

**Comments on the EPA Document, “Draft Toxicological Review of Libby Amphibole Asbestos” (EPA/635/r/002a)**

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## **Introduction**

While it was originally intended simply to serve as a central database that would ensure the consistency of EPA health and risk assessments, the IRIS database has become the primary source for information concerning the weight of evidence (hazard identification) and quantitative risk information for known and suspected carcinogens and non-carcinogens for national and international organizations. It is also widely used outside of regulatory settings by companies for product evaluation and stewardship, advocates for changes of environmental policies, and adversaries in litigation.

Because of this expanded role and the impact of the information available from the IRIS database, the IRIS program and many draft toxicological assessments have come under close scrutiny by a broad spectrum of interests, including the scientific community, the U.S. Congress, state and federal agencies, and the Government Accountability Office (GAO). Although the process and its timeliness are issues of concern, the greatest focus has been on the quality of the science, with a recent NAS panel sharply criticizing the program. EPA has made reform of IRIS a major objective (U.S. EPA 2011a).

This draft document under review by the Science Advisory Board needs to be considered in the context of the enormous impact it might have on the national and international communities. Also of importance are the recurring scientific deficiencies that have been noted in recent EPA draft health assessments and the need to restore the public's perception of the scientific quality of IRIS.

## **Comments from Interested Parties on Previous Health Assessment Documents Intended for IRIS Publication**

Because of the problems with the scientific acceptance of the draft EPA risk assessment documents intended for publication in IRIS, increasingly the NAS/NRC has been asked to provide the needed objective scientific review for many of these documents. Recent reviews have included formaldehyde, dioxin, trichloroethylene, and tetrachloroethylene, and now, by Congressional mandate, inorganic arsenic (NRC 2011; NRC 2006a; National Academies 2006a; NRC 2006b; National Academies 2006a; National Academies 2010; NRC 2010; Jacobs 2011).

In each case, the NAS/NRC found fault with the IRIS assessments, which findings have led to further delay in the review and finalization of IRIS Toxicological Reviews of these substances. Concerned with the "persistence of problems encountered with IRIS assessments over the years," and that "future assessments may still have the same general and avoidable problems. . . [i]f the methodologic issues are not addressed," NAS "encourage[d] EPA to address the problems with development of the draft assessments that have been identified" (NRC 2011, p 11).

As noted by other committees, there are many recurring and overlapping themes across these NAS reviews. These scientific concerns are best summarized by the general recommendations made by NAS to EPA in Chapter 7 of the formaldehyde review (NRC 2011) under the banner, "Reframing the Development of the IRIS Assessment":

- Consideration of how to improve each step of the process for better transparency and efficient presentation
- “Evidence Identification: Literature Collection and Collation Phase”
  - Use available evidence and understand the mode of action to select outcomes
  - Use standard protocols.
- “Evidence Evaluation: Hazard Identification and Dose-Response Modeling”
  - Use standardized approaches for study and weight-of-evidence descriptors
  - Establish protocols for reviewing major types of studies.
- “Weight of Evidence Evaluation: Synthesis of Evidence for Hazard Identification”
  - Implement and standardize the approach to using existing weight-of-evidence guidelines
  - Develop uniform language to describe the strength of evidence for non-cancer effects
  - Harmonize the approach for characterizing uncertainty and variability
  - Consolidate the outcomes around common modes of action.
- “Selection of Studies for Derivation of Reference Values and Unit Risks”
  - Establish clear guidelines for study selection
  - Balance strengths and weaknesses
  - Evaluate human vs. experiment evidence
  - Consider combining estimates among studies.
- “Calculation of Reference Values and Unit Risks”
  - Justify assumptions
  - Carefully consider and explain models used
  - Justify statistical and biological models, and describe the fit to the data
  - Determine points of departure
  - Assess analyses that underlie the points of departure
  - Provide the range of estimates and describe the effect of uncertainty factors on the estimates
  - Assess the adequacy of documentation to support conclusions and estimates.

These recommendations were described by NAS as “critical for the development of a scientifically sound IRIS assessment” (NRC 2011, p 121). They are intended to help EPA meet the challenges it faces to ensure the scientific credibility and acceptance of future health risk assessments. Further emphasizing the importance of these recommendations, the Chairman of the formaldehyde committee, Dr. Jonathan Samet, echoed these themes in his testimony before Congress: “The committee’s review of the EPA’s draft IRIS assessment of formaldehyde identified both specific and general problems with the document. The persistence of the problems encountered with the IRIS assessment methods and reports concerned the committee, particularly in light of the continued evolution of risk-assessment methods and the growing societal and legislative needs to evaluate many more chemicals in an expedient manner” (Samet 2011).

Many of these themes also are expressed by individual states and federal agencies in their reviews of these EPA draft health assessment documents, including the subject draft toxicological assessment for Libby Amphibole under current review (U.S. EPA 2011b). The agencies that have provided comments on the Draft Libby Amphibole review include the National Center for Environmental Health (NCEH)/Agency for Toxic Substances and Disease Registry (ATSDR), Centers for Disease Control and Prevention (CDC),

Department of Defense (DOD), National Institute of Environmental Health Sciences (NIEHS), National Institute for Occupational Safety and Health (NIOSH), and Office of Management and Budget (OMB).

Further, the U.S. Government Accountability Office's report on chemical assessments also makes it clear that EPA faces both long-standing and new challenges in implementing the IRIS Program (GAO 2011). The GAO report also reiterates issues raised previously by NAS concerning clarity and transparency, and the other general recommendations by the NAS (summarized above). Therefore, we are seeing a broad consensus emerge that it is a high priority to improve the scientific integrity of risk assessments. This is the context and challenge for this SAB Panel as it comes together to assess the integrity of the Draft Toxicological Review of Libby Amphibole Asbestos ("Draft Toxicological Review").

### ***EPA Charge to the SAB on Libby Amphibole Asbestos***

I was asked by WR Grace to assess the current Draft Toxicological Review, specifically to evaluate the context of the assessment, and the recommendations that have already been expressed during the review procedure. Further, given my experience implementing health assessments, I was asked to comment on the practical issues involved in this review process and the potential implication of the proposed IUR and RfC.

The EPA charge to this SAB committee requested that it "consider the accuracy, objectivity and transparency of EPA's analysis and conclusions" (U.S. EPA 2011c). In addition, EPA requested that the SAB committee respond specifically to many of the same issues identified in the recommendations of NAS, GAO, and others. These items include:

#### Noncancer/inhalation reference concentration (RfC)

- Selection of study population
- Selection of the critical endpoint and mode of action
- Methodology for the exposure reconstruction and development of exposure estimates
- Selection of exposure-response model
- Selection of model for point of departure (POD)
- Appropriateness of uncertainty factors.

#### Cancer/inhalation unit cancer risk (IUR)

- Selection of study population
- Exposure-response modeling
- Determination of POD
- Justify approaches used for confounding
- Approach for calculating the IUR
- Adequacy of descriptions of uncertainties and limitations.

## Comments Specific to the Draft Toxicological Review of Libby Amphibole Asbestos

As mentioned above, EPA has acknowledged the NAS recommendations as being important in furthering its goal to improve IRIS (EPA 2011a). For this draft toxicological review, the scientific issues that have been identified by numerous federal agencies and individual scientists echo the themes summarized by the NAS in its prior recommendations to EPA. In its charge to this SAB committee, EPA clearly requests that these recommendations be taken into consideration. Some of the examples that I have noted, and that are noted by federal agencies as particularly important, are summarized below.

For cancer, the endpoints lung cancer and mesothelioma (hazard identification) are not in question, but the choice of data for characterizing potency and the statistical methods used require careful review. Together with a number of federal agencies and other reviewers, I call your attention to the following concerns that have been identified either in comments to the SAB or in the June 2011 comments to EPA by federal agencies on the Interagency Science Consultation Draft Toxicological Review (U.S. EPA 2011b), which should be made available to this SAB Panel:

- Use of data from a subcohort (unpublished), rather than evaluation of the entire Libby miners cohort [NIEHS, OMB, Moolgavkar, S. H. (2011)]
- Choice of statistical models (e.g., Poisson distribution model used, rather than traditional Peto model previously used by EPA) and methods [ATSDR, Moolgavkar, S.H.]
- Treatment of lag time [DOD, OMB, Moolgavkar, S.H.]
- Consideration of mode of action and possibility of non-linearity [OMB, DOD, NIEHS]
- Treatment of confounding factors such as smoking [OMB, NIEHS]
- Treatment of uncertainties [ATSDR, NIEHS, Moolgavkar, S.H.].

For the non-cancer endpoints, both hazard identification and exposure-response characterization must be critically reviewed. First, basing the hazard identification on human studies, as opposed to animal experiments, presents challenges for choosing a critical endpoint that is clearly associated with the agent in question. Second, the exposures must be characterized adequately. Equally challenging are the choice of modeling approaches and uncertainty factors for derivation of the RfC. Together with a number of federal agencies and other reviewers, I call your attention to the following concerns that have been identified:

- Use of a truncated cohort instead of the full Marysville cohort [NIEHS, OMB, Moolgavkar, S.H.]
- Choice of critical endpoint, pleural thickening, and treatment of confounders [ATSDR, OMB, Moolgavkar, S.H.]
- Characterization of exposure for a selected Marysville cohort (e.g., attributing all disease to Libby amphibole when some workers were exposed to other sources at other locations) [NIOSH]
- Choice of statistical methods for exposure characterization [Moolgavkar, S.H.]
- Justification of magnitude of uncertainty factors (10 and 10) for RfC derivation [DOD, OMB, ATSDR]
- Treatment of uncertainties [ATSDR, NIEHS, Moolgavkar, S.H.].

In addition, many of the reviewers have commented on the implications and practicality of implementing the proposed RfC, particularly ATSDR and OMB. I also note some of the challenges that would be presented if this level were to be adopted by IRIS.

It is important to note that the RfC value derived in the draft assessment, 0.00002 f/cc, is below most estimates of background concentrations in the U.S. (ATSDR 2001). This issue would affect not just Libby but the entire nation, including areas of the country with naturally occurring amphibole in soils, such as Eldorado Hills, California, where the amphibole background level (about 0.0008 f/cc) is about 40 times higher than the proposed RfC (U.S. EPA 2011b).

As a practical matter, future data collection efforts will also be severely affected by the proposed RfC. If the proposed RfC were to be adopted, large amounts of current and historical sampling data from Libby would not meet the required sensitivity level for noncancer hazard evaluation. For example, the current analytical sensitivity for EPA ambient air sampling at Libby exceeds the proposed RfC. Similarly, analytical sensitivities for EPA's activity-based sampling program for Libby, which has been ongoing for several years, are 10 to 100 times above the levels needed to evaluate a hazard quotient of 1 using the proposed RfC. Furthermore, the cost of analyzing samples down to this unprecedented low level would be several thousand to tens of thousands of dollars per sample. The RfC would have significant implications for risk assessment and, in many cases, may drive a risk assessment, especially for exposure durations shorter than about 20 years, for which a hazard quotient of 1 would be reached before a  $10^{-6}$  cancer risk. These issues could extend to any site or residence where risk assessment for amphibole asbestos is necessary and where it is necessary to distinguish contaminant levels from background.

To my knowledge, this is the first effort to establish a safe level of exposure for noncancer endpoints at low levels of exposure for any form of asbestos. EPA has acknowledged that this document is the frontier of amphibole asbestos science (Jackson, 2009). Because of the enormous implications, particular attention needs to be focused on this entire approach.

In summary, the charge to this committee is important, and the committee should give careful consideration to all comments received. A thorough review by this committee, taking into consideration the recommendations from many groups—particularly the National Academy of Sciences / National Research Council—will strongly support EPA's efforts to reestablish the scientific credibility of the IRIS program and further the advancement of science and public health protection in the U.S. It will also prevent the protracted period of review that has characterized recent assessments and caused unnecessary delays for risk assessors in the field who need access to reliable toxicity values.

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### **Attachment: Background of the Author**

For the U.S. Environmental Protection Agency (EPA), Dr. Anderson is a co-author of the first federal policies that adopted risk assessment and risk management as the basis for setting health-protective policies and guidelines for conducting carcinogen risk assessment, published in 1976. She founded and directed the Agency's Carcinogen Assessment Group, the Reproductive Effects Group, the Mutagenicity Group, and the Exposure Assessment Group, which encompassed the Office of Health & Environmental Assessment. Initially, this office conducted all of the Agency's risk assessments or provided review of any risk assessment work done by a regulatory program office. This office was the central EPA risk assessment program for 10 years. As each program office began to conduct some of their own risk assessments, it became necessary to establish the Risk Assessment Forum to provide a mechanism for sharing risk assessment results and methods for use by EPA programs and regions. As Chairperson of the first EPA Risk Assessment Forum, Dr. Anderson was instrumental in establishing the Integrated Risk Information System (IRIS). The original purpose of the IRIS database was to provide a central repository of risk assessment results; where differences were noted, the Forum was the mechanism for resolving inconsistencies. Dr. Anderson has also worked extensively on international risk assessment issues to address human health and ecological consequences of exposure to environmental toxicants, including efforts for private companies, governments, the World Health Organization, and the Pan American Health Organization.

Dr. Anderson is a founder and past-President of the Society for Risk Analysis, regularly serves on peer-review panels for public agencies and institutions, has participated in numerous national and international commissions and organizations concerned with risk-based issues, and has lectured and published widely in the field of risk assessment. She was also Editor-in-Chief of the journal, *Risk Analysis: An International Journal*, from 1998 to 2008.

Dr. Anderson is a Fellow of the Academy of Toxicological Sciences and the recipient of numerous awards, including the Twentieth Century Distinguished Service Award, Ninth Lukacs Symposium (1999), Outstanding Service Award of the Society for Risk Analysis (1997), Jerry F. Stara Memorial Award (1994), SES Bonus for Outstanding Performance (1984), EPA Gold Medal for Exceptional Service (1978), Kappa Kappa Gamma National Achievement Award (1974), and a William Author Mattox Merit Scholarship (1962). She also holds a patent and continues her professional activities through memberships in the American Association for the Advancement of Science, American College of Toxicology, New York Academy of Sciences, Society for Risk Analysis, and Society of Toxicology.

Dr. Anderson is currently Vice President for Health Sciences at Exponent.