COMMENTS ON PANEL RECOMMENDATIONS TO EPA REGARDING THE DRAFT RISK ASSESSMENT OF LIBBY AMPHIBOLE ASBESTOS – JULY 2012

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I have reviewed carefully the most recent version of the draft SAB panel report on EPA's draft Libby Amphibole Asbestos IRIS assessment. Although appreciative of the panel's ongoing efforts, I am once again disappointed that the panel has not seen fit to respond to many of the fundamental scientific issues and concerns raised in earlier public comments. The latest revised report of the panel continues to support EPA positions of dubious scientific validity, and makes assertions that are simply incorrect. The panel should discuss and rectify these errors before sending its report to the full SAB for further review.

Issues arising in the derivation of the RfC

- The panel continues to support the use of pleural plaques or localized pleural thickening ("LPT") as the appropriate non-cancer endpoint for the derivation of an RfC, asserting that this condition is predictive of "risk for other asbestos-related diseases, including asbestosis, mesothelioma and lung cancer." The panel needs to clarify what exactly it means by this assertion. Adenomatous polyps of the colon are predictive of the risk of colon cancer because they lie on the pathway to disease, i.e., they represent an intermediate stage on the pathway to colon cancer. Urinary cotinine levels are predictive of lung cancer because they reflect smoking habits, but elevated cotinine levels are not on the pathway to lung cancer. Similarly, dicentrics in lymphocyte chromosomes from radiation exposures are clearly specific indicators of radiation exposure and thus measures of increased cancer risk but are in themselves not biological cancer risk factors since cells with unstable chromosome aberrations such as dicentrics will not divide. Is the panel asserting that pleural plaques are on the biological pathway to more serious pulmonary disease? Or is the panel saying, as some panel members have appeared to state during the panel's deliberations, that pleural plaques are simply markers of asbestos exposure and therefore correlated with more serious pulmonary disease? If the former, what is the evidence that, *conditional on asbestos exposure*, pleural plaques are associated with serious pulmonary disease? There is very little evidence of which I am aware to support the conclusion that pleural plaques lie on the biological pathway to serious pulmonary disease and the revised draft report does not appear to cite to any. If the panel has concluded that LPT is on the biological pathway to pulmonary disease, it is incumbent upon the panel to cite to the scientific literature supporting that conclusion. If, on the other hand, pleural plaques are simply markers for asbestos exposure, then their use for derivation of the RfC is highly questionable.
- The panel continues to assert that pleural plaques are associated with decreases in pulmonary function without a thorough evaluation of the literature. As noted in my previous comments, none of the papers cited in support of this proposition provides convincing evidence that pleural plaques are associated with decreases in pulmonary function *conditional on asbestos exposure.*
- The panel continues to make the ill-advised recommendation that all X-ray abnormalities be included for the derivation of the RfC. Employing endpoints that may have different sets of confounders is scientifically unsound. There is general agreement that small opacities are

associated with cigarette smoking. Suggesting that asbestosis be included is even more unsound because asbestosis is not a radiographic diagnosis. The X-ray may suggest the existence of pneumoconiosis, which can be caused by many exposures in addition to asbestos. Suggesting that these disparate X-ray abnormalities be combined into a single endpoint for analyses is akin to suggesting that lung cancer and mesothelioma be analyzed together as a single cancer endpoint.

- Despite the panel's clear concern for the paucity of data upon which EPA has based its proposed RfC, the draft report continues to support the use of a small subset of the original Marysville cohort for derivation of the RfC. The panel has completely ignored the analyses I presented in my previous comments that this data set has no power to discriminate among models. Furthermore, the panel recommends that the entire Marysville dataset be used for sensitivity analyses despite considerable missing information. Instead, the subset used in Rohs et al. (2008) should be utilized for this purpose. As Rohs et al. (2008) point out, of the original members of the cohort, only 280 had both readable chest X-rays and complete interviews. Since evaluation of possible confounders should be an important objective of sensitivity analyses, it is more scientifically sound to use the Rohs sub-cohort for the sensitivity analyses than the entire original cohort.

- On page 27, the panel recommends "a thoughtful approach to model selection…" I endorse this recommendation, but am at a loss to understand exactly what the panel is recommending. How does the panel expect EPA to develop a model based on "…considerations of biological/epidemiologic plausibility.." when it is relying on a miniscule dataset? How does the panel expect EPA to examine "local smoother estimates from the data" in this small dataset? To enhance the clarity of its recommendations, the panel should address these questions. Ultimately, the panel recommends use of the dichotomous Hill model. This model is no more "biologically plausible" than the Michaelis-Menten model. These models were first developed for quantitative descriptions of enzyme kinetics and receptor binding and have no foundation in epidemiology. The feature that distinguishes them from the more conventional logistic regression models is that the exposure-response relationship with these models is supra-linear in the low-dose region, rather than sub-linear as with logistic regression. Use of the dichotomous Hill model is no more scientifically justified in this context than use of the Michaelis-Menten model. In fact, the dichotomous Hill model requires the estimation of 4 parameters, one more than the Michaelis-Menten model. In order to fit this model to the small data set, the panel is recommending that EPA fix the values of the background probability of pleural plaques at 1% (as it does for the Michaelis-Menten model) and, in addition, fix the plateau at 85%. Thus, in a giant step backwards, the panel is recommending that the Agency fix two parameters at highly uncertain values.

Issues arising in the derivation of the IUR

- The panel continues to support use of the sub-cohort of workers employed after 1959 as the primary dataset for the derivation of the IUR, but fails to note the limitations of this dataset. While it is true that exposure information was missing on many of the workers hired before

1959, exclusion of these workers excludes many of the older individuals in the cohort when lung cancer, in particular, is most common. As I have pointed out in my previous comments, there is strong evidence of effect-modification by age in the Libby lung cancer data. This finding is consistent with that reported by Richardson in the North Carolina Textile Workers cohort. By eliminating many of the older individuals, the post-1959 dataset does not allow the investigation of effect-modification by age at Libby. Since the estimated IUR is based on a life-table analysis, it is particularly important that effect-modification by age be investigated and age-specific relative risks be used if at all possible. Although various members of the panel appear to have concurred that additional pre-1959 data can and should be used, the revised draft report makes no clear recommendation to that effect. For the above-state reasons, it should. For mesothelioma, use of the post-1959 dataset leads to a drastic reduction in the number of mesotheliomas used in the analyses. The small number (7) of mesotheliomas in the post-1959 data precludes a proper analysis. In a giant step backwards, the Agency analyzes these data using Poisson regression with cumulative exposure as the measure of exposure. This model for exposure-response flies in the face of all we know about the epidemiology of mesothelioma. The Peto-Nicholson model shows that mesothelioma risk depends independently on intensity and duration of exposure with the incidence being a linear function of concentration and a power function of duration of exposure. This model has been shown to be a good description of mesothelioma incidence in many occupational cohorts (Berman and Crump, 2008). The current asbestos IUR in IRIS recognizes that mesothelioma risk is NOT a function of cumulative exposure. Not to do so in this risk assessment would be a travesty.

- The panel recommendation for investigating the temporal aspects of disease risk is one that I heartily endorse. I would recommend that the panel request EPA go further and explore the temporal aspects of both exposure and risk. The best approach to doing so is to use exposure-response models based on ideas of multistage carcinogenesis. The panel recommends using the TSCE model. I concur. It is important, however, that the exact stochastic solution to the model be used, not deterministic approximations. The panel should make that clear in its report.

- In several locations in its revised draft, the panel refers to linearity of exposure-response relationships for amphibole-associated carcinogenesis, suggesting that there is limited evidence to support said linearity. Such statements are, at best, totally misleading and, at worst, completely wrong. The panel needs to be much more explicit as to what it means. What is the 'response' under consideration? What is the measure of exposure? There are currently two widely recognized exposure-response models for mesothelioma, the Peto-Nicholson model (for incidence) and the Hodgson-Darnton model (for life-time risk). Neither is linear with cumulative exposure as a measure of exposure. As noted above, the Peto-Nicholson model cannot even be expressed in terms of cumulative exposure. The Hodgson-Darnton model is couched in terms of cumulative exposure, but is not linear. For lung cancer, the Cox model is log-linear, not linear. Often a linear ERR (excess relative risk) model, in which the ERR is expressed as a linear function of cumulative exposure, is used to analyze the data. Howeverit provides a poorer description of the data than models like the TSCE model, in which the entire history of exposure is used rather than summary measures, such as cumulative exposure. The panel should either remove or revise loose statements regarding linearity from its report.

Recommendations

- The panel should recommend that EPA abandon for now the attempt to derive an RfC for Libby amphibole. In the absence of a suitable dataset, derivation of an RfC is unsupportable as a matter of sound science If the panel continues to endorse the use of pleural plaques as the appropriate endpoint, it should provide stronger support for its assertion that pleural plaques are predictive of more serious pulmonary disease and decrements in pulmonary function.

- The IUR for cancer should be based on the entire Larson dataset or, at the very least, detailed sensitivity analyses based on the full cohort should be undertaken. I endorse the use of the TSCE model for lung cancer analyses providing the exact stochastic solution is used and temporal aspects of exposure and risk, including effect-modification by age, are carefully investigated. For mesothelioma, the Peto-Nicholson model, or some variant of it should be used, at least in the sensitivity analyses. These are fundamental substantive issues. The panel should not get hung up on issues of little or no importance, such as possible correlations between lung cancer and mesothelioma in the data. There is no evidence that, conditional on exposure, there is any correlation between these two outcomes. The panel should revise ill-advised, general statements in the draft report regarding linearity of risk associated with amphibole asbestos, as outlined above.

- As I recommended in my earlier comments, the risk associated with exposure to Libby amphibole should be discussed in the context of risks associated with other amphiboles. There is sufficient information to do so for the carcinogenic potency. This task is relatively straightforward given the publications of Hodgson and Darnton (2000) and Berman and Crump (2008a,b), and can be done without getting into controversial issues. Doing so would enhance the public's understanding of the relative risks of various amphiboles.

- To enhance the transparency of its conclusions and further assist EPA, the panel should ensure that the cover letter to the EPA Administrator is revised to reflect all the central recommendations that the panel's report ultimately makes.