NCEA Proposed Draft Charge to External Reviewers for the IRIS Toxicological Review of Libby Amphibole Asbestos

August 2011

Introduction

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the draft Toxicological Review of Libby Amphibole asbestos that will appear on the Agency's online database, the Integrated Risk Information System (IRIS). IRIS is prepared and maintained by the EPA's National Center for Environmental Assessment (NCEA) within the Office of Research and Development (ORD). An existing IRIS assessment for asbestos which includes a carcinogenicity assessment was posted on IRIS in 1988. The draft on which EPA is now seeking review is the first IRIS assessment specific to Libby Amphibole asbestos[1].

IRIS is a human health assessment program that evaluates qualitative and quantitative risk information on effects that may result from exposure to specific chemical substances found in the environment. Through the IRIS Program, EPA provides quality science-based human health assessments to support the Agency's regulatory activities. Combined with specific exposure information, government and private entities use IRIS to help characterize public health risks of chemical substances in site-specific situations in support of risk management decisions.

Libby Amphibole asbestos, found in vermiculite ore deposits near Libby, MT, is comprised of a mixture of related mineral forms of amphibole asbestos: primarily winchite, richterite and tremolite with trace amounts of magnesioriebeckite, edenite, and magnesio-arfvedsonite. Health effects from exposure to Libby Amphibole asbestos are a potential concern for Libby residents, as well as workers and others who may have handled vermiculite mined in Libby, MT. Additionally, vermiculite from Libby, MT was incorporated into various consumer products, some of which may remain in place (e.g., vermiculite attic insulation in homes).

The external review draft Toxicological Review of Libby Amphibole asbestos is based on a comprehensive review of the available scientific literature on the health effects of Libby Amphibole asbestos and was developed in adherence with general guidelines for risk assessment set forth by the National Research Council in 1983 (NRC, 1983)[2] and numerous guidelines and

[1] The term "Libby Amphibole asbestos" is used in this document to identify the mixture of amphibole mineral fibers of varying elemental composition (e.g., winchite, richterite, tremolite, etc) that have been identified in the Rainy Creek complex near Libby, MT.

[2] NRC (1983). *Risk Assessment in the federal government: managing the process.* Washington DC: National Academy Press.

technical reports published by EPA (see Section 1 of the assessment)[3]. Specifically, this draft IRIS assessment provides an overview of sources of exposure to Libby Amphibole asbestos, characterizes the hazard posed by exposure to Libby Amphibole asbestos for carcinogenicity and noncancer health effects based on the available scientific evidence, and presents a qualitative and quantitative health assessment, including the derivations of a chronic inhalation reference concentration (RfC) and an inhalation unit risk (IUR) that can be combined with exposure information in a risk assessment to estimate noncancer hazard and carcinogenic risk, respectively, in humans. The assessment does not address oral exposure to Libby Amphibole asbestos.

Charge Questions

Below is a set of charge questions that address scientific issues in the draft human health assessment of Libby Amphibole asbestos. Please provide detailed explanations for responses to the charge questions. EPA will also consider the Science Advisory Board reviewer panel comments on other major scientific issues specific to the hazard identification and dose response assessment of Libby Amphibole asbestos. Please identify and provide the rationale for approaches to resolve the issues where possible. Please consider the accuracy, objectivity, and transparency of EPA's analyses and conclusions in your review.

General Charge Questions:

1. Is the Toxicological Review logical, clear, and concise? Has EPA clearly, and in sufficient detail, presented and synthesized the scientific evidence for health hazards from Libby Amphibole asbestos?

2. Please identify any additional peer-reviewed studies from the primary literature that should be considered in the assessment of noncancer and cancer health effects of Libby Amphibole asbestos.

[3] http://www.epa.gov/iris/backgrd.html

Chemical-Specific Charge Questions:

I. Background

A. Mineralogy and Toxicokinetics

1. In order to inform the hazard identification and dose response of Libby Amphibole asbestos, background material is included in the document briefly describing the mineralogy and toxicokinetics of asbestos and related mineral fibers (Section 2 and 3):

a. Please comment on whether the presentation of the available data on the mineralogy of Libby Amphibole asbestos is clear, concise and accurate.

b. In the absence of toxicokinetic information specific to Libby Amphibole asbestos, the draft assessment contains a general summary description of fiber toxicokinetics. Please comment on whether this overview of general fiber toxicokinetics is clear, concise and accurate.

II. Hazard Identification of Libby Amphibole Asbestos

A. Noncancer Health Effects:

1. An occupational cohort of workers in a Marysville, OH facility exposed to Libby Amphibole asbestos (Lockey et al., 1984; Rohs et al., 2008) was selected as the basis for the derivation of the reference concentration (RfC). Please comment on whether the selection of this study population is scientifically supported and clearly described. If a different study population is recommended as the basis for the RfC, please identify this study and provide scientific support for this choice.

2. Radiographic evidence of localized pleural thickening in humans was concluded by EPA to be an adverse effect and was selected as the critical effect for the derivation of the RfC. Pleural thickening is associated with restrictive lung function, breathlessness during exercise and, for some individuals, chronic chest pain. Please comment on whether the selection of this critical effect and its characterization is scientifically supported and clearly described. If a different health endpoint is recommended as the critical effect for deriving the RfC, please identify this effect and provide scientific support for this choice.

3. The database of laboratory animal and mechanistic studies of Libby Amphibole asbestos is summarized in the draft assessment (see Section 4.2 and 4.3, details in Appendix D) to inform the mechanisms of the biological response to Libby Amphibole asbestos and support the

epidemiology studies used for derivation of the RfC. Please comment on whether the laboratory animal and mechanistic information presented is used appropriately in the draft assessment.

B. Carcinogenicity:

1. Under EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005; www.epa.gov/iris/backgrd.html), the draft IRIS assessment characterizes Libby Amphibole asbestos as "carcinogenic to humans" by the inhalation route of exposure. Please comment on whether the cancer weight of evidence characterization is scientifically supported and clearly described.

2. Due to the limitations of the data available, the draft assessment concludes that there is insufficient information to identify the mode of carcinogenic action of Libby Amphibole asbestos. Please comment on whether this determination is appropriate and clearly described. Note that in the absence of information to establish a mode of action, a linear low dose extrapolation is recommended by the *Guidelines for Carcinogen Risk Assessment* (U.S., EPA, 2005; Section 3.3). If it is judged that a mode of action can be established for Libby Amphibole asbestos, please identify the mode of action and its scientific support (i.e., studies that support the key events, and specific data available to inform the shape of the exposure-response curve at low doses).

3. An occupational cohort of workers from Libby, MT exposed to Libby Amphibole asbestos (i.e., the Libby worker cohort) was selected as the basis for the derivation of the inhalation unit risk (IUR). Please comment on whether the selection of this study population is scientifically supported and clearly described. If a different study population is recommended as the basis for the IUR, please identify this study and provide scientific support for this choice.

4. Mortality from lung tumors and mesothelioma in the Libby worker cohort was selected to serve as the basis for the derivation of the IUR. Please comment on whether this selection is scientifically supported and clearly described. If a different health endpoint is recommended for deriving the IUR, please identify this endpoint and provide scientific support for this choice.

5. The database of laboratory animal and mechanistic studies of Libby Amphibole asbestos is summarized in this draft assessment (see Section 4.2 and 4.3, details in Appendix D) to inform the mechanisms of the biological response to Libby Amphibole asbestos and support the epidemiology studies used for derivation of the IUR. Please comment on the use of laboratory animal and mechanistic information in the draft assessment.

III. Exposure-Response Assessment

A. Inhalation Reference Concentration (RfC):

1. Exposures to Libby Amphibole asbestos for workers in the Marysville, OH facility were reconstructed based on industrial hygiene data collected in the facility from 1972 to 1994. Exposures from 1957 to 1971 were estimated based on extrapolation from the available industrial hygiene data. The information used for the exposure reconstruction was based on employee interviews, court and company records, and the expert judgment of the researchers. Is the methodology used for the exposure reconstruction reported in Appendix F and the subsequent development of exposure estimates used in the analyses scientifically supported and clearly described?

2. Exposure-response modeling was conducted using the incidence of localized pleural thickening in workers and cumulative exposure to estimate the point of departure (POD) for derivation of the RfC. EPA's estimate of the POD is based upon a Michaelis-Menten model applied to the subcohort of workers examined in 2002-2005 and first exposed to Libby Amphibole asbestos in 1972 (when measurements of fiber levels in the workplace began) or later with cumulative exposure as the explanatory variable. Is the selection of the model scientifically justified and clearly described? Has the modeling and the choice of a benchmark response (BMR) for the POD of 10% extra risk of localized pleural thickening been clearly described and appropriately conducted according to EPA's *Draft Benchmark Dose Technical Guidance* (U.S. EPA, 2000b)?

3. EPA's assessment also provides the results of alternative modeling approaches to derive a POD for localized pleural thickening. This modeling used the full Marysville worker data set with exposures from 1957 and later and a Cumulative Normal Michaelis-Menten model that incorporates both cumulative exposure and time from first exposure as explanatory variables. Please comment on whether EPA's rationale for presenting these alternative approaches is scientifically justified and clearly described. Please identify and provide the rationale if a different approach for identifying the most appropriate population within the cohort of Marysville workers is recommended as the basis for estimating a POD.

4. EPA has evaluated potential confounders and covariates where data are available. Specifically, EPA has explored the influence of age, body mass index, smoking status, time since first exposure, gender, and alternative exposure metrics on model fit and evaluated their association with the modeled health outcomes (see Section 5.3). Are these analyses clearly

described and appropriately conducted? Are the results of these analyses appropriately considered in the RfC derivation? Additionally, there is a possibility of exposure-dependent censoring in participant selection for the update of the Marysville cohort (Rohs et al., 2008) but no evidence of selection bias. Does the panel have any specific recommendations for evaluating and, if appropriate, quantitatively addressing exposure-dependent censoring in these analyses?

5. The modeled POD estimate is based on cumulative exposure estimates for the worker cohort examined. For the derivation of the RfC, this cumulative exposure is prorated over the period of environmental exposure (lifetime or shorter duration chronic exposure when appropriate). The RfC is provided in units of continuous air concentration. Is the basis of this conversion clearly explained and scientifically justified?

6. Please comment on the rationale for the selection of the uncertainty factors (UFs) applied to the POD for the derivation of the RfC. Are the UFs appropriate based on *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002; Section 4.4.5) and clearly described? If changes to the selected UFs are proposed, please identify and provide scientific support. Specifically, please comment on the rationale for the selection of the database uncertainty factor (UF_D) of 10 applied in the derivation of the RfC. The database uncertainty factor accounts for the lack of data on effects other than in the respiratory system, including other effects observed in community and laboratory animal studies (cardiovascular disease and autoimmune effects) that have not been well-studied (See Section 5.2.3 of the Toxicological Review); and lack of health data assessed at later time points. Is the rationale for the UF_D appropriate and clearly described? Please provide the rationale if a change in the UF_D is proposed.

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

B. Inhalation Unit Risk (IUR):

1. Exposure-response modeling was conducted separately for lung cancer and mesothelioma mortality. The POD estimates for these endpoints are based upon analysis of the subcohort of workers first exposed after 1959 when the exposure data were judged to be better characterized. The exposure-response modeling included consideration of a variety of exposure metrics that varied with time and incorporated different lag and decay parameters. Based on the results of the exposure-response modeling, a lifetable analysis was used to determine the PODs for each type

of cancer for the various exposure metrics. Have the exposure-response modeling and determination of the PODs from lifetable analysis been appropriately conducted and clearly described? If a different approach to exposure-response analysis is recommended as the basis for the estimating the IUR, please identify the recommended methods and provide a rationale for this choice.

2. Smoking is a strong independent risk factor for lung cancer and may be an important confounder of the lung cancer mortality analysis. Data on individual smoking habits and history were largely missing and could not be used to control for potential confounding in regression analyses. However, EPA used three approaches to evaluate the confounding issue, including restriction of the cohort and two analytic evaluations of the potential for confounding by smoking (see Section 5.4.3.6.5). Please comment on whether the methods and analyses are clearly presented and scientifically justified. If additional analyses are recommended, please identify the methods and scientific rationale.

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?

4. Please comment on the adjustment for mesothelioma mortality underascertainment. Is this adjustment scientifically supported and clearly described? If another adjustment approach is recommended as the basis for the IUR, please identify that approach and provide the scientific rationale.

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.