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September 18, 2012

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:

Thank you for the opportunity to provide comments to the chartered SAB. As Vice President of Environment, Health and Safety for W. R. Grace & Co. (Grace), I have a wide range of responsibilities, including ensuring that the company meets its ongoing environmental remediation obligations. Due to the significance of EPA's draft assessment for Libby amphibole asbestos, Grace has been following the SAB's review process carefully. Grace is particularly concerned about both the process of developing this risk assessment, as described in the letter from our counsel Beveridge & Diamond, and the scientific integrity of the report from the SAB Panel and the draft assessment itself, as addressed in this letter and its attachments. Toxicity values that are well founded in science serve everyone's interests; and we ask your support in achieving this goal.

Grace urges the Charter SAB to return the draft report to the SAB panel to correct deficiencies and then provide sound direction to EPA for the formation of toxicity values for LAA. Though the chartered SAB has only scheduled a few hours to discuss the issues next week, and has only recently received the draft report, we are asking that the chartered SAB critically assess the draft Libby Amphibole Assessment. It deserves this attention for several reasons.

First, this toxicity assessment is on the frontier of asbestos science. For the first time ever, EPA has developed a non-cancer endpoint for a mineral fiber, as opposed to a chemical substance. Furthermore, EPA has proposed to set an extremely low reference concentration for this fiber. In the words of one SAB panelist, EPA is "going out on a limb" with this non-cancer toxicity

value.¹ Another panelist remarked that the non-cancer toxicity value is “so much lower than background levels. And how should the public -- what are the scientists who are trying to deal with risk, interpret numbers like that?”² But neither EPA nor the SAB Panel has openly addressed the implications of such a low value.

Second, the non-cancer toxicity value is not well-founded. EPA selected pleural plaques as an endpoint even though the SAB Panel did not conclude that they cause an adverse health effect; the Panel only states that pleural plaques are “generally associated” with reduced pulmonary function. As explained in the Summary accompanying this letter and in public comments to the SAB panel prepared by experts in relevant fields, EPA has applied the wrong methodology, based the proposed values on a paltry dataset, selected an endpoint of pleural plaques as an ‘adverse effect,’ and failed to critically evaluate factors that could significantly influence the toxicity values (such as the confounder of age). The methodology is anomalous and the results are inaccurate. Grace is concerned not only about how these numbers will be applied in the field, but also about misperceptions the numbers will create.

Third, EPA has downplayed the broad impact of the non-cancer toxicity value, not only on LAA but also on other forms of amphibole. Amphibole asbestos fibers exist in buildings, urban areas and farmland in every corner of this nation, often with background levels above the proposed non-cancer toxicity value. As stated in the Report, “the appropriate assumption is that LAA fibers have the **same mechanisms of toxicity and quantitative risk relations as that of other asbestos fibers.**” (Section 3.2.5.7). Therefore, although EPA tries to frame this toxicity assessment narrowly, the non-cancer toxicity value’s broader application to remediation and abatement of all amphiboles is inevitable. That broad application will, in turn, result in enormous unexpected and unnecessary costs to building owners, farmers and other property holders, including the federal government. For these reasons, the SAB must thoroughly review and evaluate the science behind that toxicity value.

The SAB should instruct the panel to consider the benefits of using the wider body of available data on amphiboles to improve the analysis, instead of basing the reference concentration on a miniscule, selective sub-cohort for LAA. This will reduce the uncertainty and increase the weight of evidence. EPA’s IRIS program will have more support if the science is strong.

We also urge the SAB to instruct EPA to apply the National Academy of Sciences’ recommendations for IRIS risk assessments to this assessment. The recommendations of the NAS describe basic scientific methods integral to sound risk assessment procedures. EPA has stated that it is now implementing the NAS reforms to other IRIS assessments. It would be

¹ As described in the accompanying Summary, a transcript was prepared of public panel sessions, and this quote was an observation offered by Dr. John Balmes as the SAB Panel discussed how to strengthen the EPA Assessment with respect to the non-cancer endpoint. See accompanying Summary, Attachment 4, 2/8/12 transcript excerpts, p.15.

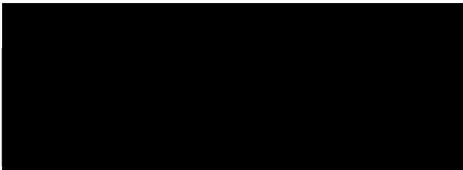
² This observation was made early in SAB Panel deliberations by Dr. Morton Lippmann. See accompanying Summary, Attachment 2, 2/6/12 transcript excerpts, pp. 48-49.

anomalous and unsound science policy to accord some ongoing assessments but not the LAA risk assessment the benefits of these reforms.

Finally, we point out a troubling lack of transparency in the development of this IRIS risk assessment. If the scientific process and opportunities for peer review are to be meaningful, all data that EPA relied on should have been available to the public at the beginning of the process; they were not. Grace and experts have requested access to data in order to evaluate, replicate if possible, and comment on the studies EPA used in forming its toxicity values. However, we have, with difficulty and only recently, obtained the specific data that was used to estimate the proposed toxicity values, and now we are seeking related data to aid a complete evaluation. A transparent, objective, open scientific process should allow ready access to the information which underlies significant findings of the agency. Such protections of the integrity of the process were lacking here.

In conclusion, Grace urges the SAB Committee to return the draft assessment to the peer review panel and instruct it to address in depth the comments of experts, to apply the recommendations of the NAS, and to assure that sound science supports its conclusions. The accompanying Summary describes selected fundamental problems that the SAB Report does not adequately address; the public comments of experts analyze these issues in more depth.

We thank the SAB in advance for its time and consideration.



Karen E. Ethier
Vice President
Environment, Health and Safety

Enclosures:

Summary of Selected Points that the Chartered SAB Should Require the SAB Panel to Meaningfully Review, and referenced attachments.

TOXICOLOGICAL REVIEW OF LIBBY AMPHIBOLE ASBESTOS: SUMMARY OF
SELECTED POINTS THAT THE CHARTERED SAB SHOULD REQUIRE THE SAB
PANEL TO MEANINGFULLY REVIEW.

1. THE CURRENT RISK ASSESSMENT FAILS TO CONSIDER THAT THE RFC DATA IS CONFOUNDED BY AGE, AND THIS FUNDAMENTAL ERROR UNDERMINES THE VALIDITY OF THE RFC. THIS IS NOT DISCUSSED IN THE SAB REPORT.

EPA's analysis of the noncancer data (a subcohort of the Rohs, et al. (2008) data set), is confounded by age, and does not provide a valid basis for deriving an RfC. EPA bases the LAA RfC entirely on data demonstrating that an association between localized pleural thickening and pulmonary function deficit is statistically insignificant when the full Rohs cohort is analyzed and age is taken into account. Until very recently, this data was unavailable to the public. Thus stakeholders were unable to fully address this issue with the SAB Panel and the Panel's Report does not address this issue at all. Drs. Moolgavkar and Hoel are now able to summarize their findings for the chartered SAB and can follow up with more detailed information if there is an opportunity to do so. Perhaps the SAB Panel missed the issue because it lacked either access to the data or the time to evaluate the raw data in this rushed process. Regardless, the Rohs data provide the basis for the RfC and the effect modification by age is central to any scientific analysis of that data.

2. THE SAB PANEL REPORT IGNORES THAT THE RFC CALCULATION SHOULD HAVE BEEN BASED UPON "CONCENTRATION" DATA, LIKE OTHER RFCS, TO YIELD A USABLE DAILY DOSE.

The SAB should reject EPA's use of "cumulative lifetime exposure" and resulting flawed assumptions that underlie the RfC calculation. EPA's novel calculation will result in erroneous "false positives" of an unacceptable hazard. Because EPA calculated the RfC based on "cumulative lifetime exposure," the RfC only arguably applies if an individual is exposed for 60 or 70 years. As calculated, the RfC provides no useful information about risks for a person exposed for 1 day, 1 year or 20 years, even though it will certainly be used as if the toxicity value applied to such situations. For example, when assessing the risk of a construction worker, an RfC that assumes a lifetime of exposure is inapplicable because it would dramatically overstate the risks. This is one real life application in which the RfC is not useful.

Like other RfCs, this RfC should be based on an average concentration of exposure to yield a valid daily exposure dose that risk assessors will know how to use in the field. This standard RfC calculation is straight-forward. It applies concentration data to achieve a reference concentration. EPA cannot justify its alternative computation that injects an assumed lifetime of exposure and in doing so introduces confusion as to how the resulting RfC can be applied. Unless this methodology is corrected, risk assessors will incorrectly apply this misleading RfC.

This point that the RfC calculation should be revisited is further reinforced by the recent analysis of raw data demonstrating that duration is a far better measure of dose than cumulative exposure.

3. THE RFC MODELLING IS IMPLAUSIBLE AND SHOULD BE CORRECTED.

The modeling upon which the RfC is based is incapable of representing the risks of asbestos exposure, but the SAB report is internally inconsistent on how to correct this problem. The report suggests consideration of plausibility but points EPA in the direction of a model – the dichotomous Hill model – that is even less plausible than the Draft Assessment’s model used by EPA (the Michealis-Menten model). Neither of these benchmark dose level models show the risks associated with high exposure levels. Each of these two models has a plateau, which means that no matter how high the exposure level, the model will assume that there is no increased health risk at the high exposure level. Decades of asbestos data tell us that this simply is not biologically or epidemiologically true; the greatest risks of asbestos inhalation are tied to high exposure levels. The dichotomous Hill model is not a better fit, and requires estimates of more parameters than the Michealis-Menten model used by EPA. The SAB report would move EPA in the wrong direction. Instead, the SAB report should advise use of a logistic regression model, to allow EPA to analyze the risks associated with a full range of exposures.

As stated by a panelist with expertise in modeling, “*My central concern with the Libby draft review is the adoption of the models which are fundamentally wrong epidemiologically for both mesothelioma and pleural thickening, and until this is addressed, the other charge questions . . . 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 or the Galilean model of the Solar System to predict where the planets will be next year . . . The analyses based on this model are therefore wrong, and should be removed from the report.*”¹

4. THE RFC ENDPOINT OF LOCALIZED PLEURAL THICKENING IS NOT SUPPORTED BY THE WEIGHT OF EVIDENCE.

“The preponderance of evidence indicates that localized pleural thickening, in and of itself does not cause statistically significant or clinically significant impairment of lung function,” as explained by Dr. Lawrence C. Mohr, M.D., who provided an intelligent and thoughtful literature review for the Panel’s use.² Dr. Mohr transcript, 5/1/12, p.34, attached hereto as Attachment 5.

The SAB should advise EPA clearly and succinctly that the symptoms postulated by EPA in the Draft Assessment (possibly restricted lung function, increased breathlessness with

¹ 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), emphasis added, attached hereto as Attachment 1.

² A transcript was prepared for each of the public panel sessions (“Transcript”).

exercise and contributions to chronic chest pain) have not been shown by the literature to be caused by localized pleural thickening (LPT).

The SAB report currently sidesteps the issue by saying that LPT is “generally associated” with reduced lung function and leaves it to EPA to find support for this conclusion, as no specific support has been identified. Use of the phrase “generally associated” begs the question. As EPA noted when it sought clarification on the same issues, “[t]he same exposure may cause two different endpoints, resulting in a statistical association solely by the nature of their shared exposure.”³

5. THE SAB PANEL REPORT MISAPPLIES EPA GUIDANCE; LPT DOES NOT CONSTITUTE AN “ADVERSE EFFECT” WITHOUT DEMONSTRATION THAT IT IMPAIRS AN INDIVIDUAL’S PERFORMANCE.

As stated by one experienced panelist whose views were not reflected in the Panel’s Report:

“the observation that something can be measured doesn't prove adversity. In fact the coal miners are more often compensated for black lung by x-ray but not for substantial pulmonary function loss which they, you know, which isn't part of the definition legally. You can get siderosis from iron oxide with little evidence of serious consequences. *So I'm reluctant to, you know, set a standard or reference concentration on simply something that can be measured. I think we need more.*” Dr. Lippmann transcript, 2/6/12, p. 213, emphasis added, attached hereto as Attachment 2.

The Panelist’s above statement reflects EPA policy. Under EPA policy, an adverse effect requires biological significance such that it “*is likely to impair the performance or reduce the ability of an individual to function or to respond to additional challenge from the agent.*” Biological significance is also attributed to effects that are consistent with steps in a known mode of action. Statistical significance quantifies the likelihood that the observed effect is not due to chance alone. Precedence is given to biological significance, and *a statistically significant change that lacks biological significance is not considered an adverse response.*⁴

³ 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, emphasis added, *available at* <http://yosemite.epa.gov/sab/SABPRODUCT.NSF/MeetingCal/DE16F40DF2BE9271852579FB0054C2BF?OpenDocument>.

⁴ EPA. A Review of the Reference Dose and Reference Concentration Process (Dec. 2002) at 4-11, emphasis added, *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.”).

EPA has also defined “Adverse Effect” as “[a] biochemical change, functional impairment, or pathologic lesion that affects the *performance* of the whole organism or reduces an organism's ability to respond to an additional environmental challenge.”⁵

Furthermore, under EPA guidance, “[f]or compounds that appear to produce their critical effect *within the respiratory system* itself, decisions concerning adversity need to be made on a case-by-case basis. *Appendix D provides specific information concerning evaluation of the severity of respiratory tract endpoints* in humans.” Under EPA’s Appendix D, an effect that is a biological marker only is not a sufficient basis for an adverse effect determination; one needs to show an impairment.⁶

6. THE RFC AND IUR ARE BOTH BASED ON INADEQUATE SUBCOHORTS OF DATA EVEN THOUGH LARGER, RICHER DATA SETS ARE AVAILABLE.

The RfC calculation is based on only 12 cases of LPT, producing a statistically weak conclusion. Using this small subcohort interferes with adjustment of the exposure-response relationship for potential confounders such as weight and age (contrary to the agency’s own criteria), selection of appropriate models, uncertainty calculations, and the development of a valid RfC. Important decisions with a broad impact should not be based on such a small amount of information.

The IUR is based on a subcohort of one study and focused on 32 cases of lung cancer deaths and 7 cases of mesothelioma deaths. The rationale for limiting the analysis to this subcohort does not stand up to scrutiny, and the SAB Panel draft report does not reflect panelists’ concerns about the paucity of underlying data:

“ . . . I think it would be preferable to compute the inhalation unit risk from cancer from a full data set . . . ” (and continuing later) “ . . . *it seems a terrible waste to effectively throw away two-thirds of the cancer mortalities that are in the data set.*” Dr. Ferson transcript, 2/7/12, p. 142, emphasis added, attached hereto as Attachment 3.

One panelist who was not an epidemiologist accepted the use of the subcohort but urged collection of more data, stating:

“So I would do everything in your power to try to make the studies continue so you get more data on the number of deaths and relook at the models then. It's -- *my statistician would hit me over the head if I tried to model seven, seven deaths with any kind of model.*” Dr. Neuberger transcript, 2/8/12, p. 64, emphasis added, attached hereto as Attachment 4.

⁵ Risk Assessment Guidance for Superfund, Volume I: Human Health Evaluation Manual, Part F, Supplemental Guidance for Inhalation Risk Assessment (Jan. 2009) at 9, available at www.epa.gov/oswer/riskassessment/ragsf/pdf/partf_200901_final.pdf.

⁶ Environmental Criteria and Assessment Office, EPA, Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (Oct. 1994) at 2-35, emphasis added, available at <http://cfpub.epa.gov/ncea/cfm/recorddisplay.cfm?deid=71993>.

Other panelists noted:

“But *it's just that there's not much data support*. I mean that's the other concept that we need to bring in in terms of this discussion. You can't -- if there's not enough data support to fit a rich model, then you are going to have a fit an incorrect model that is then useful.” Dr. Sheppard transcript, 5/1/12, p. 123, emphasis added, attached hereto as Attachment 5.

“*Of course you can't develop a model for mesothelioma based on seven cases or whatever it is. You have to look at the enormous body of evidence on what the epidemiology of mesothelioma is and choose the model that you fit on that basis. I mean it's mad to do anything else and completely disreputable.*” Dr. Peto transcript, 5/1/12, p. 100, emphasis added, attached hereto as Attachment 5.

“. . . I would like to caution my esteemed peers that a model is only as good as the data that are input. And so *we cannot generate models that produce over-reaching conclusions that are not supported by the database. . .*” Dr. Hei transcript, 5/1/12, p. 138, emphasis added, attached hereto as Attachment 5.

7. TO ADDRESS THE ABSENCE OF AN UNCERTAINTY ANALYSIS, THE SAB PANEL SHOULD RECOMMEND THAT EPA ANALYZE THE FULL COHORTS FOR ALL ENDPOINTS AND EVALUATE A POSSIBLE RANGE OF TOXICITIES.

A rigorous uncertainty analysis is essential for implementation of the NAS recommendations. A range of values would provide necessary guidance to risk managers who apply these standards in the field.

ATTACHMENT 1

From: Julian.Peto@lshtm.ac.uk
To: [John Neuberger](mailto:John.Neuberger); [Mort Lippmann](mailto:Mort.Lippmann); [David Kriebel@uml.edu](mailto:David.Kriebel@uml.edu)
Cc: [Diana-M Wong/DC/USEPA/US@EPA](mailto:Diana-M.Wong@USEPA)
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)

However, 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 ($70 \div 54$) 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 2

In The Matter Of :

**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
SCIENCE ADVISORY BOARD**

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

MERRILL LAD

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<p style="text-align: right;">Page 45</p> <p>1 confidence intervals for the two things. We use a 2 statistical approach that appropriately weights those 3 and gets us an upper bound on the sum of those. And 4 that's how we end up with the inhalation unit risk for 5 the combined cancers.</p> <p>6 It was useful to compare this to the 7 results other researchers have gotten looking at the 8 same cohort. For mesothelioma, we had one other that 9 we could look at that had estimates. In some cases we 10 had to take the estimates and convert it to the 11 calculations to what the associated lifetime risk is, 12 an inhalation unit risk would be.</p> <p>13 So for mesothelioma we found quite similar 14 results. For lung cancer we found that our results, 15 the central tendency is somewhat higher than those 16 found by others. The confidence interval is somewhat 17 narrower than some but not all. So our estimates for 18 lung cancer are somewhat higher than the smaller 19 cohort, and the estimates of mesothelioma are very 20 similar.</p> <p>21 We looked at smoking and the effect on lung 22 cancer. First we looked at whether we were getting</p>	<p style="text-align: right;">Page 47</p> <p>1 of additional papers. It may well be that peer 2 reviewers have additional citations we are unaware of 3 and we very much welcome those and appreciate those.</p> <p>4 A very quick preliminary review of 5 additional papers suggest some of these support the 6 finding that pleural thickening is observed at low 7 exposure ranges. Some support that pleural plaques 8 may contribute to observations of restrictive lung 9 function. And there's one that supports our focus on 10 subcohort and minimizing error in exposure and, 11 therefore, having more confidence in the estimate of 12 slope.</p> <p>13 Not to read, but there's references to the 14 things that we cited in the presentation. And I want 15 to thank you very much for being here. We look 16 forward to listening to your discussion and getting 17 feedback. And, lastly, I just want to recognize this 18 really has been a group effort of a diverse team 19 across Region 8 and ORD. And particularly I would 20 like to note the three chemical managers: Dr. Tom 21 Bateson, Danielle DeVoney and Robert Benson. But it 22 was really a team effort.</p>
<p style="text-align: right;">Page 46</p> <p>1 confounding of our results. We were able to look at a 2 number of tests there listed, and then we were able to 3 use a method first proposed by Richardson to evaluate 4 confounding by smoking. And at least the evaluation 5 that we could do did not suggest that there was 6 confounding.</p> <p>7 We do think it's possible that lung cancer 8 results reflect effect modification, which is somewhat 9 different issue, and that it might be possible at some 10 point to estimate risks to smoking populations and 11 non-smoking populations. This was a mixed population 12 with considerable amount of smoking, although we do 13 not have the exact data that we would need to really 14 tease that apart.</p> <p>15 So that's been a very quick walk through a 16 number of the key decisions made in the assessment. 17 And as with the non-cancer, the charge asks you to 18 evaluate the assessment. And this flags some of the 19 key decisions that we have to make along the way.</p> <p>20 As with any assessment, the science keeps 21 moving on. And since the cut-off date for our 22 assessment, we just wanted to flag that we are aware</p>	<p style="text-align: right;">Page 48</p> <p>1 And quite a number of people who 2 contributed, most are in the room here today. And we 3 also benefited a lot from conversations with others 4 and reviews within the agency and through an 5 interagency process. So with that, I would like to 6 end. I hope that was not too long of a quick overview 7 of what we did, and we'd be glad to help with 8 questions and clarifications if we can.</p> <p>9 DR. KANE: Thank you. I'd like to open up 10 questions for members of the panel, and first so we 11 don't forget them our telephone, reviewers do they -- 12 do you have any questions?</p> <p>13 DR. LIPPMANN: Yes. This is Mort Lippmann. 14 Good morning. I can appreciate the hard work that was 15 done and the very careful presentation.</p> <p>16 One thing I didn't see in the document was 17 discussion of the implications of these risks of two 18 times ten to the minus five fiber per cc and four 19 times ten to the minus six as an ultimate based on 20 sensitivity analyses.</p> <p>21 These are so much lower than background 22 levels. And how should the public -- what are the</p>

12 (Pages 45 to 48)

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<p style="text-align: right;">Page 49</p> <p>1 scientists who are trying to deal with risk interpret 2 numbers like that?</p> <p>3 MR. BUSSARD: So, one, we need to be 4 careful about background. This is really focused on 5 material from Libby. A lot of the background 6 measurements we've seen are for asbestos in other 7 settings and may not directly comparable.</p> <p>8 The second would be to note that a 9 reference concentration or a risk specific dose is not 10 meant to be an estimate of a concentration at which we 11 will easily observe effects. So it may well be below 12 where one could observe effects in an epidemiology 13 study and in case reports. It's meant to be a level 14 at which we can assure people that they are safe.</p> <p>15 The other thing I would note is that as Deb 16 McKean made reference to, in making decisions for 17 cleanups there are a range of factors that go into 18 making decisions. So we are trying to separate out 19 our best estimate of estimating the cancer risk and 20 estimating a concentration below which we are 21 confident that we won't have adverse effects. 22 The decision-making process has ways to</p>	<p style="text-align: right;">Page 51</p> <p>1 to make that more explicit in how the issue is being 2 dealt with for Libby and by extrapolation to other 3 communities that are not confounded by the presence of 4 significant chrysotile.</p> <p>5 So I just hope that you take the 6 opportunity perhaps at the end of the discussion and 7 certainly with some introduction to look into these 8 generic issues and to point out that you're less 9 confounded in the case of the amphiboles and Libby 10 than you are in asbestos in general, and to recognize 11 that in terms of the key issue of durability, one 12 amphibole is certainly just about equal to any other 13 amphibole.</p> <p>14 MR. BUSSARD: Thank you for those comments.</p> <p>15 MR. GUTHRIE: Hi. This is George Guthrie. 16 I just want to thank you for the nice overview, and I 17 don't have any questions at this point, but thanks.</p> <p>18 DR. KANE: Any questions from other members 19 of the panel?</p> <p>20 DR. NEWMAN: This is Lee Newman. Thank you 21 for a very clear presentation. You made reference to 22 some of the additional papers that have come out.</p>
<p style="text-align: right;">Page 50</p> <p>1 look at ways to make decisions even though exposures 2 are above background. So it's a good question, but we 3 are trying to follow where the science takes us. And 4 we are deliberately trying to develop numbers where 5 there will not be an effect. That's often below 6 levels at which you might see effects.</p> <p>7 DR. LIPPMANN: There are two comments, and 8 thank you for the very clear explanation. I think we 9 know that, but I think it's a generic problem with 10 high risk. And I think EPA needs to have the 11 appropriate discussion of that rather than just pass 12 over it.</p> <p>13 The second comment is that fortunately for 14 this review you are dealing with the amphiboles, and 15 the issue is not confounded by the very different 16 issues with chrysotile. And so it may be possible to 17 look for background data with other amphiboles that 18 could be relevant to the discussion in those studies 19 where chrysotile is not an issue.</p> <p>20 Because, you know, the issue with the risks 21 from fibers among the amphiboles is much simpler than 22 dealing with all asbestos. And this is an opportunity</p>	<p style="text-align: right;">Page 52</p> <p>1 Clearly you had to reach some point where you say we 2 are cutting off what we are including.</p> <p>3 The Minneapolis expoliation community 4 studies though seemed to be of particular interest, 5 and I'm wondering what is your sense in terms of how 6 you would like to incorporate some of the more recent 7 publications that have come out into our discussions 8 and into how you move forward.</p> <p>9 MR. BUSSARD: That's an interesting process 10 conundrum. One of the things that we found when we've 11 done reviews and there's additional literature that 12 becomes available, it's hard for us to quickly revise 13 the assessment prior to the review. But it's very 14 helpful if the committee thinks that a paper is 15 important, that if the committee has looked at it and 16 discussed it, then sometime we are able to put it 17 together with the work that we have prior to the peer 18 review.</p> <p>19 So I would urge members, if there are a few 20 papers that you think are very important, it's helpful 21 to us to have the record be clear if the committee 22 looked at the paper and had opinions about its value</p>

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<p style="text-align: right;">Page 53</p> <p>1 or its use.</p> <p>2 DR. KANE: Dr. Sheppard?</p> <p>3 DR. SHEPPARD: So I have a question about</p> <p>4 calculating the reference concentration. And</p> <p>5 considering the outcomes why not, since it was --</p> <p>6 since the data were all prevalence data, why not</p> <p>7 consider multiple outcomes? Why restrict it to</p> <p>8 localized pleural thickening?</p> <p>9 MR. BUSSARD: In the subcohort we actually</p> <p>10 I think only had one diffuse pleural thickening, so</p> <p>11 I'm not sure it would make a big difference there.</p> <p>12 And when you have effects that are really quite</p> <p>13 different from each other in terms of severity error,</p> <p>14 it becomes a little bit tricky.</p> <p>15 I am not sure myself that I think it adds a</p> <p>16 lot if you've got sufficient information on the lower</p> <p>17 dose effect since we are trying to find a value at</p> <p>18 which we don't have adverse effects to add in other</p> <p>19 effects that occur at higher doses. But we do try to</p> <p>20 capture them in the discussion of hazard and not leave</p> <p>21 any impression that they are not there.</p> <p>22 DR. KRIEBEL: Hi. This is Dave Kriebel.</p>	<p style="text-align: right;">Page 55</p> <p>1 from a certain policy perspective about when it's</p> <p>2 appropriate from your perspective to draw from other</p> <p>3 literatures and when we really should not?</p> <p>4 Do you have any guidance for us on that?</p> <p>5 Are there studies of amphibole-exposed workers,</p> <p>6 completely different contexts?</p> <p>7 MR. BUSSARD: I guess I would look at it as</p> <p>8 a scientific question that if the committee feels that</p> <p>9 other studies of amphibole are highly informative to</p> <p>10 this one, and the studies are of good design and good</p> <p>11 quality, I think that could help corroborate, or if it</p> <p>12 went the other way, cast question about what we've</p> <p>13 done.</p> <p>14 It's not unlike when we've got study -- a</p> <p>15 range of studies and different kinds of information we</p> <p>16 end up deciding that there's one body of data that</p> <p>17 produces the best quantification but we do try to put</p> <p>18 it in the light of other things. But as you can</p> <p>19 imagine, we were trying not to get into a</p> <p>20 comprehensive review of all the asbestos literature.</p> <p>21 It would take considerably longer.</p> <p>22 Does that help at all?</p>
<p style="text-align: right;">Page 54</p> <p>1 Thank you very much. That really did help a lot. A</p> <p>2 couple of questions to just help me understand better</p> <p>3 how to think about this new assessment in the context</p> <p>4 of the EPA's 1988 IRIS review.</p> <p>5 So, two things: One is the -- could you --</p> <p>6 I understand that this is our task is to focus on the</p> <p>7 Libby amphibole asbestos. Maybe could you just</p> <p>8 comment on just quantitatively what the IUR, how it</p> <p>9 compares to the 1988 result for asbestos?</p> <p>10 MR. BUSSARD: I think the IUR, I don't have</p> <p>11 the numbers at the top of my head, but the IUR comes</p> <p>12 out a little bit lower than the IUR that was</p> <p>13 calculated in 1986.</p> <p>14 DR. KRIEBEL: But fairly close?</p> <p>15 MR. BUSSARD: But fairly close.</p> <p>16 DR. KRIEBEL: And the other thing is a more</p> <p>17 general question. So I guess I'm having a little bit</p> <p>18 of trouble thinking about how to use all of the vast</p> <p>19 literature on other asbestos and other context and</p> <p>20 amphibole in other studies in informing this, and</p> <p>21 something we'll be thinking about I think a lot over</p> <p>22 the day, but is there anything you want to add for us</p>	<p style="text-align: right;">Page 56</p> <p>1 DR. KRIEBEL: Yes. I think that's good.</p> <p>2 FEMALE SPEAKER: May I just follow up a bit</p> <p>3 on that. There have been some other studies, perhaps</p> <p>4 not as -- certainly not as thorough as this, but they</p> <p>5 may be informative, and I was wondering why you didn't</p> <p>6 include them in the report; and that is studies that</p> <p>7 have looked at environmental exposures and some of</p> <p>8 these outcomes.</p> <p>9 MR. BUSSARD: So when we looked at this, at</p> <p>10 studies of environmental exposures, the difficulty is</p> <p>11 often it's very hard to estimate what the exposure</p> <p>12 levels are, what the population is, what the duration</p> <p>13 is, what the exposure concentrations are. So they are</p> <p>14 a useful perspective, but it's hard to use them to</p> <p>15 come up with a reference concentration per se or</p> <p>16 inhalation unit risk per se.</p> <p>17 FEMALE SPEAKER: Yes, I appreciate that.</p> <p>18 But they are sort of useful though as a test, as a</p> <p>19 barometer of whether what you've derived sort of fits</p> <p>20 with what has been observed in other exposure</p> <p>21 scenarios, particularly with amphiboles.</p> <p>22 MR. BUSSARD: And that may be a comment</p>

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<p style="text-align: right;">Page 209</p> <p>1 but it's certainly a reasonable suggestion.</p> <p>2 DR. KANE: Dr. Redlich, I would like to ask</p> <p>3 another pulmonologist.</p> <p>4 DR. REDLICH: I think we would all sort of</p> <p>5 feel more comfortable because of this question of how</p> <p>6 significant our pleural plaques is if there was enough</p> <p>7 data to do a risk estimate on other outcomes, but in</p> <p>8 that same paper there were only 12 participants, I</p> <p>9 believe, or 8 with interstitial changes.</p> <p>10 So it ends unbeing a much smaller number.</p> <p>11 And of the 80 with pleural changes, only 12 had</p> <p>12 diffuse pleural thickening. So -- what number was it?</p> <p>13 Did I have it wrong?</p> <p>14 I am sorry. Even less. So I think the</p> <p>15 problem is there haven't been enough of those other</p> <p>16 endpoints.</p> <p>17 DR. SHEPPARD: Yeah, but I'm talking about</p> <p>18 adding them all together, not looking at one outcome</p> <p>19 versus another.</p> <p>20 DR. WOSKIE: So you are saying any --</p> <p>21 DR. SHEPPARD: Yeah, any change.</p> <p>22 DR. KANE: Yes, Dr. Salmon.</p>	<p style="text-align: right;">Page 211</p> <p>1 had at the point of writing the report, I think they</p> <p>2 made an excellent choice of endpoint.</p> <p>3 And I think it's interesting that they made</p> <p>4 a -- what I should probably say a good effort at</p> <p>5 defending that as being not only an observation but an</p> <p>6 observation in adverse effect. But I think one of the</p> <p>7 things to bear in mind is that if this was an animal</p> <p>8 study, then the simple pathological observation, which</p> <p>9 of course would have been obtained by slicing up the</p> <p>10 rat rather than just looking at x-rays, so it would be</p> <p>11 a bit easier in some respects, but nevertheless we are</p> <p>12 looking here at an actual structural change which we</p> <p>13 regard as being a deviation from normality in tissue</p> <p>14 structure which was associated with the exposure, that</p> <p>15 in itself would be regarded as a relatively severe</p> <p>16 endpoint in an animal study.</p> <p>17 It wouldn't have to be associated with the,</p> <p>18 you know, detriments in lung function which you can</p> <p>19 measure in rats but it's not usually done because it's</p> <p>20 difficult and the blighters bite when you are trying</p> <p>21 to do it. But the fact of the matter is that in, you</p> <p>22 know, in the spectrum of endpoints which are typically</p>
<p style="text-align: right;">Page 210</p> <p>1 DR. SALMON: I just wanted to put in a</p> <p>2 comment here from the risk assessment point of view as</p> <p>3 opposed to lung, lung physiology. One of the things</p> <p>4 which we actually saw earlier about the National</p> <p>5 Academy's recommendations was the importance of</p> <p>6 comparability between different risk assessments.</p> <p>7 And this is important for a whole variety</p> <p>8 of reasons, but certainly it's from a practical point</p> <p>9 of view it's a very useful attribute for the agency if</p> <p>10 the different risk assessments are comparable at some</p> <p>11 level. And in order to assure that at least for the</p> <p>12 simple case of laboratory studies in animals, the</p> <p>13 EPA's gone to quite some lengths to define degrees of</p> <p>14 severity of the effects and what they would regard as</p> <p>15 a suitable effect to use as basis of an RfC or some</p> <p>16 other guidance level.</p> <p>17 There's a considerable problem arises when</p> <p>18 we move away from the well-trodden paths of analyzing</p> <p>19 animal studies and getting into epidemiology which as</p> <p>20 always is a lot more complicated. And I think one of</p> <p>21 the things to bear in mind is I think the agency made</p> <p>22 a good choice here, certainly with the data that they</p>	<p style="text-align: right;">Page 212</p> <p>1 taken up for use in risk assessment, just the</p> <p>2 observation of a structural change of this sort in</p> <p>3 response to exposure would in itself be regarded as</p> <p>4 quite a severe endpoint.</p> <p>5 It's not -- it's not as minimal as you --</p> <p>6 as you sometimes would be tempted to regard it from</p> <p>7 the way it's described in x-rays. And I think this is</p> <p>8 a not uncommon problem with epidemiological studies</p> <p>9 that we often don't have access to the sort of minimal</p> <p>10 type responses which are typically regarded as if you</p> <p>11 write the entry point for adversity in the animal</p> <p>12 studies.</p> <p>13 And I think that's something that needs to</p> <p>14 be borne in mind when we are debating things like, you</p> <p>15 know, is this a sufficient -- is this a truly adverse</p> <p>16 effect. There's absolutely no question whatsoever</p> <p>17 that it would be regarded as not merely adverse but</p> <p>18 quite substantially adverse if this was an animal</p> <p>19 study.</p> <p>20 DR. KANE: Let me ask Mort Lippmann first,</p> <p>21 and then we'll come back to you, Jeff, and other</p> <p>22 person here. Mort, do you have something to add?</p>

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<p style="text-align: right;">Page 213</p> <p>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</p>	<p style="text-align: right;">Page 215</p> <p>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.</p>
<p style="text-align: right;">Page 214</p> <p>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.</p>	<p style="text-align: right;">Page 216</p> <p>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</p>

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<p style="text-align: right;">Page 217</p> <p>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</p>	<p style="text-align: right;">Page 219</p> <p>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</p>
<p style="text-align: right;">Page 218</p> <p>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 far 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</p>	<p style="text-align: right;">Page 220</p> <p>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</p>

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ATTACHMENT 3

In The Matter Of :

**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
SCIENCE ADVISORY BOARD**

**LIBBY AMPHIBOLE ASBESTOS REVIEW PANEL
MEETING - DAY 2
*February 7, 2012***

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<p style="text-align: right;">Page 13</p> <p>1 with the full cohort, full Marysville cohort, we get 2 an RfC that ranges from five to ten times lower than 3 the RfC that was derived using the truncated cohort. 4 And so we have to ask ourselves is that factor of five 5 to ten a result of us underestimating the fiber 6 concentrations in pre-1972, or is it simply because we 7 have increased power because of a large cohort. 8 So I think that that's a question that we 9 can't really answer, and I think it was appropriate to 10 limit the analysis to real data rather than 11 speculative data. 12 DR. KANE: Thank you. Dr. Lippmann? 13 DR. LIPPMANN: I had no problem -- 14 SPEAKER: Microphone please. 15 DR. LIPPMANN: I had no problem in terms of 16 accepting what was done with the methodology and the 17 uncertainties associated with the reliance on 18 imperfect exposure in disease and expert judgment. 19 Considering state of knowledge on many aspects of the 20 issue, I think they were quite reasonable in the way 21 they approached this particular aspect and relied on 22 expert judgment. And I have no problem with the</p>	<p style="text-align: right;">Page 15</p> <p>1 it is from a long experience in the field is that 2 expert judgments are pretty useful and often pretty 3 reliable if they have the right experts making the 4 judgment. 5 Clearly in occupational health the expert 6 judgments of the threshold limits committee have very 7 well stood the test of time in terms of worker health 8 protection. And so I'm going from this where I have 9 no problem recognizing its limitations to saying that 10 if you can use expert judgment here, why do you 11 refrain from using it elsewhere. That's my comment. 12 DR. KANE: Thank you, Mort. Dr. Woskie? 13 DR. WOSKIE: I agree with everything said 14 so far. I do think that to some extent they did 15 include non-Libby fiber counts because in the 16 subcohort they continued to accumulate exposures from 17 1980 when they stopped using the Libby -- although 18 they were small concentrations, the fiber counts were 19 accumulated in the cumulative exposure and used for 20 that subcohort. 21 So in some kind of an odd way I think they 22 did incorporate beyond the Libby if I'm -- if I'm</p>
<p style="text-align: right;">Page 14</p> <p>1 judgments made. 2 It, however, raises a more generic issue 3 that springs from this. If the expert judgment is the 4 basis for this aspect of the report, why don't we see 5 expert judgment used in other critical aspects of the 6 study such as the toxicity of Libby amphibole fibers. 7 We discussed this issue yesterday that I 8 think one could look holistically at the literature 9 and conclude that if it's a fiber meeting the 10 dimensions, durable in the lung, the length accounted 11 for, at least to some extent, then an amphibole is an 12 amphibole. Looks like a duck, walks like a duck, 13 quacks like a duck. 14 We have a situation where an expert 15 judgment is possible. I urge staff to think about 16 coming to expert judgments that can be reviewed by 17 this panel at a subsequent teleconference. And so is 18 Libby amphibole equivalent to tremolite and to other 19 amphiboles in its toxicity potential? 20 How far off would we be if we made the 21 judgment that it was? Probably no further off than we 22 are in judging the exposure issues. My bias such as</p>	<p style="text-align: right;">Page 16</p> <p>1 correct, which I agree with. I think that's a good 2 idea. 3 DR. LIPPMANN: Well, the use of phase 4 contrast fiber counts certainly has its limitations. 5 On the other hand, if the alternative is TEM, then I 6 say the PCM counts are better for our purpose than the 7 TEM which doesn't look at long fibers at all. You'll 8 rarely get a long fiber in the field of view because 9 when they count 200 or 500 fibers in a TCM, they are 10 almost all shorter than five microns, and in my view 11 not hazardous. 12 And so imperfect as it is, going to 13 interpret TEM counts would be even worse as an index. 14 Considering that nobody is doing TEM properly, that is 15 looking at the larger areas of the filter so that they 16 can get a statistically significant number of long 17 fibers and then you could relate it to T -- the PCM 18 equivalent, again assuming that a fiber is a fiber, 19 but current TCM counts are worthless. 20 DR. KANE: Yes. 21 DR. HARRIS: I'd like to respond to the TEM 22 questions, since that's my background.</p>

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<p style="text-align: right;">Page 17</p> <p>1 Well, there is a TEM method that does 2 provide PCM equivalency. By just lowering the 3 magnification, we are able to scan a much larger area, 4 so we are basically doing the same thing as a PCM, and 5 only counting the five micron fibers. 6 What we do is what's called a stratified 7 account where we start with high magnification so we 8 can get a count of all the fibers, and then we switch 9 over to a low magnification and scan over several ribs 10 and so forth like that to try to get that area that 11 you are suggesting. 12 DR. LIPPMANN: That's exactly what's needed 13 because historically there's virtually no data out 14 there that we can use. 15 MR. HARRIS: You'll see some of that data 16 through EPA at some of the vermiculite sites. They'll 17 have what they call a stratified count, and that would 18 include the PCM in lower magnification analysis. 19 DR. WOSKIE: I just have a question. I 20 know we are kind of stuck with the PCM because that's 21 what is there back in time, but is there any sense of 22 what we have missed in terms of a -- my understanding</p>	<p style="text-align: right;">Page 19</p> <p>1 point-four microns instead of point-two microns. So 2 there's an assumption that a lot of the fibers that we 3 would see today using current technology were not 4 visible in the 1970s. 5 And let me just add that PCM exposures are 6 only an index of exposure. It doesn't tell you what's 7 going to the lungs because it's recognized that there 8 is quite a bit of stuff, Number 1, that is unseen 9 because its too thin or its too short to be counted by 10 PCM rules. And, number 2, there are a lot of things 11 in there that as John said are not asbestos. 12 So PCM at best is just an index of 13 exposure. And TEM was not available in 1980s, so it 14 was not used. And we are stuck with PCM because it is 15 what it is, and that's what all the models are based 16 on. But I would contend that TEM will provide you a 17 better set of true exposure because, number 1, I've 18 done a lot of TEM analysis and I do count all the long 19 fibers. And the fact that the number of long fibers 20 might appear proportionally less than in a PCM sample 21 is only because you are able to see everything that's 22 there, so that if you do the final number crunching at</p>
<p style="text-align: right;">Page 18</p> <p>1 is there's a lot of very thin fibers here that would 2 not have been seen by PCM but which are long enough 3 and thin enough to be problematic. Is that accurate? 4 MR. HARRIS: That's true. That's true. 5 You oftentimes have long, much longer than five micron 6 fibers that are below the point-two-micron width range 7 for PCMs. So we see those relatively common in 8 certain sites. It just depends on the source of the 9 material that you begin with. 10 DR. WOSKIE: So is that a characteristic of 11 Libby amphibole asbestos that it would have a large 12 percentage of those very thin, long fibers that would 13 not be counted by PCM? 14 DR. WEBBER: My experience with Libby 15 amphiboles is that they tend to be a little bit 16 thicker than say chrysotile and crocidolite, but still 17 if you read the literature and you look at some of the 18 profiles, you will see that probably anywhere from 19 half to maybe a little bit more than a half probably 20 are not resolvable by PCM. And certainly if what they 21 say, if you read the report in some of the literature 22 here that the resolution back in the 1970s was about</p>	<p style="text-align: right;">Page 20</p> <p>1 the end, you have the same number of long fibers by 2 TEM as you would like by PCM. 3 And just -- I don't want to open anything 4 up here as far as argument because it's not germane to 5 our task today, but we are seeing short fibers in the 6 last ten years are indeed contributors. The work with 7 recent reconstruction of exposures to South Carolina 8 plant by Dement and Standard has shown that the short 9 fibers do contribute. And the work by Dodds and 10 Suzuki are showing that the short fibers are all you 11 see with the mesothelioma tissue. There are questions 12 about whether the short fibers are translocated to the 13 pleura where they cause mesothelioma. 14 So I think that we have to keep our minds 15 open as to the different modes. And I really like the 16 fact that it came up yesterday that it's not a mode of 17 action. There are multiple modes of action that make 18 asbestos such a nasty particle. 19 DR. WOSKIE: So I guess I would like to 20 think about whether or not -- we are stuck with PCM. 21 We have to use that for our resultant RfC or even the 22 cancer estimates, but is there a recommendation or is</p>

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<p style="text-align: right;">Page 137</p> <p>1 thinking of maybe looking at a multiplier of the meso 2 specific in order to incorporate that. That is an 3 interesting idea. 4 We were less concerned about the issue of 5 smoking that Dr. Redlich brought up. We have a charge 6 question specifically on smoking that I believe we are 7 going to come to, and we might revisit this then, but 8 we did take steps to evaluate the potential for 9 confounding by smoking other lung cancer, and we were 10 generally satisfied and were interested in hearing the 11 panel's comments on our treatment of that. 12 So given that we were comfortable that 13 there was not a meaningful confounding of the lung 14 cancer numbers, we were comfortable using both lung 15 cancer and mesothelioma as the basis of the IUR. Is 16 there further comments? 17 DR. KANE: Anyone else on the panel have 18 comments or questions? 19 DR. REDLICH: I guess I am a little 20 confused as how you can say that you are confident 21 that there was no confounding by smoking when just 22 about every study on asbestos and lung cancer, not</p>	<p style="text-align: right;">Page 139</p> <p>1 they conform to their own guidance, I think that they 2 did. I can't actually tell because I can't reproduce 3 the calculations, but at least I can't say that they 4 do. But if you take the question more broadly, then I 5 think there is maybe a bit more to say, and I 6 apologize that it's already noon. It's up to you. 7 DR. KANE: No, we have to do this. 8 DR. FERSON: Okay. See, it's her fault. 9 Okay. So I preface it by saying I'm not an 10 epidemiologist or a toxicologist or a particularly 11 smart person, so maybe I'm just the Chauncey Gardener 12 or as Dr. Salmon may say, Bozo the Clown, by the end 13 this. 14 So let me start casually by saying that the 15 guidance says that the inhalation unit risk is defined 16 in terms of one microgram per cubic meter of air. But 17 in the case of the asbestos, they don't do that. They 18 say it's one fiber per cubic centimeter of air. 19 And this little change is justified, it's 20 an allowance for the nature of what's relevant about 21 asbestos. Asbestos is different from the other things 22 that might be distributed more evenly. As Dr. Redlich</p>
<p style="text-align: right;">Page 138</p> <p>1 mesothelioma has shown -- 2 DR. SALMON: That's effect modification, 3 not confounding. 4 DR. REDLICH: Okay. 5 DR. KANE: Okay. Let's move on now. We 6 are going to be moving to section Roman numeral 3. 7 And this starts on page 6 of our original charge 8 questions. And now we are going to be talking about 9 Roman numeral 3B1 and B2, exposure response modeling, 10 and then the confounders. 11 The lead discussers here, first Dr. Ferson. 12 DR. FERSON: I don't know how I got to be 13 the lead discussant. I have only to say you have 14 yourselves to blame. 15 The charge question seems to ask whether 16 the exposure response modeling is appropriate as 17 conducted and clearly described, and I guess clearly 18 described kind of reminded me of reading the IRS 1040 19 instructions, but I guess something that's not 20 valuable. 21 If we take the question about being 22 appropriately conducted to be a question about whether</p>	<p style="text-align: right;">Page 140</p> <p>1 explained yesterday, if there's a biological or other 2 sound reason to change what the guidance says we 3 should do, then an assessment can deviate from that 4 rigid guidance. And I think that it seems to me that 5 some of the points in Dr. Peto's premature explanation 6 yesterday, and his unwilling discussion today really 7 to my mind at least constitute sound biological 8 reasons to rethink what's been done. 9 It seems very odd as he said to discard a 10 mechanistic model that's been in wide use for multiple 11 decades merely because it appears not to fare as well 12 in a peer -- against purely statistical models and an 13 anonymous measure of fit. I say anonymous because we 14 didn't really see the visual plots of the models 15 performances that maybe would have been more 16 compelling than the tables of the AIC or the IC 17 values. 18 You know Dr. Salmon suggested that all of 19 these statistical models seem to be giving similar 20 results. And he emphasized that that's really 21 pointing to the robustness of this purely phenomenal 22 logical approach, a purely statistical approach.</p>

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<p style="text-align: right;">Page 141</p> <p>1 But it might also be more the result of a 2 narrowness of the categories of the models that were 3 considered than any real robustness of the approach 4 itself. 5 The idea that I'm getting at here is that 6 old adage that when all minds think alike, none thinks 7 too deeply. So maybe I'm being very presumptuous here 8 about that, but just trying to see what it looks like. 9 There are after all are not a lot of data 10 in this data set, especially considering how 11 widespread it is, the effects of the Libby mine have 12 been around the country. Katherine Walker was saying 13 yesterday, really, none of these people have data; 14 none of these other spots on the map have any data 15 anywhere? None? It's kind of surprising, right? 16 I find myself agreeing with Dr. Moolgavkar, 17 as much as I hate to admit that. I think it would be 18 preferable to compute the inhalation unit risk -- I 19 was going to declare conflict of interest, but I think 20 it would it would be preferable to compute the 21 inhalation unit risk from cancer from a full data set 22 rather than just those prior to 1969.</p>	<p style="text-align: right;">Page 143</p> <p>1 not to be handled using interval statistics, there's 2 some other traditional approaches that are available 3 for interval sensitive data, but I think that doing 4 this is critical. And the previous analyses with 5 unsophisticated treatment of measurements don't really 6 tell us what's what. 7 Doing the measurement uncertainty correctly 8 within essence replaced point values that might have 9 been used for exposure values with intervals. And 10 when those intervals are narrow as they might be for 11 at least the 21 percent that have job titles, then 12 there's a lot of information present. And we can make 13 use of that information in the analysis and reach our 14 results. 15 When the intervals are much wider, of 16 course there's less information. And maybe the 17 intervals are variable from a really small number to a 18 really pretty big number, but that's certainly better 19 than leaving out the data point entirely when in 20 principal it equates to replacing the interval between 21 zero and infinity. 22 So when you do this analysis what you get</p>
<p style="text-align: right;">Page 142</p> <p>1 The decision to exclude them seems 2 inexplicable to me, although it's a carefully 3 considered decision by the agency. I'm not suggesting 4 it would be a good idea to have all (inaudible) 5 Mr. Doug might use, but we can make serious use of the 6 full data set if we employ a well-structured 7 uncertainty analysis that projects the measurement 8 uncertainty of what's associated with those unknown 9 exposures for the early half. 10 So from a stupid statistical perspective it 11 seems a terrible waste to effectively throw away 12 two-thirds of the cancer mortalities that are in the 13 data set. Arguments that we needed to do that to 14 modernize the cohort seems like a close call but 15 statistically significant failure of the assumption of 16 proportionality of -- okay, it fails. 17 But maybe it suggests to me that instead of 18 whittling away the data so it can no longer 19 demonstrate that failure, maybe we should just try a 20 different statistical model that doesn't use this 21 apparently false assumption. 22 Okay. So this fuller data set can be, and</p>	<p style="text-align: right;">Page 144</p> <p>1 is effectively an interval range for the final 2 results. And I think that that is actually useful 3 because it directly feeds into the need that we have 4 coming up in later discussion points about, you know, 5 our need to undertake a serious quantitative 6 assessment of uncertainty that National Academy of 7 Sciences have argued for. 8 So I think that a traditional model favored 9 by Dr. Peto should be given another shot, with the 10 full data set and the appropriate methods to handle 11 the measurement uncertainty that will yield explicit 12 uncertainty statements about results. And that will 13 yield with that assessment that reassessment will 14 yield several models that in principal could be fairly 15 good fit to the data. 16 And we might even look at the performance 17 of Dr. Peto's model to tell how wide we are going to 18 call the refitting models, because after all we also 19 need to express our model uncertainty in this 20 projection process. And that surely if nothing else 21 we have learned in these last several hours, it's that 22 there's some uncertainty about the model. And maybe</p>

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<p style="text-align: right;">Page 145</p> <p>1 it's incumbent upon the agency to project that.</p> <p>2 And I think the agency is doing effectively</p> <p>3 this already. When they take the health protective</p> <p>4 model among all the models that have similar fits</p> <p>5 according to the AIC or BIC criterion.</p> <p>6 Now, you know, certainly could turn out</p> <p>7 that this doesn't change anything in the final numbers</p> <p>8 that we get and will eventually post to the IRIS, but</p> <p>9 I don't know how you could tell whether that's the</p> <p>10 case until you do the assessment to figure that out.</p> <p>11 I think I understand Dr. Salmon's argument</p> <p>12 that we don't need the slope factor to mean anything</p> <p>13 biological. It only needs to be a good predictor. He</p> <p>14 says all we want is a slope factor or maybe an RfC in</p> <p>15 a (inaudible) but we might pause to ask, okay, well,</p> <p>16 what's going to be done with this slope factor once it</p> <p>17 gets, you know, guarded (ph) into the database.</p> <p>18 But then anybody can look at it and make</p> <p>19 use of it. And you know how people are, you know,</p> <p>20 just the confusion that I have by myself is evidence</p> <p>21 of a much broader community of (inaudible) perhaps</p> <p>22 even deeper, lthough it's not clear.</p>	<p style="text-align: right;">Page 147</p> <p>1 model. I mean it's been formulated in slightly</p> <p>2 different ways, but they really make any difference.</p> <p>3 I mean what it boils down to is, I mean,</p> <p>4 Dr. Moolgavkar's got a model which is based on the</p> <p>5 specific biological process, but the actual predictors</p> <p>6 are very similar.</p> <p>7 I mean the model that I proposed was</p> <p>8 basically just that every bit of inhalation produces a</p> <p>9 risk that goes up with or without a lag. I mean it's</p> <p>10 probably sensible for the lag of 10 or 15 years in,</p> <p>11 but it doesn't actually make any difference, I mean</p> <p>12 putting a lag in prevents you from predicting cases in</p> <p>13 the first 10 or 15 years, which is a sign of benefit</p> <p>14 to the data because there are so few cases, I mean,</p> <p>15 virtually none within 15 years of exposure which is</p> <p>16 biological plausible, whether you put in a lag of</p> <p>17 efficient exposure, the actual lag beyond 20 or 25</p> <p>18 years really makes no difference to the predictions.</p> <p>19 And so a model of that sort, I mean, I</p> <p>20 think the EPA fit in a lag of 10 years when they did</p> <p>21 it. Having chosen a lag of 10 years, you do have to</p> <p>22 choose an exposure. And, yes, I don't know what's the</p>
<p style="text-align: right;">Page 146</p> <p>1 And I just would, you know, well, I won't</p> <p>2 go on to talk about the slope factor. I'm thinking</p> <p>3 outside of the slope factor box, although maybe that's</p> <p>4 too much before lunch, but I would just invite you to</p> <p>5 think with compassion about the larger community that</p> <p>6 might be using this number that eventually goes in</p> <p>7 there.</p> <p>8 And I see the bit of frowns over on that</p> <p>9 side of the room, and I would like to say that it's</p> <p>10 really not as bad as it maybe sounds. It's really</p> <p>11 kind of straightforward. And I think that you can do</p> <p>12 it without a lot of, well, some of you probably, but</p> <p>13 most of you will not be crying at any point. So I</p> <p>14 think it can be fast and cheap.</p> <p>15 And I will try to explain how using what</p> <p>16 methods you can do that with in the data.</p> <p>17 DR. KANE: Dr. Peto, do you concur with</p> <p>18 Dr. Ferson's three main points?</p> <p>19 DR. PETO: I mean -- (inaudible.)</p> <p>20 I think I said it all yesterday really.</p> <p>21 And the EPA and I think we have other agencies have a</p> <p>22 look at mesothelioma and use essentially the same</p>	<p style="text-align: right;">Page 148</p> <p>1 best basis for that is, I mean, I mean, it's</p> <p>2 somewhere -- it's somewhere in the region of two. I</p> <p>3 mean it's -- I mean there aren't enough data here to</p> <p>4 estimate the experiment but, I mean, basically the</p> <p>5 model should be chosen from other data as a larger</p> <p>6 cohort with a larger numbers of mesotheliomas. And</p> <p>7 having chosen that model, these data should be used</p> <p>8 simply to estimate the coefficient and the concept of</p> <p>9 the equation (inaudible) the fiber.</p> <p>10 As far as lung cancer is concerned, I mean,</p> <p>11 I think the evidence says smoking acts synergistically</p> <p>12 to asbestos in causing lung cancer is really very</p> <p>13 strong. And so there are two issues which both</p> <p>14 actually are quite difficult to do perfectly. I mean</p> <p>15 one is that you have to know what lung cancer rates</p> <p>16 are going to be in the population you are interested</p> <p>17 in.</p> <p>18 I think lung cancer rates have changed so</p> <p>19 much that it does require a cohort analysis. But I</p> <p>20 am -- I guess somebody has already done that in the</p> <p>21 U.S. I don't know. It's a fairly straightforward</p> <p>22 thing to do to sort of look at the national data in</p>

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ATTACHMENT 4

In The Matter Of :

**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
SCIENCE ADVISORY BOARD**

**LIBBY AMPHIBOLE ASBESTOS REVIEW PANEL
MEETING - DAY 3
*February 8, 2012***

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<p style="text-align: right;">Page 61</p> <p>1 those there was inconsistency at least in the tone of 2 the conclusions in Section 4.7.11 and 6.3.3 to support 3 or refute early life stage susceptibility. 4 We encourage the continued monitoring of 5 the relevant Libby residents for early onset asbestos 6 associated diseases and a further examination of other 7 models that might better fit for the determination of 8 early life susceptibility. 9 There isn't enough to come to firmer 10 conclusions either, and not necessarily failure of EPA 11 to do so, but a lack of information. And for example 12 evidence of early life stage carcinogenesis is really 13 due to susceptibility or due to dose considerations. 14 For example the kids playing on the waste 15 piles might be getting heroic doses and it might -- 16 and the evidence for excess disease might be more due 17 to that than any inherit susceptibility. I think 18 that's the last one. 19 So we are hitting high points in our 20 conclusions and analysis. We hope these will be 21 helpful to EPA. Other members of the panel want to 22 add in?</p>	<p style="text-align: right;">Page 63</p> <p>1 the total population before you get down to the dose 2 response calculations. 3 The comparisons to the early year, I 4 thought that was one of the things that struck me the 5 most early on when I read this report that it didn't 6 really write up front, or somewhere in the 7 conclusions, compare the results to the earlier EPA 8 1986 data set so we could compare the slopes of the 9 lines. And I believe they are different, but I don't 10 know how statistically significantly different they 11 would be, but it would be worthwhile. 12 I think the report was repetitious in 13 spots, but then when I got the new version, I didn't 14 get a chance to really get into that. So maybe that's 15 been worked on in the interim since the time I got the 16 original version. 17 So the comments maybe already have been 18 dealt with. I don't know. There were some studies I 19 think of cities that had vermiculite processing 20 facilities to see if they had elevated mortality 21 rates, and I think there was a case study. And I 22 found I got nothing from that. Those are big cities,</p>
<p style="text-align: right;">Page 62</p> <p>1 DR. NEUBERGER: I wanted to pick up on a 2 couple of points that you mentioned. I thought the 3 subcohort analysis was the way to go, but it does 4 really reduce the number of deaths. So 7 5 mesotheliomas from 18. 6 So there's -- there was 880 deaths in the 7 1959 cohort and only -- I'm sorry, 230 deaths and only 8 39 of them were either lung cancer or mesothelioma. 9 So there were a lot of other deaths. 10 So I thought usually when I look at a city 11 or a setup of some kind of group of people I like to 12 see what the breakdown is before I get into dose 13 response discussion, which I think I mentioned that 14 before. So which ones to add without being overly 15 burdensome, I thought a few, particularly COPD and 16 maybe if there's any other large number of deaths. 17 And I also like to see standardized 18 mortality ratios for the population comparing it to 19 Montana or to U.S. Which ones to do, I don't think 20 make much sense to do mesothelioma because that would 21 be infinity. On the other hand, for lung cancer it 22 might be interesting to see what that looked like in</p>	<p style="text-align: right;">Page 64</p> <p>1 Los Angeles, whatever. And I didn't expect to see 2 much of impact of a processing facility on the overall 3 mortality rates of that area. 4 And I think you have a great opportunity 5 here. You have got NIOSH and ATSDR both already 6 interested in this area. This is a hot, important 7 area. So I would do everything in your power to try 8 to make the studies continue so you get more data on 9 the number of deaths and relook at the models then. 10 It's -- my statistician would hit me over 11 the head if I tried to model seven, seven deaths with 12 any kind of model. He would just beat me. I get 13 beaten up readily by my statistician. 14 He would do a better job if I came up to 15 him and ask him to model seven deaths. So maybe you 16 have a kinder statistician, kinder, generous 17 statistician than I do, but -- 18 DR. BALMES: Your statistician must not be 19 passionless. 20 (Laughter) 21 DR. NEUBERGER: So I think we should look 22 for kinder, gentler statisticians in the future. So</p>

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<p style="text-align: right;">Page 65</p> <p>1 those are my comments as to Dr. Lippmann's and other 2 members of the committee and Dr. Hei and Everitt. And 3 Dr. Everitt actually put the slides together, so it 4 was a consensus.</p> <p>5 DR. LIPPMANN: We want to thank Jeff for 6 really helping expedite the preparation of these 7 slides. Tom, do you have anything you want to add? 8 Jeff? Okay. Other panel members?</p> <p>9 DR. WALKER: Yeah, I had a question. I 10 thought the reference concentration folks had an 11 interesting idea of trying to use different exposure 12 metrics going back using the full cohort. And if that 13 were to be done, those could be available also for the 14 cancer assessment.</p> <p>15 And I think it's part of our comments we'd 16 be thinking about some analysis that would do 17 something like that. So I wondered whether you had 18 any thoughts along that line.</p> <p>19 DR. NEUBERGER: Well, the problem with full 20 cohort is we don't have good exposure information. 21 All you do is an MSR, which is what I suggested. They 22 already do the observers as expected for lung cancer,</p>	<p style="text-align: right;">Page 67</p> <p>1 One comment would be we do not expect the 2 group to do any detailed editing of our documents, but 3 to the extent that you point to this section seemed 4 particularly good, or this section needs tightening 5 up, that's fine. We do not discard that information.</p> <p>6 In terms of the determinant of toxicity in 7 putting this in the context of other asbestos fibers, 8 I understand the intellectual interest in doing that, 9 and I understand how it could strengthen the 10 assessment. I guess I would also ask for guidance in 11 terms of how to do that without again taking on the 12 burden of whatever controversies there are with that.</p> <p>13 So to the extent that you can help point us 14 towards these things are pretty well agreed upon in 15 consensus and try to help us avoid taking on in this 16 document a full disposition of a complex field, that 17 would be helpful to us.</p> <p>18 DR. LIPPMANN: Just by example, and 19 consistent with prior panels we all seem to seek more 20 information on comparative toxicity of amphibole 21 fibers. But to me -- my recommendation would be 22 selective. If inhalation, long-term inhalation</p>
<p style="text-align: right;">Page 66</p> <p>1 maybe COPD for total group and again for the subcohort 2 just to see what it looks like and get a little more 3 information out of -- try to eke out a little more 4 data from this unique, high-exposure situation.</p> <p>5 DR. WALKER: No, my point was I think they 6 were thinking about some sort of bounding exercises to 7 really think about what those levels might have been 8 at some reasonable way and which I think is a 9 reasonable thing to do for analysis. And it could be 10 done here also with the cancer.</p> <p>11 DR. LIPPMANN: Any other panel members' 12 comments?</p> <p>13 DR. KANE: Dr. Salmon? If no other 14 comments from the panel, I would like to invite EPA to 15 ask us any questions or ask the subgroup any 16 questions. Is what they are saying and recommending 17 clear to you?</p> <p>18 MR. BUSSARD: Thank you. I also recognize 19 that we are not trying to caucus as a group as we hear 20 this, so as we think about this we may have other 21 clarification questions that we may want to raise 22 later.</p>	<p style="text-align: right;">Page 68</p> <p>1 studies in animals are the most relevant to kind of 2 toxicological information, certainly the long-term 3 inhalation study with tremolite is something that 4 should be covered in as much detail as relevance 5 exists.</p> <p>6 And then by extension, if in fact dimension 7 of fibers is an important factor, and I think we all 8 agree that it at least is important, then the long 9 term inhalation studies of John Davis and group with 10 amosite in which three different length regions were 11 explicitly compared, the original UICC study followed 12 up by studies of both long and short amosite from the 13 same source, where in one case much longer fibers and 14 in the other case much shorter amosite fibers, and in 15 the UICC original study.</p> <p>16 And the influence of length was clearly 17 apparent in much greater yield in both fibrosis and 18 cancer in the longest, virtually none in the short 19 stuff and intermediate in the UICC. So I wouldn't go 20 over every long-term inhalation study, but pick out 21 those that illuminate the issues that we are dealing 22 with.</p>

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ATTACHMENT 5

In the Matter of:

***UNITED STATES ENVIRONMENTAL PROTECTION AGENCY SCIENCE
ADVISORY BOARD***

**LIBBY AMPHIBOLE ASBESTOS REVIEW PANEL MEETING
May 1, 2012**

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LIBBY AMPHIBOLE ASBESTOS REVIEW PANEL MEETING
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<p style="text-align: right;">Page 29</p> <p>1 that are being used in a curve-fitting activity with a 2 very small base set. 3 Now, using such limited, inadequate data 4 also is a practical problem for estimating the effects 5 of known covariants such as we know BMI and we know 6 age, and there are probably some others that modify 7 the prevalence of pleural plaques. 8 Another question is the importance of 9 separating out dose rate and duration from cumulative 10 exposure. This could be a significant model issue, 11 but unfortunately we can't do anything with it with a 12 limited data. Therefore, I would recommend additional 13 data sets and straightforward and transparent 14 proof-setting approaches. 15 A couple other points I would like to make, 16 one is if you look at full data Rohs data set there 17 were about I would say I found 59 instances of pleural 18 plaques. And eleven of the workers had diffuse 19 pleural thickening, which is more of a serious issue. 20 And none of the pleural plaques were present in the 21 cases where you had the pleural thickening, diffuse 22 pleural thickening. So you probably don't have</p>	<p style="text-align: right;">Page 31</p> <p>1 information that can be gained from using these data 2 sets or what? 3 DR. MOOLGAVKAR: That is what I'm 4 suggesting. I'm suggesting that these data sets 5 cannot be used to set a reference concentration for 6 non-cancer endpoints. And my own feeling is that this 7 is the first time that the agency is trying to set an 8 RfC and they need to justify the setting of an RfC 9 adequately. 10 If there isn't an appropriate data set, I 11 think the agency simply has to say at this point we 12 cannot set an RfC. 13 DR. KANE: Dr. Hoel, do you have any 14 comments? 15 DR. HOEL: No. I agree with that. And but 16 I would also say that probably, hopefully there are 17 other data sets around. I mean you had your full real 18 data set which I guess is chose not to use because of 19 the quality of the dose response in individuals, but I 20 mean certainly at least work with that and work with 21 some of the other data sets that are out there and try 22 to get a feeling of what is the variability between</p>
<p style="text-align: right;">Page 30</p> <p>1 pleural plaques on the disease pathway to diffuse 2 pleural thickening. 3 And by the way, Walter Rogan, who was with 4 me at NIHS, he's studying Ann Haynes (ph) looking at 5 prevalence in the country, and his most recent in 6 (unclear) Haynes 2 he had for 45-to-74-year-olds he 7 had as high as 7.8 percent pleural plaques known males 8 and 2.3 percent among females, which is considerably 9 greater than the one percent that is assumed in the 10 model exercises. 11 And with -- I say all the modeling and 12 whatnot and limited data, it will be interesting at 13 least for me to use this as a classroom exercise or 14 instruction. And that's it. Thank you. 15 DR. KANE: Thank you very much. Are there 16 any questions or comments from the panel? 17 DR. WALKER: This is Katie Walker. And I 18 actually have a question for Dr. Hoel and also 19 Dr. Moolgavkar. I'm just curious, I mean, you know, 20 we know these data sets are limited, but what is their 21 suggestion that EPA use an alternative here? 22 I mean are you saying that there's no</p>	<p style="text-align: right;">Page 32</p> <p>1 data sets and -- and also on the modeling I am 2 particularly concerned that that isn't as transparent 3 as it is because to my thinking it's just some rather 4 simple non-linear curve setting and not using 5 biologically-driven dose response functions. 6 DR. KANE: Thank you. Do any other members 7 of the panel have any other questions? Diana? 8 MS. WONG: Next speaker is Dr. Lawrence 9 Mohr. 10 DR. MOHR: Yeah, good afternoon. And thank 11 you for the opportunity to speak. 12 I would like to address localized pleural 13 thickening, also known as pleural plaques, from a 14 clinical and clinical risk perspective. I am 15 professor of medicine. I am a physician. I am also a 16 clinical investigator and director of the 17 Environmental Biosciences Program At the Medical 18 University of South Carolina. 19 First of all, it's important to realize 20 that localized pleural thickening and pleural plaques 21 are indeed the same thing. And that's something that 22 people commonly misconstrue.</p>

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<p style="text-align: right;">Page 33</p> <p>1 I will refer to localized pleural 2 thickening as LPT. LPT consists of one or more benign 3 fibrotic growths on the pliable pleura of the interior 4 of the chest wall. And when I say growths I really 5 mean bundles of collagen fibers in a basket weave type 6 of appearance. 7 The histology is well worked out. 8 Localized pleural thickening is a reliable, benign 9 marker of asbestos exposure. It has been reported in 10 up to 50 percent of workers as exposed to asbestos. 11 In general the total area of the parietal pleura 12 involved with localized pleural thickening is related 13 to the cumulative total dose of inhaled asbestos 14 fibers. It typically takes 20 to 30 years from first 15 exposure to the development of LPT in those who do 16 develop it. 17 Localized pleural thickening has no further 18 path of biological potential. That is it does not 19 transform into anything else, and it does not cause 20 any other asbestos-related diseases such as 21 mesothelioma, lung cancer, asbestosis or indeed 22 diffuse pleural thickening. As a corollary to that,</p>	<p style="text-align: right;">Page 35</p> <p>1 non-malignant diseases related to asbestos. 2 Localized pleural thickening is almost 3 always asymptomatic. And this is the position of both 4 the British Thoracic Society and the U.S. ATSDR. Of 5 importance is the fact that overweight and obese 6 individuals can have restrictive mental impairment due 7 to increased body mass alone. 8 In reviewing some of the papers, some of 9 the reports related to the Libby cohort, there are a 10 significant number of overweight or obese individuals 11 in that cohort by body mass index. 12 DR. KANE: Dr. Mohr, please try to wrap it 13 up. 14 DR. MOHR: Okay. This in and of itself 15 could be a cause of restrictive spirometry in that 16 cohort. Chest pain or discomfort among individuals 17 with localized pleural thickening is rare and may not 18 be caused by the pleural thickening per se. 19 I would say from a clinical perspective any 20 individual that presents with localized pleural 21 thickening and chest discomfort needs to have a very 22 thorough evaluation for other causes.</p>
<p style="text-align: right;">Page 34</p> <p>1 localized pleural thickening is not in a 2 pathobiological pathway for the development of any 3 benign or malignant asbestos-related disease. 4 It's important to realize -- and this was 5 mentioned previously, that sub pleural fat can be 6 mistaken for localized pleural thickening on chest 7 radiographs, even by the most astute and experienced 8 radiologists. 9 The preponderance of the evidence over many 10 years of reports indicates that localized pleural 11 thickening, LPT, in and of itself does not cause 12 statistically significant or clinically significant 13 impairment of lung function. 14 It is generally thought today, and the 15 lit -- and the most recent literature suggests that 16 impairment of lung function that occurs among 17 individuals with localized pleural thickening or LPT 18 is most likely due to coexisting subradiographic 19 interstitial fibrosis, that is asbestosis, and is not 20 caused by the pleural -- localized pleural thickening 21 per se. And indeed this is a position taken by the 22 American Thoracic Society in its 2004 document on</p>	<p style="text-align: right;">Page 36</p> <p>1 There are conflicting reports of the 2 efficacy of the LPT as a marker for the risk of 3 developing asbestos related diseases such as 4 mesothelioma, lung cancer and asbestos. The potential 5 risks of developing these other diseases among 6 individuals with pleural plaques are poorly understood 7 and have never been quantified by formal risk 8 assessments. 9 So, in summary, LPT is a reliable, benign 10 marker of asbestos exposure. It is my recommendation 11 to the SAB to carefully study, carefully consider and 12 bring scientific clarity to the potential -- 13 (inaudible) -- LPT as a disease endpoint. Thank you. 14 DR. KANE: Thank you. Do any members of 15 the panel wish to ask questions or comments? Okay. 16 Diana, next? 17 DR. WONG: Elizabeth Anderson. 18 DR. ANDERSON: Yes. Good afternoon, or 19 good evening, as the case may be. Previously I have 20 posted comments on February -- January 27, February 7, 21 and a recent report that I coauthored with Dr. David 22 Quarle (ph) on April 9. I call your attention because</p>

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<p style="text-align: right;">Page 97</p> <p>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</p>	<p style="text-align: right;">Page 99</p> <p>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</p>
<p style="text-align: right;">Page 98</p> <p>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.</p>	<p style="text-align: right;">Page 100</p> <p>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</p>

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<p style="text-align: right;">Page 121</p> <p>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</p>	<p style="text-align: right;">Page 123</p> <p>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 --</p>
<p style="text-align: right;">Page 122</p> <p>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</p>	<p style="text-align: right;">Page 124</p> <p>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.</p>

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<p>1 makes various assumptions which we've talked about 2 which are not particularly good for extrapolating 3 outside of the range of the model, the model is not 4 used to adjust between the duration of exposure and 5 follow-up from the data set and the 70 years. 6 I'm reading from page 535 of EPA's 7 document, and it says as this POD is in units 8 cumulative exposure, the RfC's given in continuous 9 lifetime exposure. The POD was adjusted to 70 years 10 of exposure lagged by 10 years for non-occupational 11 lifetime exposure. 12 Thus the adjusted lifetime BMCL 10 is 1.96 13 times 10 to the 3. And that's actually -- that count 14 was -- it shows the calculation. That was done on a 15 simple proportion, in other words, assuming that the 16 incidence was proportional -- over lifetime was 17 proportional to the exposure duration lagged by 10 18 years. 19 So we are not using this plateauing model 20 for making the extrapolation from the point X to the 21 BM -- (inaudible) -- which is derived by the model. 22 We are not using the model. We are using that linear</p>	<p>1 obviously you can't adjust for lifetime exposure in a 2 model-free way. To do so implies a model. 3 And the idea that you can extend them, I 4 mean, the same thing was done for mesothelioma, 5 unbelievably, whereas the opposite (inaudible). 6 Because exposure to asbestos late in life has no 7 effect on mesothelioma because you die before it has 8 any effect. It's only what happens in the first 20 9 years of life that matter basically when you have a 10 lifetime exposure to asbestos as far as cancer is 11 concerned. 12 DR. SALMON: Well, just so long as in 13 crafting the alternative model we are clear what the 14 EPA's model is, which is not using the 15 Michaelis-Menten models to conduct extrapolation 16 outside the time and data range which it's fit to. 17 That's the point I'm making. 18 DR. PETO: Well, the point I'm making is if 19 you multiply by 70 over 10 or 70 over whatever it is 20 is wrong under any plausible model. 21 DR. SALMON: If you want to argue -- 22 DR. PETO: I mean the idea that you do this</p>
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<p>1 extrapolation to handle the lifetime incidence 2 question. I just wanted that to be clear. 3 DR. PETO: I know. But if the incidence is 4 proportional to a cumulative dose, for example, which 5 is the simplest model to fit, then the prevalence will 6 rise linearly after the exposure ceases. And -- 7 DR. SALMON: Based on the assumption that 8 they are using in order to -- 9 DR. PETO: Let me finish. If the exposure 10 is continuous, then the cumulative dose will rise 11 linearly. And the prevalence will rise more linearly. 12 So that's a completely inappropriate calculation. 13 The incidence rate will rise linearly, you 14 know, the prevalence. It will go for more than that. 15 I mean if the incidence is constant after exposure 16 ceases, if the cumulative dose -- the cumulative dose 17 will rise linearly during continuous exposure. And, 18 therefore, the prevalence will go up as a square of 19 time, which is wrong. 20 I mean the adjustment is based on the -- is 21 based on the assumption that you should be analyzing 22 prevalence rather than the incidence. I mean</p>	<p>1 calculation and then simply apply those linear 2 adjustments, I mean, that makes very strong 3 implausible assumptions about what the underlying 4 model is. That's the point I'm making. 5 This discussion and the way it's adjustment 6 is done, I mean, it's a function of the model you 7 assume. And this should precede the calculation of 8 the RfC, not come after it. 9 DR. SALMON: That's not the method that was 10 used, but I -- 11 DR. PETO: I know. 12 DR. SALMON: Hold on. I would actually 13 agree with you that there's an argument to be made 14 that they should use a steeper, a more possibly higher 15 exponential rather than a linear adjustment, but 16 that's a separate discussion. It's -- 17 DR. PETO: It's not. It's exactly -- 18 DR. SALMON: -- separate discussion. 19 DR. PETO: What adjustment you make is 20 entirely determined by the model that you fit. 21 DR. SALMON: Absolutely not. 22 DR. PETO: You don't fit a model and then</p>

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<p style="text-align: right;">Page 137</p> <p>1 make an adjustment. The model implies the adjustment. 2 DR. SALMON: No, it doesn't. 3 DR. PETO: Yes, it does. 4 DR. SALMON: No, it doesn't. 5 DR. PETO: Yes, it does. If you've got -- 6 DR. KANE: Wait a minute. We are not 7 getting anywhere here. 8 DR. SHEPPARD: I suggest that Julian 9 provide these comments in writing so that we can vet 10 them that way. 11 DR. KANE: I agree. I think we are not 12 going to resolve this on such a large conference call, 13 and we haven't really finished our task for today 14 anyway. So I think we do need to have something. 15 Julian, you have to write something that's 16 clear. And I think Lianne and Michael should review 17 it, and maybe we can add something, an additional 18 bullet on page 27 that will provide some clear 19 guidance on what the panel recommends EPA use. 20 DR. HEI: This is Tom. 21 DR. KANE: Yes. 22 DR. HEI: You know for the</p>	<p style="text-align: right;">Page 139</p> <p>1 how different would the outcome be under the other 2 ranges of models. 3 DR. KANE: Well, I think Lianne tried to 4 address that in her -- she put a draft kind of 5 statement on the table and did try to address that 6 issue. And I think that is an important point. 7 Are we just going around in circles for no 8 reason. But I think we just have to leave that for 9 the epidemiologists to grapple with. 10 DR. HEI: And that's what give the 11 epidemiologists a black eye. 12 DR. SHEPPARD: But you have a very good 13 point. If the data support is not there, there's not 14 much you can do. So we certainly can look at this 15 more carefully, and I'd be happy to continue to work 16 on it off-line with Julian. 17 DR. KANE: And include Michael as well 18 please. 19 DR. SHEPPARD: Of course. Of course. And 20 anyone else who would like to participate. 21 DR. KANE: I think it's very important now, 22 we have another conference call scheduled for next</p>
<p style="text-align: right;">Page 138</p> <p>1 non-epidemiologist on the panel, I thought that 2 listening for the past hour on the various discussion, 3 I would like to caution my esteemed peers that a model 4 is only as good as the data that are input. And so we 5 cannot generate models that produce over-reaching 6 conclusions that are not supported by the database. 7 And that's all I wanted to point out. And 8 I hope that when we rephrase our statement, please put 9 that in mind. Thank you. 10 DR. PETO: Well, I just repeat that the 11 model is not based on this database. The model is 12 based on whatever literature is available on these 13 sorts of endpoints. And you use the database to 14 adjust a single parameter of potency. Of course you 15 don't do it -- derive the model from these data. 16 DR. REDLICH: This is Carrie Redlich. 17 DR. KANE: Yes, Carrie. 18 DR. REDLICH: I don't dare open my mouth as 19 another non-epidemiologist, but I think the other 20 purpose of the model is what outcome you get. And so 21 in the discussion of is there a better model or which 22 model and which data, what would be the different --</p>	<p style="text-align: right;">Page 140</p> <p>1 week on May 8, same time, same number. And we were 2 going to talk primarily on the IUR which also has its 3 own difficulties, and we haven't finished the RfC. 4 DR. SHEPPARD: So I would like to suggest 5 that we defer further conversation until we have 6 something in writing that we can respond to. 7 DR. SALMON: I would like to see that when 8 it comes out. This is Andy Salmon here. 9 DR. SHEPPARD: And otherwise we not revisit 10 the issue if we don't get anything in writing. 11 DR. KANE: Okay. Does the rest of the 12 panel agree? 13 DR. HEI: Yes. 14 DR. KANE: Diana and Vanessa? 15 DR. VU: I just want to make sure that I 16 know that you are scheduled to talk -- to have a 17 conference call next week by May 8, but I believe that 18 Diana Wong has also scheduled a teleconference call 19 should the panel not able to finish all the -- 20 (inaudible) -- on May 8th. 21 DR. KANE: I can't hear at this point. 22 There's a lot of background noise.</p>

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