EPA'S RESPONSE TO MAJOR INTERAGENCY SCIENCE COMMENTS ON THE INTERAGENCY SCIENCE DISCUSSION DRAFT OF THE IRIS TOXICOLOGICAL REVIEW OF LIBBY AMPHIBOLE ASBESTOS

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Purpose: The Integrated Risk Information System (IRIS) assessment development process of May 2009 includes two steps (Step 3 and 6b) where the Executive Office of the President and other federal agencies can comment on draft assessments. Recently, Step 6b comments were provided for the Interagency Science Discussion drafts of the IRIS Toxicological Review of Libby Amphibole asbestos (LAA) and IRIS Summary for LAA. For a complete description of the IRIS process, including Interagency Science Discussion, visit the IRIS website at www.epa.gov/iris.

MAJOR INTERAGENCY SCIENCE DISCUSSION COMMENTS AND RESPONSES:

Topic #1: Selection of the critical effect of localized pleural thickening (LPT) for derivation of the RfC

The National Institute of Environmental Health Sciences (NIEHS) commented that they agreed with the selection of LPT as the appropriate toxicological outcome for derivation of the RfC. They stated that LPT represents an irreversible physiological alteration of the lung resulting from asbestos exposure. NIEHS also stated that they independently agree with the Science Advisory Board (SAB) and the American Thoracic Society that LPT is more than a "marker for asbestos exposure" and that it represents an irreversible and progressive pathological alteration of the pleura and is generally associated with reduced lung function and decrements in quality of life.

The National Institute for Occupational Safety and Health (NIOSH) commented that the structured literature review and meta-analysis (Appendix I) were particularly useful to document that LPT (pleural plaques) were associated with small, but statistically significant decrements in forced vital capacity (FVC) at the population level. They stated that, as noted in the draft, even though plaques alone are not generally associated with clinically significant decrements in FVC at the individual level, the analysis at the population level still provides an excellent rationale for using LPT (pleural plaques) as a critical effect in the RfC analysis.

The National Aeronautics and Space Administration (NASA) stated that they question EPA's reliance on studies of pleural plaques – a health endpoint that NASA believes has not been conclusively documented as an adverse effect. They stated that EPA had received significant questions on this choice of an adverse effect.

> **EPA Response:** Localized pleural thickening (LPT) is a pathological alteration that involves thickening of one or more of the pleura, membranes in the chest cavity that envelop the lungs. Due to differences in the terminology and usage over time, it is important to note that under the 2000 International Labour Organization (ILO) definitions, the terms "LPT" and "pleural plaques" are the same but older definitions of pleural plaques differ. EPA concluded in its external review draft that LPT is an appropriate critical effect for the derivation of the inhalation reference concentration

(RfC). The SAB agreed that LPT is an appropriate health endpoint for the derivation of the inhalation RfC and that LPT is generally associated with reduced lung function. The SAB recommended that the Agency include a more detailed review of the literature to further support this conclusion. As recommended, EPA conducted a well-documented systematic literature search and review of the published literature on the relationship between LPT and lung function to further support the decision to use this endpoint for the derivation of the RfC. This information is presented in Appendix I and discussed in Section 5.2.2.3 of the Toxicological Review. This analysis further showed that LPT from asbestos generally, or from LAA, is associated with a decrease in two key measures of lung function (FVC and FEV_1), and that these decreases are unlikely to be due to other factors such as excess body fat or to undetected by x-ray changes in the lung tissue (asbestosis) that might also have been caused by exposure to asbestos.

In addition, EPA notes that two Health and Human Services agencies (NIEHS and NIOSH) support of the use of this health endpoint. NIEHS commented that LPT is an irreversible physiological alteration, and NIOSH supported EPA's rationale on the adversity of LPT based on pulmonary decrements at the population level.

Topic #2: Application of the subchronic-to-chronic uncertainty factor (UF) in the derivation of the RfC

EPA used a data-informed subchronic-to-chronic UF of 10 in the Step 6 draft assessment (final Agency and interagency review; 2014) to address the fact that studies show the prevalence of LPT increases with time since first exposure (TSFE) to asbestos. In the external review draft, EPA had instead addressed the uncertainty associated with TSFE as a component of a database UF.

The Office of Management and Budget (OMB) and the Office of Science and Technology Policy (OSTP) commented that the subchronic-to-chronic UF used in the final interagency review draft assessment should be a 1 rather than a 10. OSTP stated that the use of such a UF was an important precedent and was not necessary because the average duration of exposure in the primary subcohort was 18 years.

NASA commented that the use of uncertainty factors was not justified due to the lack of an adverse effect (i.e., LPT). NASA also stated that EPA's use of a subchronic-to-chronic UF was not justified because the average exposure duration in the critical study was of sufficient duration to address chronic exposures.

The Agency for Toxic Substances and Disease Registry (ATSDR) commented that merely modeling a lifetime exposure from the chronic data and noting that the difference is the same magnitude as the UF was insufficient as it does not capture the full extent of the uncertainty.

EPA Response: The principal study subcohort serving as the basis for the LAA RfC had a mean exposure duration of 18 years and mean follow-up time (the TSFE and subsequent X-ray evaluation) of 28 years (with a range in individual TSFEs of 23−33 years).

The epidemiological literature on LAA and asbestos other than LAA shows that the number of people with pleural plaques in any studied group increases steadily with time, even after exposure has stopped or been significantly reduced. The available data for

asbestos and the critical endpoint (LPT) indicate that an average follow-up time in the principal study subcohort of 23−33 years underestimates the expected lifetime incidence of LPT following LAA exposure.

EPA's external peer-review draft assessment (2011) addressed the lack of sufficient follow-up time (or TSFE) as a database uncertainty and applied a database UF of 10 and a subchronic-to-chronic UF of 1. The SAB review panel (SAB, 2013) agreed that the observed follow-up was insufficient to characterize lifetime risk and recommended that EPA use a more sophisticated modeling strategy to better evaluate the impact of the follow-up time (or TSFE) on noncancer toxicity. The SAB also recommended that EPA reevaluate the two uncertainty factors—specifically to consider decreasing the database UF and increasing the subchronic-to-chronic UF. The SAB stated that the uncertainty associated with less-than-lifetime follow-up could be better addressed with the subchronic-to-chronic UF rather than with the database UF.

EPA followed each of the SAB's recommendations by revising the modeling strategy and reconsidering the two uncertainty factors. EPA decreased the database UF from 10 to 3 and increased the subchronic-to-chronic UF from 1 to 10. A database UF of 3 was maintained because studies in the Libby population have also demonstrated an association between exposure to LAA and autoimmune effects. Because the available studies of autoimmune effects did not provide exposure-response information, it is unknown whether a lower point of departure (POD) or RfC would be derived for these effects and thus the application of a database UF of 3 is warranted. EPA utilized the analysis of epidemiologic data and results of the primary modeling effort to inform the choice of a subchronic-to-chronic UF of 10. EPA modeled the impact of TSFE on the central estimates of prevalence for data specific to the Marysville subcohort exposed to LAA and used this as a reasonable estimate of the likely impact of TSFE beyond what was observable in that cohort.

EPA is not proposing that a 28-year follow-up is generally insufficient to describe lifetime hazards for most substances or health endpoints; therefore, a new precedent requiring long follow-up times is not being set in this analysis. The judgment is based on data specific to asbestos exposure and the risk of developing LPT (pleural plaques). The judgment is consistent with EPA's 1994 RfC guidance (U.S. EPA, 1994) which states that there is not a default definition of subchronic duration for a human study and data on the progression of disease should be considered (see page 4−67): "…[T]he amount of exposure in a human study that constitutes subchronic is not defined, and could depend on the nature of the effect and the likelihood of increased severity or greater percent response with duration.…Information on the natural history and progression for the disease should be considered and explained; information on follow-up after exposure, often available in epidemiologic studies, is important." EPA concluded that the data support an adjustment factor of 10 in this instance based on the epidemiologic data and analyses conducted using TSFE as recommended by the SAB; thus, a data-informed subchronic-to-chronic UF of 10 was applied.

With respect to ATSDR's comment about the full extent of uncertainty, EPA notes in Section 5.2.3 of the Toxicological Review that some studies of general asbestos indicate a lifetime follow-up time might have a greater than 10-fold impact on the prevalence of LPT. The assessment also notes one study indicating the impact of TSFE on prevalence

might be less. ATSDR is correct that there remains uncertainty with estimating the lifetime prevalence of LPT.

EPA considered the comments and clarified the text describing the application of subchronic-to-chronic UF in Section 5.2.2.3 of the Toxicological Review. As to the adversity comment by NASA, EPA concluded that LPT is an appropriate critical effect as noted in response to Topic #1.

Topic #3: Applicability of the results of the LAA assessment to other types of asbestos

NASA commented that they were concerned the EPA planned to consider LAA as an index chemical for all forms of asbestos.

EPA Response: EPA is not aware of any plans, nor does it intend to imply, that the results of the LAA assessment be used as an index chemical for all forms of asbestos. The assessment is explicit in stating that the toxicity values are specific to LAA. The values would be applicable to sites outside of the Libby, MT area for evaluating inhalation exposures to asbestos from the Libby, MT mine. More than 6 million tons of Libby vermiculite contaminated with LAA were shipped to over 200 facilities outside Libby, MT (ATSDR, 2008). The RfC is derived from a cohort employed at a plant in Marysville, OH that was using Libby vermiculite.

However, to address NASA's concerns and to provide further clarification, EPA revised the Foreword of the Toxicological Review to include the following:

> The purpose of this Toxicological Review is to provide scientific support and rationale for the hazard and dose-response assessment in the Integrated Risk Information System (IRIS) pertaining to chronic inhalation exposure to Libby Amphibole asbestos, a mixture of amphibole fibers identified in the Rainy Creek complex and present in ore from the vermiculite mine near Libby, MT. It is not intended to be an assessment of the toxicity of asbestos generally (nor a comprehensive treatise on the agent or toxicological nature of Libby Amphibole asbestos). The purpose of this document is to establish a Libby Amphibole asbestos-specific reference concentration to address noncancer health effects and to characterize the carcinogenic potential and establish an inhalation unit risk for Libby Amphibole asbestos-related lung cancer and mesothelioma mortality.

Furthermore, EPA added the following text after the derivation of the inhalation reference concentration and the inhalation unit risk in Sections 5.2.3, 5.4.5.3, and 6.2.1 of the Toxicological Review, and in the IRIS Summary: "While this assessment is informed by studies of other types of asbestos, it is not a complete toxicological review of other amphiboles or of chrysotile asbestos."

Topic #4: EPA's consideration of previous interagency comments

NASA encouraged EPA to ensure that they addressed comments provided by NIOSH, considered to be a lead federal agency in the study of the health impact of asbestos, from the earlier Step 3 of the IRIS Process.

NIOSH supported the EPA assessment of LAA and stated that EPA was very responsive to the SAB review.

> **EPA Response:** EPA appreciated NIOSH's comments in Step 3 of the IRIS Process and extensively revised the external review draft to address their comments. Further, EPA received additional comments from NIOSH during the Step 6 interagency review process. EPA has addressed the comments from NIOSH as well as the comments from the other federal agencies and the Executive Office of the President.

Topic #5: Mineralogy nomenclature

NIOSH noted that the nomenclature (i.e., physical and chemical morphology) used in defining the asbestos minerals and other related minerals (e.g., amphiboles in Libby, MT vermiculite) can often vary among disciplines (e.g., health scientists, geologists) and provided suggestions to clarify definitions and criteria on how to identify these materials to achieve consistent application of the toxicity values.

> **EPA Response:** EPA has revised Section 2 of the document to address NIOSH's comments and clarified terminology and mineralogical descriptions. EPA agrees with NIOSH that nomenclature for describing asbestos mineralogy and physical form can differ across disciplines. EPA included a list of common nomenclature (see Text Box 2-1) and glossary of terms (see Appendix H) to clarify the terminology used in the assessment.
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> The derivation of the toxicity values for LAA is based on the analysis of the health effects of occupational exposures to the amphibole mineral fibers of varying elemental composition (e.g., winchite, richterite, tremolite, etc.) that have been identified in LAA.
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> EPA included information on the composition of LAA (both morphological and mineralogical) based on the analysis of the samples. The description of detailed mineralogy and morphology is provided as additional information in Section 2.4 (e.g., see Table 2-1, Figures 2-6, and 2-7) of the Toxicological Review to facilitate identification of amphibole fibers in ore products originating from the Libby mine.

Topic #6: Understanding changes in the definition of localized pleural thickening (LPT) in the 2000 International Labour Organization (ILO) classification

NIOSH provided comments on the changes in the ILO classification system between the 1980 ILO revision and the 2000 ILO revision for localized and diffuse pleural thickening to clarify the guideline's intent to identify asbestos-related diseases.

> **EPA Response:** EPA has revised the description of the revisions in ILO guidelines from 1980 to 2000 in accordance with the NIOSH comment. Appropriate edits have been made to Sections 4 and 5 of the Toxicological Review and Appendices A and I.

Topic #7: Selection of the primary analysis for deriving the point of departure for the derivation of the RfC

OMB orally asked for clarification on the selection of the primary analysis for deriving the point of departure for derivation of the RfC. OMB was concerned about a loss of precision in using the subcohort compared to the use of the larger cohort.

EPA Response: EPA has revised the description of the selection of primary analysis for deriving the BMCL and included some new text in Section 5.2.6.2.2 after Table 5-9. The model fit to that larger cohort confirms that there is an exposure-response relationship. The analysis derived from the modeling of the subcohort is based on the higher quality exposure data of the subcohort and yields more reliable estimates of the effect of exposure concentration.

REFERENCES

ATSDR (Agency for Toxic Substances and Disease Registry). (2008). Summary report: Exposure to asbestos-containing vermiculite from Libby, Montana, at 28 processing sites in the United States. Atlanta, GA: U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/asbestos/sites/national_map/Summary_Report_102908.pdf

SAB (Science Advisory Board). (2013). SAB review of EPAs draft assessment entitled toxicological review of Libby Amphibole Asbestos (August 2011). (EPA-SAB-13-001). Washington, DC: U.S. Environmental Protection Agency. http://yosemite.epa.gov/sab/sabproduct.nsf/0/4F2A245C7160456B85257B030072E5D3/$File/EPA-SAB-13-001-unsigned.pdf

U.S. EPA (U.S. Environmental Protection Agency). (1994). Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. (EPA/600/8-90/066F). Research Triangle Park, NC: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=71993