

May 4, 2012

**MEMORANDUM**

**SUBJECT:** Information Requested by the SAB Panel in Their May 1, 2012 Conference Call and Additional Clarification Related to their Review of EPA's Draft Assessment Entitled "Toxicological Review of Libby Amphibole Asbestos"

**FROM:** David Bussard, Director  
National Center for Environmental Assessment-Washington, (8623P)

**TO:** Dr. Agnes Kane, Chair  
Libby Amphibole Asbestos Review Panel  
EPA Science Advisory Board

EPA is providing two items of information in response to specific requests made by the Panel on their May 1, 2012, conference call.

We would also like to further request clarification one draft recommendation.

And, EPA would like to offer some information to the panel should it be useful when they further discuss how EPA can account for expected increases in prevalence of noncancer respiratory effects as a function of time since first exposure.

**1) National Research Council statement on independence of tumor types in animal studies:**

The NRC document we referenced in item 10 of our table of comments (memo dated April 30, 2012) is Science and Judgement in Risk Assessment. The text we quoted came from the discussion on pgs. 230-231. The text on pages 230-231 reads:

Appendix I-2 summarizes an investigation of independence in interanimal tumor-type occurrence in a subset of the National Toxicology Program (NTP) 2- year cancer-bioassay data, which has been used by EPA as the basis for quantifying the potency of most chemical carcinogens. Separate analyses were conducted for four sex-species combinations (male and female mice, male and female rats) by using control-animal data from 61 rat studies and 62 mouse studies and treated-animal data from a subset of studies in which there were significant increases in multiple tumor types. Correlations in the

occurrence of pairs of tumor types in individual animals were evaluated. Little evidence was found of tumor-type correlation for most of the tumor-type pairs in control and treated mice and rats. Some tumor-type pairs were statistically significantly (and generally negatively) correlated, but in no case was the correlation large. These findings indicate that a general assumption of statistical independence of tumor-type occurrences within animals is not likely to introduce substantial error in assessing carcinogenic potency from NTP rodent-bioassay data.

NRC (National Research Council), 1994. Science and Judgement in Risk Assessment. Washington, DC: National Academy Press [Chapter 11, Appendix I-1, Appendix I-2] {A free download is available at [http://www.nap.edu/catalog.php?record\\_id=2125](http://www.nap.edu/catalog.php?record_id=2125) }

If the Panel does recommend that EPA formally analyze the potential impact of dependent risks on the derivation of the cancer IUR, as noted in the prior EPA comments, EPA would appreciate any specific examples the panel can provide of successful implementation of such analysis on similar data.

## **2) Calculation of the Cumulative Human Exposure Equivalent Concentrations (CHEEC):**

*As Dr. Benson wrote to you on May 1, 2012: "Figure F-1 is presented as ln transformed data. These data were "exponentiated" prior to the development of Table F-4 (exposure matrix). The data in Table F-4 are presented as fibers/cc for each department for each year. The Cumulative Human Exposure Equivalent Concentrations (CHEEC) as described in Section F.5 are also presented in units of fibers/cc-yr taking into account the work histories of each individual in the cohort."*

As described on pages F11 - F13 of the draft EPA assessment, the air sampling data were log transformed and the individual data were plotted. For selected years, the yearly averages of the log-transformed data were also plotted. (Figure F-1 shows these data for non-track trionizing jobs as the green triangles. The corresponding graph for track jobs is not shown.) The curve in Figure F-1 was fit to the three years with more than 40 data points (1973, 1976, and 1978). The yearly averages for track jobs were fit to a straight line. The resulting graphs were used to fit a curve estimating average exposure concentrations for each year on a log scale.

However, before those values for each year and job location were used in the job exposure matrix, they were exponentiated back to a non-log-transformed scale. The Cumulative Human Exposure Equivalent Concentrations (CHEEC) were thus calculated using estimated average values for each year and job location on a non-log scale.

For the year 1973, for example, the Cumulative Human Exposure Equivalent Concentrations (CHEEC) for non-track trionizing jobs used the exponentiated average of the log-transformed air measurements (i.e., the geometric mean of the measured values on the normal, untransformed, scale) of approximately 3.3 f/cc and not the natural log of that geometric mean of approximately 1.2 f/cc as shown in Figure F-1.

As Dr. Benson noted, we will try to clarify the document, but any specific suggestions as to which current descriptions need to be modified are appreciated.

**3) Clarification of EPA’s comment on the SAB Panel’s recommendation to group all radiographic outcomes:** EPA provided the Panel with information in its April 30, 2012, memo indicating that combining these endpoints may not add many cases for the O.M. Scott worker subcohort. On May 1, the Panel discussed making this a general recommendation for future amphibole studies.

In the context of some other endpoints (such as hematopoietic cancers), EPA has sometimes received peer review advice to model different endpoints separately rather than modeling combined endpoints.

EPA would appreciate any clarification the Panel can provide on their intent and whether it is to model the combined endpoints or to consider the importance of the effects together even if they are modeled separately. Of particular interest is the recommendation to combine the radiographic signs of small opacities in the lung parenchyma with radiographic signs of pleural thickening (both LPT and DPT). Recent studies published by Larson and colleagues demonstrate specifically for Libby exposed individuals that different radiographic findings may be associated with different pathobiologies, exposure metrics, exposure-response relationships and may have different expected latencies:

1) Larson TC, Antao VC, Bove FJ, Cusack C. Association between cumulative fiber exposure and respiratory outcomes among Libby vermiculite workers. *J Occup Environ Med.* 2012 Jan;54(1):56-63. PubMed PMID: 22227874.

2) Larson TC, Meyer CA, Kapil V, Gurney JW, Tarver RD, Black CB, Lockey JE. Workers with Libby amphibole exposure: retrospective identification and progression of radiographic changes. *Radiology*. 2010 Jun; 255(3):924-33. PubMed PMID: 20501730.

4) **Discussion of the increase in prevalence of localized pleural thickening (LPT) with time since first exposure (TSFE):** EPA appreciates the importance of this issue in deriving an RfC appropriate for lifetime exposure. We recognize that the proposed RfC is derived from exposure-response modeling of prevalence at time of observation in a subcohort which represents a very tight range of TSFE values, (mean 28.2 years, range of 23.2 - 32.7 years).

During the panel discussion, the importance of how to provide an estimate of LPT prevalence after a full-lifetime was discussed. One key question during discussion was how to determine the effect of exposure over a lifetime. EPA would like to note the following studies (in addition to those cited on Pg. 5-37 of EPA's draft assessment) to aid in this discussion. Several researchers have provided models which include both exposure and TSFE in order to illustrate the increased prevalence of LPT across time and report a several fold increase in prevalence across several decades TSFE in exposed workers (Paris et al 2008; Ehrlich et al., 1992 and Lilis et al. 1991). Additionally, Metintas et al. (2005) reported the prevalence of pleural plaques attributed to environmental (on-going) exposure to amphiboles increased from 6.5% in males aged 30-39 to 25.5% in males aged 60-69.

- 1) Paris C, Martin A, Letourneux M, Wild P. Modelling prevalence and incidence of fibrosis and pleural plaques in asbestos-exposed populations for screening and follow-up: a cross-sectional study. *Environ Health*. 2008 Jun 20;7:30. PubMed PMID: 18570653; PubMed Central PMCID: PMC2441611.
- 2) Ehrlich R, Lilis R, Chan E, Nicholson WJ, Selikoff IJ. Long term radiological effects of short term exposure to amosite asbestos among factory workers. *Br J Ind Med*. 1992 Apr;49(4):268-75. PubMed PMID: 1315154; PubMed Central PMCID: PMC1012109.
- 3) Lilis R, Miller A, Godbold J, Chan E, Selikoff IJ. Radiographic abnormalities in asbestos insulators: effects of duration from onset of exposure and smoking. Relationships of dyspnea with parenchymal and pleural fibrosis. *Am J Ind Med*. 1991;20(1):1-15. PubMed PMID: 1867212.
- 4) Metintas M, Metintas S, Hillerdal G, Ucgun I, Erginel S, Alatas F, Yildirim H. Nonmalignant pleural lesions due to environmental exposure to asbestos: a field-based, cross-sectional study. *Eur Respir J*. 2005 Nov; 26(5):875-80. PubMed PMID: 16264049.