, to the incidence of LPT, not the
21 prevalence, the rate of the appearance of new cases
22 per year, people who haven't yet got it, to cumulative

Page 98

1 dose and time since first exposure. I mean that's the
2 natural thing to do.
3 That's the natural way to analyze any
4 epidemiological cohort with any endpoint whether it's
5 cancer or LPT or FPL. And that's the typical way to
6 analyze data. You have got a chronic condition which
7 develops and continues to develop many years after
8 exposure has ceased.
9 DR. KANE: Julian, that's an excellent
10 suggestion but I don't -- we have not been -- evidence
11 that there's any such data set that could be used to
12 do that because there -- this data set has got two
13 times when x-rays were done. That's it.
14 So there's no way that you are going to get
15 at incidence in any meaningful way in this data set.
16 DR. PETO: No, I know that, but you have
17 got some idea of how it changed between the two
18 follow-ups. And you have got other studies and other
19 data sets which were looking at, you know, various
20 measures of asbestosis, I mean, in which it has been
21 done. And the observation is that the incidence
22 continues to increase after exposure's ceased.

Page 99

1 And so you should measure incidence of
2 cumulative dose, not prevalence. And you should
3 include time since first exposure in your model. I
4 mean you go get Jeff Berry's paper in the New York
5 Academy of Science in 1979, there's a whole volume on
6 the big meaning/meeting (?) of asbestos. And Jeff
7 Berry had an analysis which showed just how wrong his
8 previous analysis on which the two-fiber standard was
9 based had been when you looked at it this way rather
10 than that way.
11 And that's exactly what he did in 1970. He
12 plotted a graph of cumulative dose against prevalence.
13 It was early signs of asbestosis. And the two-fiber
14 standard was based on it. And when he analyzed the
15 six-year follow-up in the same cohort and looked at
16 the incidence, he found that the earlier conclusions
17 were wrong by a vast factor.
18 DR. SHEPPARD: I wanted to bring up a
19 different point.
20 DR. PETO: Can I just say in relation to
21 this point before we leave it, exactly the same issue
22 replies in relation to mesothelioma. I mean the

Page 100

1 reason for choosing a model for mesothelioma, of
2 course you can't develop a model for mesothelioma
3 based on seven cases or whatever it is.
4 You have to look at the enormous body of
5 evidence on what the epidemiology of mesothelioma is
6 and choose the model that you fit on that basis. I
7 mean it's mad to do anything else and completely
8 disreputable. I mean --
9 DR. KANE: Lianne, you had some other issue
10 to raise.
11 DR. SHEPPARD: Yeah. I'm relooking at this
12 and I'm noting that we are only talking about
13 including time since first exposure in as a separate
14 covariant, and there's no real mention in this
15 response about alternative exposure metrics that would
16 sort of -- sort of naturally include time since first
17 exposure in the calculation of the exposure metric.
18 And, um, I am trying to remember now where
19 that might have come up in our response. I know we've
20 had -- we had considerable conversation about that at
21 the meeting and a little bit afterwards in terms of
22 the recommendation of the group that talked about the

Page 101

1 RfC. And I'm wondering if we should incorporate that
2 a little bit better into this response.
3 DR. LIPPMANN: This is Mort. Let me speak
4 up for Julian, if that's necessary. I think he's
5 absolutely right. I think there's a consensus, and
6 tell me if I am wrong, that we should consider Libby
7 amphibole to be another amphibole that has similar
8 biological response as the other amphiboles. And the
9 mineralogists have done us sturdy by telling us that
10 only certain things are true amphiboles.
11 Now, if you take that to be true, then
12 there's a lot of literature, as Julian suggests, about
13 the progression of the diseases without further
14 exposure. And it's entirely appropriate to look at it
15 that way if not as the only way to look at it, at
16 least as a way to look at it.
17 DR. SHEPPARD: So following up on Mort's
18 comment, that might suggest that one of the things
19 that could be done to substantiate the estimate of the
20 RfC is to suggest that the further increase in
21 incidence would suggest if anything that the RFP would
22 be lower, would presumably be lower.

Page 102

1 DR. SALMON: I think there's a couple of
2 things to be said about this question of comparing
3 with other amphiboles. I think we've come to a pretty
4 solid conclusion, you know, from reading the analysis
5 of the data that in terms of the hazard identification
6 we are saying that Libby amphiboles look very much
7 like other amphiboles. But we also, for the purposes
8 of this report, for the EPA's report we need to have
9 an estimate of the carcinogenic and non-cancer
10 potency.
11 And it's not automatically established that
12 because the mechanism and behavior of the material is
13 similar to other amphiboles, it's not automatically
14 established that the potency is similar. Certainly
15 when you are talking about carcinogenic potency, for
16 which we do have a number of exponential materials,
17 there has been alleged to be rather considerable
18 variation in the potency, although nobody's arguing
19 that the mechanism and general behavior is different.
20 So I think that we have to get to the point
21 of establishing as in fact this -- the cancer analysis
22 by EPA shows that in fact Libby asbestos not only

Page 103

1 looks like other amphiboles from a mechanistic
2 standpoint but also looks like other amphiboles from
3 the point of view of the degree of carcinogenic
4 potency. It's definitely in the same ballpark as the
5 other amphiboles.
6 That is an independence and very important
7 observation which can then, you know, in follow-up
8 they use, you know, both to inform further studies of
9 the potency of other amphiboles and also in turn
10 perhaps to include Libby asbestos as part of the
11 overall amphibole picture. But the thing is that we
12 have to make that step first and say we are in the
13 same ballpark.
14 It's not a given until we actually have
15 done an analysis which establishes -- (inaudible,
16 someone coughing) -- and that's important both for the
17 cancer number and also for the non-cancer number for
18 which we don't in fact have very much in the way of
19 other precedence.
20 DR. LIPPMAN: Well, not entirely so. And
21 pneumoconiosis certainly progress after the end of
22 exposure.

Page 104

1 DR. SALMON: I'm not saying that we don't
2 have precedence for the mechanism. I'm talking about
3 the actual numeric or potency or the value of the RfC,
4 if you like. That's where we are on somewhat thin
5 ground in making comparison with other asbestos
6 type --
7 DR. LIPPMANN: Amphiboles are a cause of
8 pneumoconiosis. That's well established.
9 DR. SALMON: Oh, yes. No. That's not
10 what -- that's not what I am disagreeing with at all.
11 I'm saying that we are on strong ground in making that
12 qualitative comparison. It's the quantitative
13 comparison that needs to be established.
14 DR. PETO: But that's exactly what I'm
15 suggesting, that you choose a model on the basis of
16 other evidence. One of the components in that model
17 is the potency, which is the single parameter related
18 to the type of fiber you are studying. And fitting
19 that model, you estimate the potency. That's exactly
20 what I'm suggesting. But my --
21 DR. SALMON: -- Phase 2. We are still at
22 Phase 1 of establishing whether we are in the right

Page 105

1 ballpark. And I think this first analysis does that.
2 It immediately opens the door to doing other things,
3 including exactly what you are talking about, but we
4 have to do this first.
5 DR. PETO: Do what first?
6 DR. SALMON: We have to get an independent
7 estimate of the -- both the qualitative analysis and
8 also quantitative analysis to establish --
9 DR. PETO: Well, the thing is the Michaelis
10 model is fitted. And the RfC is calculated. What I'm
11 saying is that a more plausible model should have been
12 fitted for that calculation.
13 DR. SHEPPARD: But, Julian, you are not
14 giving us any specific suggestions based on the data
15 that we have to analyze.
16 DR. PETO: Well, the incidence of RfC is
17 proportional to the cumulative dose, for example.
18 That relinquishes any increase in prevalence once you
19 stop exposure. I'm not saying that's the right model
20 but that, I mean, the fundamental point is you should
21 model the incidence, and the model should include time
22 since first exposure.

Page 106

1 The minimal picture included cumulative
2 dose and time since first exposure. And it's a
3 question of looking at the literature on non-cancer
4 effects of amphiboles to see what else there is on it.
5 But, I mean, those are the two, I mean, the simplest
6 analysis would relate the incidence rate to the
7 cumulative dose.
8 DR. SHEPPARD: Where are you going to get
9 incidence from in this data set?
10 DR. PETO: You don't need to. The
11 prevalence is the integral of incidence. So when you
12 look at the prevalence in an individual, the
13 particular time after first exposure, you integrate.
14 I mean it -- cumulative dose, multiply it by sort of
15 linearly increasing -- the prevalence goes up linearly
16 if the incidence is constant.
17 The prevalence is implied by the incidence.
18 But the incidence is the rate of appearance in new
19 cases. By modeling the prevalence of the function of
20 cumulative dose, you've assumed that it's zero, the
21 incidence is zero, which we know is wrong. And you
22 shouldn't model prevalence. You should never model

Page 107

1 prevalence.
2 If you model incidence, then in any case
3 you've got the prevalence data. You work out what
4 your incidence model implies for the prevalence that
5 you are observing. But you don't sort of graph a
6 prevalence against cumulative dose which you know is
7 wrong before you even draw the graph, let alone what
8 model you fit to it.
9 DR. KANE: Well, to me not being an
10 epidemiologist, I am not clear about how EPA would go
11 about doing this. And we have to be clear if we are
12 going to recommend that EPA do it. And Lianne is
13 raising some questions about whether it can be done
14 with this data set.
15 Does anyone else have any insights about
16 this? Can we derive incidence from the this set?
17 - - -
18 (Discussion off the Record, Phone interruption)
19 - - -
20 DR. KANE: Who's on the line?
21 FEMALE SPEAKER: This is Ricia. I had to
22 get off the phone for a moment. I was about to call

Page 108

1 back, but evidently my phone called you back.
2 DR. KANE: I'm sorry, what is your name?
3 FEMALE SPEAKER: Ricia Patraf (sp). I
4 already signed in earlier.
5 DR. WONG: Is one of the registered
6 participants.
7 FEMALE SPEAKER: Right.
8 DR. KANE: All right. Fine. Can we get
9 back to Julian's question and my question to the other
10 members of the panel.
11 Is it possible to derive incidence from
12 this data set?
13 DR. PETO: Can I just comment on what I
14 mean. Depending on the form of the employment
15 histories, if you have the date of first exposure and
16 you have some idea, I mean, you know that the
17 cumulative doses were accumulated a long time before
18 the last follow-up, you can certainly, I mean, you
19 don't know exactly what the pattern of exposure was
20 over time, but you can work out a pretty good
21 approximation for each individual based on that sort
22 of model by assuming, for example, that the cumulative

Page 109

1 dose was accumulated by sort of, I mean, well, you can
2 make what assumptions you like about what the actual
3 pattern was. It's not going to make a huge
4 difference.
5 But for an individual who is observed 40
6 years after first exposure with a cumulative dose of
7 X, then you know if you -- if you -- what the
8 incidence rate is with or without a lag in relation to
9 cumulative dose, you can calculate what their
10 prevalence ought to be. And the only -- and the
11 variable is the constant, I mean the constant -- the
12 potency constant for that type of asbestos.
13 So you basically accumulate those. You put
14 those into boxes and you choose your potency factor so
15 there's an expected or equal. I mean that's the
16 method. It's very straightforward. You can do it
17 more or less with more or less complexity. You can
18 make various different assumptions about the actual
19 pattern over time over which a cumulative dose was
20 accumulated. But that's based on employment records
21 anyway, so I think you have got the data exactly for
22 what you need.

Page 110

1 DR. KANE: Mort, do you think as an
2 industrial hygienist that data is available or
3 reliable for this kind of thing?
4 DR. PETO: Before you answer that, can I
5 just say how would the cumulative dose be calculated?
6 What was the form of the employment records from which
7 the cumulative doses were calculated? There must be
8 an effect boils down to a cumulative dose of, you
9 know, accumulated in each year of employment. I mean
10 how else do you calculate that. So you have got to
11 estimate it.
12 DR. LIPPMANN: It's likely that such data
13 exists. One has to look.
14 DR. WOSKIE: Hi. This is Susan Woskie.
15 DR. KANE: Yes, Susan.
16 DR. WOSKIE: That certainly does exist that
17 what's used in the modeling is the cumulative exposure
18 of the 118 workers that began work in 1972. So, I
19 mean, the availability to do that, it's available.
20 Beyond that I can't -- whether (inaudible, phone
21 noise) -- make a bad, calculated incident somehow. I
22 just don't know.

Page 111

1 DR. PETO: You don't calculate incidence.
2 You know whether somebody has it or not. Therefore,
3 you have got, I mean, if you fit a model which
4 predicts a certain incidence pattern over somebody's
5 life as a result of their exposure history, then the
6 only variable is the unknown potency factor.
7 I mean just as the simplest example, as I
8 said, you can see they had constant exposure for ten
9 years, then you observe them 30 years later, then you
10 have got a cumulative dose. You've estimated the
11 exposure level, so you have got their cumulative
12 exposure, their cumulative exposure times their
13 potency is that component.
14 And under the simplest model, the incidence
15 is proportional to that. So the prevalence is just
16 that multiplied by the 40 years of follow-up. And you
17 make a little bit of allowance for, you know.
18 DR. WOSKIE: I guess, you know, I would
19 have to defer to the epidemiologist here, but I
20 thought one of our recommendations was examination of
21 other models like a dichotomous hill model which
22 allows the slope to be estimated, which is what you

Page 112

1 are talking about, isn't it, the potency factor?
2 Isn't that essentially what that is then?
3 DR. SALMON: Well, the problem is that if
4 we are estimating an RfC, for instance, then the
5 business of assuming a constant slope kind of
6 undermines the whole process because, you know, the
7 constant slope idea works for cancer because that's
8 the underlying assumed dose response characteristic.
9 For the RfC you have to fit something like
10 the hill model or what -- or some such model to, you
11 know, to identify a safe dose or least -- (inaudible)
12 -- substantially safe dose. So it's difficult to use
13 these linear type models in an RfC context. That's
14 part of the problem.
15 DR. PETO: The RfC is calculated as a risk
16 of ten percent, not zero risk. I mean you are on the
17 threshold.
18 DR. SALMON: That's one of the things we
19 have to argue about, of course.
20 DR. PETO: That's been done. And you can
21 obviously do that, which is what's been done anyway.
22 There are difficulty --

Page 113

1 DR. SALMON: There are things that you can
2 do, but they become even more contentious when you are
3 trying to fit that into a linear model than they are
4 with one which at least considers the concept that
5 there may be such a thing as a safe dose.
6 DR. PETO: But you are calculating, I mean,
7 a safe dose hasn't been calculated. A sort of
8 acceptable limit has been calculated. Surely that's
9 what was done in this case. It wasn't a threshold
10 model that was fitted.
11 DR. SALMON: Actually, kind of, but it --
12 it doesn't make the same assumptions as the linear
13 model would. I think the point I'm making, it's more
14 difficult -- I'm not saying it's impossible. It's
15 more difficult to accommodate a linear model in the
16 concepts of -- (inaudible) -- RfC. That's all I was
17 saying.
18 DR. KANE: Well, the recommendation that is
19 written in our draft report seems to be to me fairly
20 clearly stated at the top of page 27 in lines 1
21 through 8. And how is that different from what Julian
22 is suggesting? Or does it help to alleviate some of

Page 114

1 Julian's concern?
2 DR. SHEPPARD: My understanding is that
3 this response is all based on prevalence model and
4 direct analysis of the data. What Julian is
5 suggesting is a transformation of the data based on
6 certain assumptions in order to look more directly at
7 an incidence or to derive the model based on
8 assumptions about an incidence model that then you can
9 use the prevalence model.
10 That would involve certain assumptions that
11 are probably not directly evaluated. We don't have
12 very good ability to evaluate in this data set, so.
13 DR. PETO: The model has been fitted,
14 assumes that the incidence is zero after it's finished
15 to cease, which is wildly wrong.
16 DR. SHEPPARD: So one very --
17 DR. PETO: -- as soon as you write the
18 equation down, you are making an assumption. As soon
19 as you plot a graph, you have made an assumption.
20 DR. SHEPPARD: So that would be a useful
21 thing I think to state that this model, this
22 prevalence model assumes no additional incidence

Page 115

1 afterwards. And, if anything, that means that this
2 model understates the risk. It -- excuse me. It
3 overstates the risk. I always get that backwards.
4 This model, if anything, this is less
5 protective of public health than it should be because
6 there's likely to be more incidence in this population
7 than is reflected in the data set or in the modeling.
8 So that seems like a useful addition that we could
9 make in our recommendations, that because of this
10 assumption of no additional incidence after -- after
11 the data have been assessed, that the RfC if anything
12 is less protective of public health than it should be.
13 DR. LIPPMANN: This is Mort again. It's
14 certainly true that for pneumoconiosis-producing dust,
15 the internal dose keeps on going because a quartz or a
16 fiber doesn't just disappear. It continues within the
17 tissue to stimulate the biological response.
18 DR. SALMON: I think it's important that we
19 do put that caveat in as you mentioned. I mean it's
20 based on very legitimate sources of information
21 outside of the data set we are specifically looking
22 at. And I think it also plays into the later

Page 116

1 discussion about the justification for the data.
2 DR. KANE: So, Lianne, you proposed that we
3 must add a statement somewhere, perhaps under the
4 recommendation to include another bullet on page 27,
5 lines 12 through 16, that the model that EPA used
6 based on prevalence of LPT assumes that there is no
7 progression or additional incidence after --
8 (inaudible) -- of exposure.
9 DR. PETO: So, this is Julian. Am I on?
10 DR. KANE: Yes, you are on.
11 DR. PETO: That fact is obvious in the
12 report. But as I say, the RfC is calculated, and then
13 in discussing uncertainties, that area is
14 acknowledged. And it states there's an uncertainty
15 factor of ten is -- this is a major reason for
16 assigning a database uncertainty factor of ten.
17 I haven't got a database uncertainty
18 factor. I call it, well, uncertainty is the wrong
19 word. The model is wrong. But, I mean, it's on page
20 5, straight 45 of the report Section 5.3.3 just means
21 to me extraordinary you can't get the RfC, and then
22 three pages later say the model is totally wrong

Page 117

1 because it fails to acknowledge this enormous effect.
2 DR. SALMON: This is the only one that
3 plays into the database uncertainty factor.
4 DR. PETO: I know. But what I'm saying is
5 it's silly to fit a model that is wrong and then
6 modify the conclusions. You just fit a model which is
7 more plausible to start with.
8 DR. SALMON: Unfortunately, we don't have
9 divine inspiration to know what the right model is.
10 DR. PETO: Well I've just told you what a
11 better model is. I mean whether it increases
12 linearly, whether incidence varies over time giving
13 you good cumulative dose, I don't know. Maybe Mort
14 knows whether other data address that issue. But the
15 model that has been fitted is grossly wrong. There's
16 blatant reasons.
17 DR. SHEPPARD: So, Julian, you have made an
18 important point. And I think if you can give very
19 specific direction that I would embrace, and I imagine
20 EPA would embrace as well, that exactly how to do the
21 modeling in this data set that you are suggesting,
22 that would be valuable. But for purposes of moving

Page 118

1 forward with respect to the report and helping to
2 resolve this, I think that what I would suggest is in
3 our recommendations we include a bullet that is
4 something of the form, this is what I've drafted now,
5 we can tweak the wording, incorporate a caveat that
6 the model is based on prevalence of LPT and assumes no
7 additional incidence in the future. It suggests the
8 RfC is not adequately protective of public health.
9 DR. PETO: Yes, but the specific suggestion
10 is that the -- a more plausible model should have been
11 used for calculating the RfC.
12 DR. SHEPPARD: But I don't know how to --
13 DR. PETO: Not for discussion of
14 uncertainty factors afterwards.
15 DR. SHEPPARD: Well, we are not on the
16 uncertainty factor question, Julian.
17 DR. KANE: That doesn't come up until page
18 30. We are only on page 27.
19 FEMALE SPEAKER: But he's right in the
20 sense we are trying to account for this, it is in his
21 view of an error in judgment here we are making
22 earlier on, so I sort of understand where he's going

Page 119

1 with that. But I'm just thinking we might be able to
2 deal with it more explicitly if Julian could give us
3 an alternative approach that would show us really how
4 big the difference is between this model based on the
5 prevalence and a model based on incidence and what
6 assumptions that entails.
7 DR. SHEPPARD: Yeah. That has to be laid
8 out quite clearly. This is basically a descriptive
9 model based on a prevalent data set is clearly limited
10 but it's useful. And I think that is the way to view
11 it. It's clearly limited but it's useful.
12 That doesn't mean we can't do better. That
13 doesn't mean we shouldn't do better. But we -- but it
14 already is providing a useful measure for moving
15 forward and based on our scientific understanding that
16 if anything it's not adequately protective of public
17 health. And that -- we incorporate that and then we
18 can figure out how to move forward with more specific
19 direction in the future, but -- and it needs to be
20 more concrete than it is so far. And I would embrace
21 getting that from you, Julian.
22 FEMALE SPEAKER: I have another point of

Page 120

1 clarification on language with EPA or to the SAB
2 board. In truth of what our judgment is about what's
3 adequately protective or not, I mean, aren't we really
4 supposed to be making more neutral (inaudible)
5 decision about whether risks are overestimated or
6 underestimated, and the level of risk that EPA
7 determines as adequate for protect -- public health is
8 really their decision, not ours?
9 DR. VU: This is Vanessa. I just want to
10 point out that, you know, the charge of the Science
11 Advisory Board is to provide science advice. So as
12 much as you can review the agency scientific document
13 and point out your scientific comments with regard to
14 whether the Agency's analysis is scientifically sound,
15 and I know that from now and then the SAB tends to
16 point out some comments about policy, but it has to be
17 the science inform the policy choice.
18 And the agency will make that policy
19 choice, but it's important that you, as a SAB panel,
20 you point out the scientific soundness of your advice.
21 DR. SHEPPARD: Yeah, I apologize for that,
22 what may seem value laden. I just wanted to make sure

Page 121

1 I got the direction right.
2 In the comments it wasn't really about
3 making a value judgment. It's about making sure that
4 it's clear that if anything the RfC is potentially too
5 high based on the scientific understanding.
6 FEMALE SPEAKER: That's already -- yeah.
7 DR. SHEPPARD: Yeah.
8 MALE SPEAKER: -- comments from EPA?
9 MR. BUSSARD: Just a couple thoughts. One
10 is I don't think I would say the model assumes
11 prevalence didn't increase, but the model is not
12 trying to model such an increase. There is a
13 discussion on 5-38 of the document trying to look at
14 some other sources of data to get a sense of how much
15 prevalence appears to increase over time from other
16 exposures that are close to environmental exposures.
17 I mean I think part of the question you are
18 wrestling with is is it okay to model this data and
19 then use data not from this data set to say how does
20 this prevalence change, or if you can follow people
21 for longer, or I think Dr. Peto is arguing is there a
22 way to take a model form that reflects other data and

Page 122

1 applies to this data set but given the sparsity of
2 observations in the data set.
3 So just to recap, I don't think we are
4 assuming the prevalence doesn't increase, we are just
5 not trying to model that given the data set. And then
6 the question is how to take into account information
7 from outside this data set as to how prevalence
8 changes over time, whether to do it inherently in the
9 model or whether to do it after we have the results
10 without trying the models out.
11 DR. PETO: Can you hear me?
12 DR. KANE: Yes.
13 DR. PETO: I mean surely you have to put it
14 in the model. I mean how can you even ask the
15 question. You can't fit a model which you know is
16 wrong and then discuss how you should modify your
17 predictions. I mean the predictions are a consequence
18 of the model.
19 And the adjustment for lifetime exposure is
20 a consequence of the model. The effect of childhood
21 exposure is a consequence of the model. The model
22 will make all those predictions. I mean you can't

Page 123

1 produce a model that does that. You can't fit a model
2 which is wrong and then add factors to allow for it,
3 multiply it by 70 over 54 or something.
4 I mean it's completely unreasonable. It's
5 not the way to do science.
6 DR. SHEPPARD: Well, Julian, all models are
7 wrong. All models are wrong.
8 DR. PETO: Yeah, but some are wronger than
9 others. We know that. I mean Einstein was better
10 than Newton, but Newton wasn't bad. I mean clearly
11 you do the best you can. But, I mean, this model is
12 not the best you can.
13 DR. SHEPPARD: But it's just that there's
14 not much data support. I mean that's the other
15 concept that we need to bring in in terms of this
16 discussion. You can't -- if there's not enough data
17 support to fit a rich model, then you are going to
18 have a fit an incorrect model that is then useful.
19 DR. PETO: You have to fit a model with a
20 model incidence, not prevalence. You have to keep
21 prevalence from it. They keep saying it because it's
22 a fundamental --

Page 124

1 DR. SALMON: The model predicts -- the
2 whole point of the exercise in using this approach is
3 to keep the base -- is to not consider the models to
4 be making any predictions outside of the range of the
5 data to which it's fitted. That model --
6 DR. PETO: Neither.
7 DR. SALMON: -- that model is not
8 considered to be predictive of what's going on outside
9 of the range of the data either in time or exposure
10 levels to which it's been fit. That's the whole point
11 of a benchmark method.
12 DR. PETO: You should abandon the benchmark
13 method then. I mean you ought to choose models which
14 you think are likely to fit the data outside the range
15 of observation obviously.
16 DR. SALMON: The benchmark method was
17 chosen to replace previous attempts to fit supposedly
18 biologically or epidemiologically accurate models. It
19 was because those specific models have been screwing
20 up so badly, and it was felt overall necessary to
21 retreat to a method which didn't make so many
22 contentious assumptions.

ATTACHMENT E

From: Katherine Walker
To: Diana-M Wong/DC/USEPA/US@EPA
Subject: RE: Revised comments on SAB LAA report
Date: 05/07/2012 03:18 PM

These changes are fine with me. I'll let the others weigh in but they're not too controversial!

This has been very challenging. This group is coming from very different perspectives and degree of familiarity both with the details of the Libby cohort data, with the risk analysis process, and with the Libby AA risk assessment itself. I would have preferred that we back up, start with the Risk Assessment document again, and make sure everyone was really grounded in what had been done.

Katy

From: Diana-M Wong [mailto:Wong.Diana-M@epamail.epa.gov]
Sent: Monday, May 07, 2012 3:01 PM
To: Katherine Walker
Cc: Salmon, Andy@OEHHA (Andy.Salmon@oehha.ca.gov); David_Kriebel@uml.edu; Julian.Peto@lshtm.ac.uk; Pennell, Michael; SandP8
Subject: Re: Revised comments on SAB LAA report

Katy et al.,

Thank you all for your hard work to come to this revised responses.

I have made a few minor edits. Please review and get back to me ASAP before I post your memo. Thank you very much.

(See attached file: dw Libby SAB Report revisions_IUR_ May 7 2012_revised.docx)

Diana

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Katherine Walker ---05/07/2012 02:34:52 PM---Diana: Let me know if these instructions are now clear.

From: Katherine Walker <KWalker@healtheffects.org>
To: Diana-M Wong/DC/USEPA/US@EPA
Cc: SandP8 (b) (6) [redacted] "Pennell, Michael" <mpennell@cph.osu.edu>, "Salmon, Andy@OEHHA (Andy.Salmon@oehha.ca.gov)" <Andy.Salmon@oehha.ca.gov>, "Julian.Peto@lshtm.ac.uk" <Julian.Peto@lshtm.ac.uk>,

"David_Kriebel@uml.edu" <David_Kriebel@uml.edu>
Date: 05/07/2012 02:34 PM
Subject: Revised comments on SAB LAA report

Diana:

Let me know if these instructions are now clear.

Katy

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(See attached file: Libby SAB Report revisions_IUR_ May 7 2012_revised.docx)

From:	Katherine Walker
To:	SandP8; scott@ramas.com; Pennell, Michael; Salmon, Andy@OEHHA (Andy.Salmon@oehha.ca.gov); Julian.Peto@lshtm.ac.uk; David_Kriebel@uml.edu
Cc:	Diana-M Wong/DC/USEPA/US@EPA
Subject:	RE: REVISED DEADLINE: EPA Questions and Remarks - Libby Charge Questions IIIB 1_2_ 3 and 5
Date:	05/03/2012 03:05 PM

Hi All:

My apologies for the multiple emails. Diana – rightly so – has suggested that I make clearer that all we are looking for is the few lines, bullet point or paragraph that clarifies, by page and line number, the disputed language in the draft report I have outlined in my previous emails. EPA is not looking for a re-write of our section of the report.

Just clear advice on the 3 issues 1) independence assumption 2) model selection and 3) "full" uncertainty analysis.

Katy

From: Katherine Walker
Sent: Thursday, May 03, 2012 2:51 PM
To: 'SandP8'; 'scott@ramas.com'; 'Pennell, Michael'; 'Salmon, Andy@OEHHA (Andy.Salmon@oehha.ca.gov)'; 'Julian.Peto@lshtm.ac.uk'; 'David_Kriebel@uml.edu'
Cc: Diana-M Wong (Wong.Diana-M@epamail.epa.gov)
Subject: REVISED DEADLINE: EPA Questions and Remarks - For our subgroup - Libby Charge Questions IIIB 1_2_ 3 and 5
Importance: High

Hi All:

Diana has just informed me that she needs to post our revisions to the SAB report on Monday morning by 9AM or so.
This means that the Monday times I suggested will be too late.

We will need to have the call with as many people as possible TOMORROW – Friday - I have a preference for the Noon to 1 time slot given other commitments.

Mike Pennell – I know that you have said you cannot be available on Friday, so please send in writing any specific suggestions today or tomorrow. Barring that, I'll try to do a last revision on Sunday night.

Thanks all.

Katy

From: Katherine Walker
Sent: Thursday, May 03, 2012 12:17 PM

To: 'SandP8'; scott@ramas.com; Pennell, Michael; Salmon, Andy@OEHHA (Andy.Salmon@oehha.ca.gov); Julian.Peto@lshtm.ac.uk; David_Kriebel@uml.edu
Cc: Diana-M Wong (Wong.Diana-M@epamail.epa.gov)
Subject: RE: FW: EPA Questions and Remarks - For our subgroup - Libby Charge Questions IIIB 1_2_ 3 and 5

Hi all:

We are specifically charged with Libby Charge Questions IIIB 1_2_ 3 and 5 and the EPA's requests for clarification. Although some of the issues we're charged with are also linked to discussions we had the other day -- whether and to what extent the larger amphibole asbestos literature should be brought to bear on the Libby Risk Assessment – we need deal with them within the context of the development of the IUR.

I've laid out the questions before us below, but first…

I would like to make sure that we are in basic agreement about the goal of the risk assessment and our job in this enterprise. While ultimately of course EPA wants to develop an inhalation unit risk (IUR) that meets their policy criteria for protectiveness, our job is, ideally, to help them estimate the "true but unknown" risk associated with an increased unit of exposure including with what error or uncertainty we know it. EPA can presumably make an informed choice about how protective their selected IUR is, without unwittingly missing some major underestimation of the risk, or needlessly compounding a lot of conservative assumptions so the level of protection is more extreme than they think it is.

In various panels U.S. NAS has suggested to EPA that they improve the scientific underpinnings of their IRIS assessments and in the case I'm most familiar with (air pollution), to improve their characterization of uncertainty. As we've heard in the discussions from the panel, and from the public comments, scientists aren't necessarily going to agree on interpretation of the science.

But we do have to decide what we can agree on and what advice we can give to EPA.

The issues are:

1) P33 IUR Question 1. The assumption of independence of mesothelioma and lung cancer. I think we're close (if we can answer the questions from a previous email) and this is likely a smaller issue than that of model selection and uncertainty analysis.

2) P33 IUR Question 1. Second paragraph on model selection/uncertainty. (This relates also to the broader question of whether and what to request from EPA in terms of uncertainty analysis (next question)).

    a. In their request for clarification EPA has asked, inter alia, "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?"

        i. It appears that EPA is agreeing to a discussion of alternative models and the rationales for them.

ii. The real question is the second part on whether use of one model is sufficient to address and illustrate model uncertainty. **What do you think?**

b. In the second part of the paragraph, the EPA asks whether the list we provided are proscriptive or whether there are other models to be considered?

i. Can we agree that we were not being prescriptive but illustrative?

ii. Can we give specific examples of other models that should be considered that have not?

iii. OR, can we agree on a set of criteria by which they might consider alternative models (e.g. prior experience in appropriate (to LAA) data sets; biological plausibility; statistical fit criteria, others?) Do these differ from what EPA has attempted to do already?

3) Diana Wong asked that we discuss and decide on several specific suggestions that Scott Ferson included in his most recent comments before we get on the call on Tuesday.

a. P 13-14 of compiled comments. We discussed at the meeting the suggestion that EPA consider analyzing the full Libby worker cohort including hires before 1959. Scott has suggested addition of a paragraph. As you may recall, we did get push back at the meeting from the industrial hygienists who did not think there was enough information to assign exposure estimates.

i. Please review Scott's recommendation. My question to Scott and to the panels is 1) whether or not there is sufficient information about job categories or concentrations that the interval exposure estimates would not be "vacuous" .

ii. how the interval statistics to characterize exposure would be incorporated into the epidemiologic models.

4) "Full uncertainty analysis" for the IUR – what is it that we really are asking EPA to do?

a. We've asked for the treatment of model uncertainty. And the question above which is essentially about the data set used, so how are we defining a full uncertainty analysis in the context of developing an IUR?

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

analysis with these features?”

b. What I am unclear on is that EPA is essentially undertaking a model selection and fitting process -- subject to sensitivity analyses about exposure primarily – in order to estimate the C-R relationships (slopes) and from those to develop their IUR (for meso and lung cancer).

   i. **Scott –** can you be more specific how, in this epidemiologic setting, we can do a joint and integrated uncertainty analysis? Such that EPA would come up with an interpretable distribution or informative set of bounds on the

Please consider these questions and respond to all via email. I will also look to set up times for a conversation.

Katy