To: Diana Wong, DFO

From: Libby AA Subgroup on Charge Questions IIIB 1_2_ 3 and 5

Date: May 7, 2012

RE: Revisions to the SAB Report Section 3.2.5 Inhalation Unit Risk (IUR)

The following comments are intended to clarify three of the major points made by the IUR subgroup in the SAB Report Section 3.2.5 Inhalation Unit Risk (IUR) dated 4/11/12.

Insert the following paragraph on Page 34, lines 5–6:

"As a sensitivity analysis to evaluate the potential impact of omitting the Libby workers hired before 1959, we recommend analyzing the entire Libby cohort using interval statistics (Nguyen et al 2012; Manski 2003; inter alia) or other traditional approaches for data censoring in predictors (cf. Küchenhoff et al. 2007). It is inappropriate to use midpoint substitution (as described in section 5.4.6.1.2) that assumes poorly measured or missing predictors have some constant value. Interval statistics and traditional censoring approaches to measurement uncertainty would, in essence, replace point values with interval ranges. When the intervals are narrow, as they might be for 21% of the early hires for which jobs titles are available, there might be a good deal of recoverable information present. When the intervals are much wider, there would be accordingly less information. Whatever empirical information may be present, it is worth evaluating whether its inclusion is better than leaving out the data entirely, which in principle amounts to replacing them with intervals that are completely vacuous, from zero to infinity. This approach can produce an interval range for the final outputs, which would provide the explicit quantitative uncertainty statement as recommended by previous National Academy of Science reviews."

Like any of the sensitivity analyses recommended later under discussions of uncertainty, the results of this analysis (compared to those of the sub-cohort) would then be discussed in the section on uncertainties.

Replace the response to Question 3 (bottom p 35 – 36) in the Deliberative Draft (4/11/2012) of the SAB peer review of the EPA draft *Toxicological Review of Libby Amphibole Asbestos (2011)* with the following:

3. *In order to derive an IUR which represents the combined risk of mortality from lung cancer or mesothelioma, a cancer-specific unit risk for each tumor type was calculated according to the Guidelines for Carcinogen Risk Assessment (U.S., EPA, 2005; Sections 3.2 and 3.3) by linear*

extrapolation from the corresponding POD (i.e., the lower 95% confidence limit on the exposure associated with 1% extra risk of lung cancer or 1% absolute risk of mesothelioma mortality). The IUR was then determined as a combined upper bound risk estimate for mortality considering both cancers. Has this approach been appropriately conducted and clearly described?

The SAB found the description of the procedure used to be clear but considered the justification for independence assumption to be lacking in depth. The EPA should provide a discussion of the potential consequences of assuming that the estimated IURs for mesothelioma and lung cancer mortality are independent, noting the possibility that the upper bound on the IUR may be understated if the risks are positively correlated. The EPA may include in their discussion the 1994 NRC report suggesting that treating different tumor occurrences as independent is "not likely to introduce substantial error in assessing carcinogenic potency". However, they should acknowledge this statement was made in the context of animal bioassays and that human populations are more heterogeneous in risk factors related to mesothelioma and lung cancer mortality. If any risk factors are shared across outcomes and not accounted for in the modeling, the risk estimates generated by the different models are likely correlated. Given the small size of the data set and lack of an appropriate statistical method, this correlation cannot be estimated reliably. One approach might be to undertake bounding analysis using the Fréchet inequality for disjunctions that makes no assumption about the nature of the dependence. This analysis could reveal how large the impact of dependence might be. At the very least, the restrictive assumption of independence must be mentioned and the potential consequences of a violation of this assumption must be discussed.

Recommendation:

• The EPA should acknowledge that the assumption of independence is a theoretical limitation of the analysis and should provide a fuller justification for this assumption. EPA may cite the (2005) cancer risk assessment guidelines and the NAS (1995) analysis as suggesting the impact of issue is likely to be relatively small. However, this impact should be quantitatively accounted for, either by specific analysis, or a bounding study that evaluates the numerical consequences of an assumption of independence between the risks of mesothelioma and lung cancer mortality in particular.

Replace the response to Question 5 in the Deliberative Draft (4/11/2012) (page 37-38) of the SAB peer review of the EPA draft *Toxicological Review of Libby Amphibole Asbestos (2011)* with the following:

5. *Please comment on whether the document adequately describes the uncertainties and limitations in the methodology used to derive the IUR and whether this information is presented in a transparent manner.*

In Section 5.4.6.1 of the draft document, the EPA should be commended for summarizing the many sources of uncertainty considered in the course of this document and evaluating at least qualitatively, and sometimes quantitatively, the direction and magnitude of the likely impact of each source of uncertainty. This is a welcome advance in the discussion of uncertainties for IRIS toxicity reviews.

However, the SAB pointed out that most of what the document has accomplished is through targeted sensitivity analyses that examine one assumption at a time, while holding all others more or less constant. For example, the agency has indeed done a thorough job of exploring sensitivity of the IURs to a range of investigator analyses of lung cancer (Table 5-20) and mesothelioma (Table 5-21) for the 26 Libby worker subcohort (Tables 5-20 and 5-21) and to a wide range of assumptions about the exposure 27 metrics to be used in the basic models (e.g. Table 5-9). The basic underlying models chosen for lung cancer and for mesothelioma are the same.

The sensitivity analyses in the document are individually well described, appear well-done and provide reassurance that, under the assumptions of the basic models and approaches chosen to estimate the IUR that the particular exposure metric and lag, for example, do not appear to make a big difference in the value of the IUR. However, they are currently presented somewhat in isolation, and thus do not take into account the magnitude and likelihood of multiple sources of uncertainty in the same analysis or address the overall distribution of uncertainty in the IUR. Consequently, the SAB did not think that the following statement had been fully justified:
*"the selected combined IUR from of mesothelioma and lung-cancer mortality accounts for (emphasis added) both the demonstrated cross- metric uncertainty as well as several additional uncertainties, which could have resulted in underestimates of the mesothelioma and lung-cancer mortality risks" (p 5-*39 *105, lines 1-5).*

The SAB identified that an important source of uncertainty that might well not be accounted for by using the 95% UCL on the IUR and the combined IUR -- or at least that had not been represented by the sensitivity analyses provided -- was model uncertainty, the issue raised in the response to question 1 in Section 3.2.5 above.

Recommendations:

- The SAB recommends that a more straightforward and transparent treatment of model uncertainty would be to estimate risks using a more complete set of plausible models for the exposure- response relationship (discussed in response to question 1 in Section 3.2.5), including the Cox and Poisson models. This sensitivity analysis would make the implications of these key model choices explicit.

The SAB recommends that, as an initial step in conducting an integrated and comprehensive uncertainty analysis the agency provide a tabular presentation and narrative evaluation of the IUR estimates based on a reasonable range of data selections (*e.g.*, all or part of the earlier hires as well as the "preferred" subcohort), model forms and input assumptions (as discussed, illustratively, in the comments on question III.B.1. These input assumptions should include *inter alia* exposure metrics and externally defined parameters, as discussed in the response to question III.B.1.

As noted in the current cancer risk assessment guidelines (EPA, 2005, page 3-29);

> *The full extent of model uncertainty usually cannot be quantified; a partial characterization can be obtained by comparing the results of alternative models. Model uncertainty is expressed through comparison of separate analyses from each model, coupled with a subjective probability statement, where feasible and appropriate, of the likelihood that each model might be correct (NRC, 1994).*

The preferred model or models will be selected as a judgment based on quality of fit, plausibility (including consistency with mechanistic data insofar as this is available), and public health

protection. EPA (2005) provides a number of suggestions for comparing and synthesizing multiple estimates (Section 3.3.5, page 3-24 *et seq*.). Their suggestions (primarily addressing animal data, but equally applicable in principle to epidemiological results), include:

- Combining data from different datasets in a joint analysis;
- Combining responses that operate through a common mode of action;
- Presenting a range of results from multiple datasets (in this case, the dose-response assessment includes guidance on how to choose an appropriate value from the range);
- Choosing a single dataset if it can be justified as most representative of the overall response in humans,
- A combination of these options.

Ideally, different estimates might be quantitatively incorporated in an overall estimate by modeling the joint distributions of the major sources of uncertainty it has identified in its evaluation. However, the SAB recognizes the challenge of conducting such an analysis, and notes that simplified approaches such as using the geometric mean of several consistent and plausible upper bound estimates, or selection of a single preferred value based on health protection are frequently used in practice.

There is uncertainty associated with a composite IUR for mesothelioma and lung cancer, because it relies on an assumption of independence of the endpoints. Other methods that do not require this assumption should be explored (See response to question 1 in Section 3.2.5.)