

**NCEA's Proposed Draft Charge to External Reviewers for the IRIS Toxicological Review
of Libby Amphibole Asbestos
May 2011**

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment of Libby Amphibole asbestos that will appear on the Agency's online database, the Integrated Risk Information System (IRIS). An existing IRIS assessment for asbestos was posted on IRIS in 1988. The draft on which we are now seeking review is the first IRIS assessment specific to Libby Amphibole asbestos.

IRIS is a human health assessment program that evaluates quantitative and qualitative 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 magnesioarfvedsonite. Libby Amphibole asbestos is a potential concern for former vermiculite processing and waste disposal sites which 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 current 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) and numerous guidelines and technical reports published by EPA (see Section 1 of the assessment). 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 non-cancer health effects based on the available scientific evidence, and presents a quantitative risk assessment, including the derivations of a chronic inhalation reference concentration (RfC) and an inhalation unit risk (IUR) of carcinogenic mortality. The assessment does not address oral exposure.

Below is a set of charge questions that address scientific issues in the human health risk assessment of Libby Amphibole asbestos. Please provide detailed explanations for responses to the charge questions. 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. If there are any additional, existing, studies that would have a significant impact on the conclusions of the Toxicological Review, please identify and provide the rationale for their inclusion.

Chemical-Specific Charge Questions:

(A) Inhalation Reference Concentration (RfC) for Libby Amphibole Asbestos

1. An occupational cohort of workers in a Marysville, OH facility exposed to Libby Amphibole asbestos was selected as the basis for the derivation of the RfC (Lockey et al., 1984; Rohs et al., 2008). Please comment on whether the selection of this study population is scientifically supported and clearly described. If a different study is recommended as the preferred 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 selected as the critical effect for the derivation of the RfC. Please comment on whether the selection of this critical effect is scientifically supported and clearly described. If a different health endpoint is recommended as the preferred critical effect for deriving the RfC, please identify this effect and provide scientific support for this choice.
3. Exposures were reconstructed by the University of Cincinnati from the industrial hygiene data collected in 1972 and afterwards for workers in the Marysville, OH facility. Exposures to Libby Amphibole were estimated for 1957 to 1971. Please comment on whether the methodology used for the exposure reconstruction is scientifically supported and clearly described. [As a cross-reference, note that EPA used the subcohort of employees first exposed after 1972 as the basis

for its preferred statistical analysis in support of the RfC.]

4. Exposure-response modeling was conducted using the incidence of localized pleural thickening in humans and cumulative exposure to derive the point of departure (POD) for the RfC. EPA's estimate of the POD is based upon a log-logistic 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. Has the modeling been appropriately conducted and clearly described? Is the benchmark response (BMR) selected for use in deriving the POD (i.e. a 10% extra risk of localized pleural thickening) scientifically appropriate for the assessment and clearly described? Please comment on whether the rationale for selecting the preferred POD is scientifically justified and clearly described.

5. EPA's assessment provides results of alternative modeling approaches to provide information on the sensitivity of the POD to cohort selection criteria and modeling form. Are these alternative approaches and their strengths and weaknesses clearly described? Please comment on whether EPA's rationale for presenting these alternative approaches is scientifically justified and clearly described. If a different modeling approach is recommended as the basis for estimating a POD, please identify specifically and provide scientific support.

6. The modeled POD estimate is based on cumulative exposure estimates for the worker cohort examined (for the preferred subcohort, exposures were concentrated in the period 1972-1980, although some low level of exposure is assumed to occur from after this time). For application in 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 for lifetime exposures. Is the basis for this conversion clearly explained and scientifically justified?

7. 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 scientifically supported and clearly described? If changes to the selected UFs are proposed, please identify and provide scientific support.

8. Please comment on whether, overall, the document describes the uncertainties and limitations in the methodology used to derive RfC in a transparent manner.

(B) Carcinogenicity of Libby Amphibole Asbestos

1. Under the EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (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. The draft assessment concludes that data are not sufficient to characterize the mode of carcinogenic action of Libby Amphibole asbestos. Please comment on whether this determination is scientifically supported and clearly described. If it is judged that a mode of action can be established for Libby Amphibole asbestos, please specifically identify this mode and its scientific support (as discussed in EPA Guidelines for Carcinogen Risk Assessment (2005), Section 2.4.3).

Inhalation Unit Risk (IUR)

3. An occupational cohort of vermiculite miners and millers exposed to Libby Amphibole asbestos (Sullivan, 2007) was selected as the basis for the derivation of the IUR. Please comment on whether the selection of this study population is scientifically supported and clearly described. If a different study is recommended as the preferred basis for the IUR, please identify and provide scientific support for this choice.

4. From this cohort, mortality from mesothelioma and lung cancer in humans was selected to serve as the basis for the quantitative inhalation cancer assessment. Please comment on whether this selection is scientifically supported and clearly described. If other health endpoints are recommended as the preferred basis for the IUR, please identify and provide scientific support for this choice.

5. Exposure-response modeling was conducted separately for lung cancer and mesothelioma mortality. The preferred point of departure (POD) estimates for these endpoints are based upon analysis of the subcohort of workers first exposed post 1960 when the exposure data was judged to be better characterized. The exposure-response modeling included consideration of a variety of dose 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 points of departure (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 preferred basis for the estimating the IUR, please identify the recommended methods and provide scientific support for this choice.

6. 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 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% 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?

7. Please comment on the adjustment for mesothelioma mortality under-ascertainment. Is this adjustment scientifically supported and clearly described? If another adjustment approach is recommended as the preferred basis for the IUR, please identify that approach and provide scientific support for this choice.

8. Please comment on whether, overall, the document describes the uncertainties and limitations in the methodology used to derive the IUR in a transparent manner. Examples of issues that warrant consideration include potential impacts from uncertainty in the historical exposure estimates for the Libby workers and the potential for “masking” of some of the cancer mortality by exposure dependent competing risks from asbestos-related noncancer mortality. Has EPA appropriately considered these issues?