

APPENDIX A

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SUMMARY OF INFORMATION QUALITY ACT (“IQA”) REQUESTS FOR CORRECTION REGARDING THE LIBBY AMPHIBOLE ASBESTOS (“LAA”) IRIS ASSESSMENT

SECTION 3 OF THE IQA REQUEST FOR CORRECTION: THE DRAFT ASSESSMENT FAILS TO MEET THE BASE IQA OBJECTIVITY STANDARDS

A. *Base Substantive Requirements: The Draft Assessment is Substantively Unreliable, Inaccurate and Biased in its Evaluation of the Noncancer Critical Effect and Reliance on Small Subcohorts*

1. *For the RfC, the Draft Assessment’s Selection of Localized Pleural Thickening (“LPT”) as the Critical Effect is Unreliable, Inaccurate, and Biased*

Overview: The Draft Assessment fails to provide scientific support for the selection of LPT as an adverse effect because it: (a) lacks a demonstration that LPT is adverse as defined by EPA’s own guidance; (b) fails to demonstrate a “causal” relationship between LPT and an impairment; (c) confuses LPT with other distinct conditions; (d) fails to consider important scientific literature; and (e) for the literature it did reference, fails to consider the quality of the data and studies. For these and other reasons described below, the IQA the Assessment is inaccurate, unreliable, and biased.

Requested Corrective Action: The petition requests EPA to perform the following:

- Identify all Agency guidance relevant to determining “critical,” or “adverse” effects, and either apply that guidance or provide a reasoned explanation as to why its application is unwarranted in this case;
- Decline to select LPT, which is solely a marker of exposure, as the RfC critical effect;
- Apply a definition of LPT that is specific to plaques located on the parietal pleura and excludes biologically and anatomically distinct structures on the visceral pleura;
- For discussions of LPT and the scientific literature, use consistent and accurate terminology and avoid the blurring of distinctions between different radiological findings on the visceral pleura, such as DPT or other general or unclassified pleural thickening;
- For the assessment of the critical effect: i) apply EPA’s own definition of “adverse” to ensure selection only of a critical effect that is “[a] biochemical change, functional impairment, or pathologic lesion that *affects the performance* of the whole organism, or *reduces an organism’s ability* to respond to an additional environmental challenge;”¹ and ii) explain precisely the basis for the selection and how the critical effect satisfies EPA guidance;

¹ EPA RAGS for Inhalation Risk Assessment, 2009, at 9 (Exhibit 12) (emphasis added).

- If LPT is the selected RfC critical effect, then set forth the reasoned justification for how LPT fully satisfies EPA guidance (including guidance cited in footnotes 29 - 32 of the main text), or alternatively, the reasoned justification for EPA to depart from its guidance and the implications for risk management of LAA, other asbestos fibers and other IRIS assessments;
- For its assessment of whether LPT is adverse, identify all of the relevant literature (including but not limited to the additional literature cited in Sections III.A.1. d and IV.A of the main text), explain the process for identifying the literature, and perform an unbiased weight-of-evidence analysis of the literature;
- For its assessment of whether LPT is adverse, integrate the evidence across all studies to rigorously assess the quality, strengths, and weaknesses of relevant studies, transparently identify all findings (including conflicting information, inconsistencies, and data gaps), and perform the following analyses for each study:
 - Identify whether each study finds a strong and clinically significant causal relationship between LPT and impairment, or whether the study finds only a statistically significant or measurable change that would not meet EPA's definition of adverse;
 - Identify the definition of LPT that the study uses, and if the definition differs from the one EPA uses in its assessment then explain the implications and uncertainty introduced by applying differing definitions;
 - Identify and account for potential confounders, effect modifiers and study limitations such as: i) whether the study rigorously addresses smoking and obesity; ii) whether the study uses x-rays to diagnose LPT (rather than more sensitive radiographic diagnostic tools) and takes into account the possibility that subpleural fat is mistaken for LPT; iii) the reliability and relevance of pulmonary function measures used, and whether the study relies upon a single or multiple measurements; and iv) whether the study compares participants with reference populations, and assesses work histories and sources of asbestos exposure;
 - Assess the quality of each study that relies upon the ATSDR Libby Data that contain database inaccuracies (such as the error rate in job history data and any data deficiencies in documenting pleural fat (Box 4.D)); and
- To objectively assess whether LPT is "responsible for" or "causes" an asserted impairment, which is a prerequisite to concluding that LPT is adverse: i) transparently identify the impairment that is asserted (specifically addressing pulmonary deficits, chest pain, dyspnea and any other asserted impairment); ii) transparently apply the Hill factors (such as strength, consistency and specificity of an association, and biologic plausibility) or other appropriate EPA guidance to assess causation; and iii) for its discussion of any biologic plausibility of impairment from LPT, explain the mode of action and the scientific basis for the conclusions.

2. The Draft Assessment Inappropriately Relies on Unduly Restricted and Confounded Datasets, Thereby Rendering the Assessment Inaccurate, Unreliable and Biased when Calculating Toxicity Values

Overview: For both its proposed noncancer and cancer values, the Draft Assessment relies on severely and inappropriately restricted data sets that bias and undermine the reliability of the assessment.

Requested Corrective Action: The petition requests EPA to perform the following for both the noncancer and cancer toxicity assessments:

- Abandon use of unduly weak subcohorts;
- Assess the availability of and employ larger cohorts that have the power to: detect confounding influences such as weight (or BMI) and age; assess association between dose and probability of the effect under all relevant durations of exposure; distinguish among models; support a proper dose-response analysis that is accurate and unbiased; and support a sound calculation of a range of uncertainty; and
- At a minimum, present analyses using both the subcohorts and the full cohorts, and evaluate and identify the uncertainty, potential error sources, and statistical weaknesses inherent in use of the full cohorts and subcohorts. Among other things, the analyses should address each of the topics identified in the above bullet point.

3. The Assessment Fails to Address Information Presented by Commenters Identifying Fundamental Flaws in the Draft Assessment's Analysis

Overview: EPA has not yet addressed information in comments on the Draft Assessment central to evaluating fundamental flaws that violate the IQA Guidelines.

Requested Corrective Action:

- EPA should address in full all comments submitted to it and to the SAB.

B. *Base Substantive Requirements: The Draft Assessment Was Not Generated by Sound Scientific Methods and Objective Scientific Practices and Fails to Identify The Potential Error Sources In It*

Overview: The Draft Assessment fails to apply EPA guidance and NAS recommendations that represent “sound science,” and fails to reflect sound statistical methodology due to: the lack of uncertainty analyses; reliance on unreliable small subcohorts; and inadequate support for model selection.

Requested Corrective Action:

- Make the corrections described in Sections III.A, III.B.3, and IV.A, B, and C of the main text;
- For the RfC, evaluate a range of biologically plausible models using both full and subcohorts to assess whether the results are consistent and to demonstrate the range of uncertainty associated with model selection; and

- For the RfC, select and explain the basis for selecting an alternative model that is biologically plausible and allows EPA to account for high exposure levels and important confounders like age and body mass index.

For the RfC and IUR:

- Use the entire data sets for conducting and assessing model selection;
- More fully explore use of other models and address each of the public comments regarding the modeling, including the recommended use of flexible statistical methods such as spline smoothers to explore carefully effect modification by age in the data;
- Explain and demonstrate the ramifications of each modeling choice, including why choices to select certain models and to abandon others are scientifically sound;
- Evaluate and discuss the sources of error associated with modeling choices;
- Identify the range of uncertainty associated with model choices, including the varied toxicity values that would result from use of the full cohorts and different models; and
- Thoroughly explain any decisions not to use statistical models and methods that enjoy widespread scientific consensus, such as the models used for the current asbestos IUR.

C. *Base Presentation Requirements: The Draft Assessment is Incomplete and Inaccurate, Lacks Transparency, and Fails to Identify the Potential Sources of Error*

Overview: The Draft Assessment fails to present supporting data, models and other sources of information in a clear, complete, accurate, and unbiased manner, and fails to present potential sources of error so that the public can assess for itself whether the analysis and resulting information disseminated are objective.

Requested Corrective Action:

Identify and quantify the potential sources of error in EPA's: (i) selection of the critical endpoint; (ii) determinations as to whether that endpoint is truly adverse and has a causal relationship with the asserted symptoms; and (iii) choices of subcohorts and models. More specifically, EPA should:

- Set forth clearly and completely the basis for its selection of the RfC critical effect, including specification in detail as to the functional impairment that makes the critical effect "adverse," how that satisfies EPA policy, and the basis for determining a causal relationship with the asserted impairment;
- Where literature findings are inconsistent, explain how the Agency is analyzing and reconciling the disparate findings and the ramifications and uncertainty associated with the positions that it is taking;
- Avoid departing from well-established norms within the medical and scientific communities (which normally view LPT as an asymptomatic marker of asbestos exposure), particularly without presenting solid and weight-of-evidence support for the Agency's precedential decision, including the range of toxicity values resulting from selection of different subcohorts/cohorts and models;

- Present and quantify the potential sources of error in the information underlying the selection of the RfC critical effect and the selection of small subcohorts; and
- More thoroughly explain the basis for model selection, information underlying EPA's rejection of other models and methodologies, and the uncertainty and range of error associated with these decisions.

SECTION 4 OF THE IQA REQUEST FOR CORRECTION: THE DRAFT ASSESSMENT FAILS TO MEET THE HEIGHTENED OBJECTIVITY STANDARDS APPLICABLE TO "INFLUENTIAL" SCIENTIFIC INFORMATION

A. *Heightened Substantive Standards: The Draft Assessment Fails to Identify Relevant Studies That Address Inconsistencies in the Scientific Evidence*

Overview: The Draft Assessment fails to identify all relevant literature, including studies that fail to support the Assessment's conclusions, and does not specify how it reconciles inconsistencies in the literature that it does identify.

Requested Corrective Action:

- Perform each of the literature identification and integration corrections set forth under Section III.A of the main text and transparently report the analysis and findings;
- Consider and transparently explain EPA's evaluation of the HRCT-based studies and assessment cited herein (Exhibit 23) and perform an additional weight-of-evidence evaluation or systematic accounting for the evidence furnished by this HRCT-based literature; and
- Thoroughly and transparently discuss key literature, including but not limited to each of the reports cited in Section III.A. of the main text (by the American Thoracic Society, the British Thoracic Society, the American College of Chest Physicians and the British Industrial Injuries Advisory Council, and ATSDR), and openly identify and apply a methodology for reconciling any inconsistencies in the literature.

B. *Heightened Substantive Standards: The Draft Assessment Does Not Reflect a Rigorous "Weight-of-Evidence" Approach Evaluating All Relevant Studies*

Overview: The Draft Assessment selected the RfC critical effect without applying a "weight-of-evidence" approach to evaluating evidence.

Requested Corrective Action:

- Perform a rigorous weight-of-evidence evaluation, consistent with EPA's IQA Guidelines, EPA's January 30, 2013 representations to the NRC, and its IRIS and other guidance, to assess and determine the RfC critical effect;
- At minimum, ensure that the Agency's evaluation follows the IQA requirement for "careful consideration of all [relevant] information, . . . in an integrative assessment that takes into account the kinds of evidence available, quality and quantity of the evidence, the strengths and limitations associated of [sic] each type of evidence, and [that] explains how the various types of evidence fit together";

- Conduct its evaluation so as to address: i) the strength of the relationship between the exposure and response and the presence of a dose-response relationship; ii) the specificity of the response to chemical exposure and whether the exposure precedes the effect; iii) consistency of the association between the chemical exposure and response; and iv) biological plausibility of the response or effect; and
- Disclose the weight-of-evidence evaluation, explaining the results and how the evidence from the literature is integrated in an unbiased manner.

C. *Heightened Substantive Standards: The Draft Assessment Otherwise Fails to Reflect Best Available, Peer-Reviewed Science And Supporting Studies Conducted in Accordance With Sound and Objective Scientific Practices*

Overview: The Draft Assessment fails to apply best available science and sound and objective scientific practices identified by NAS and EPA.

Requested Corrective Action:

- Implement the April 2011 Formaldehyde Peer Review Report “Chapter 7” IRIS recommendations as “best available science” and “sound and objective scientific practices”;
- For those IRIS reforms that EPA has instituted for other ongoing draft IRIS assessments, either implement these reforms for this IRIS assessment or explain why the reforms do not represent “best available science” or “sound and objective scientific practices”;
- Apply EPA relevant IRIS and RfC guidance, including the examples provided in Sections III.A.1 a. and b. of this petition and elsewhere herein;
- Identify existing EPA guidance that addresses the subject matter of the NAS Formaldehyde Peer Review Report recommendations and apply relevant and appropriate guidance to implement those recommendations; and
- To enhance the transparency of this effort, identify (i) the guidance EPA reviewed, (ii) whether the Agency considered that guidance relevant and appropriate to address the NAS recommendations, (iii) if so, how it applied that guidance in evaluating and presenting to the public the toxicity of LAA, and (iv) if EPA concludes that any such guidance does not represent “best available science” or “sound and objective scientific practice,” and should not be followed, objective scientific reasons for this decision.

D. *Heightened Process Standards: Certain Methods and Data Underlying the Draft Assessment Have Not Been Made Available to Provide for the High Degree of Transparency and Reproducibility Required by the IQA Guidelines*

Overview: EPA has failed to provide to the public data and methods relevant to EPA’s conclusions in the Draft Assessment, thereby depriving interested parties of the opportunity to determine if the conclusions in the Draft Assessment are scientifically sound.

Requested Corrective Action:

- Transparently identify how conflicting study results have been reconciled and the analytical method for selection of LPT as the critical effect;

- Make available to the public in a useful and complete format (de-identified to protect the privacy of individuals), all government-funded data created or used to evaluate the very issues addressed by the Draft Assessment, such as the updated Marysville, OH data;
- Provide an explanation of the significance of these data (including the updated Marysville, OH and ATSDR Libby Data) and how they are being used by the Agency, or why they are not relied upon by the Agency;
- If the Agency is relying upon studies that use the ATSDR Libby Data, disclose EPA's understanding of the errors in the database (such as the 27% error rate described in Exhibit 8, inadequate accounting of pleural fat in the Box 4.D. data field, and any other sources of error), and present information regarding EPA's assessment of the quality of studies that rely upon these data;
- Provide a reasonable opportunity for public analysis of this information;
- Provide a reasonable opportunity for public comment on these data and the reproducibility of EPA's analysis of these data; and
- Provide a transparent, objective, and thorough response to such public comments.

E. *Heightened Process Standards: The Draft Assessment Lacks a Meaningful Discussion of the Population Likely to be Affected by the Assessment*

Overview: Although the Draft Assessment focuses on LAA, no support has been provided for any position that this Assessment cannot or will not be applied broadly to other asbestos.

Requested Corrective Action:

- Address whether the RfC proposed would have implications for populations exposed to asbestos minerals other than LAA and, if not, why not; and
- Explain the various populations who may be affected by the assessment, including populations exposed to other forms of asbestos whose toxicity is likely to be comparable to that of LAA.

F. *Heightened Process Standards: The Draft Assessment Does Not Address the Expected "Central Tendency" Risks to Affected Populations*

Overview: The Draft Assessment made no attempt to discuss the expected risk or central tendency estimate of cancer and noncancer toxicities from exposure to LAA, even though EPA views such "central tendency" estimates as useful in deciding whether to remediate very low levels of contaminants.

Requested Corrective Action:

- Determine and issue an expected risk or central tendency estimate of cancer and noncancer toxicities from exposure to LAA, and discuss the implications of this information on the usefulness and applicability of the assessment results.

G. *Heightened Process Standards: The Draft Assessment Fails to Set Forth Upper and Lower Bound Estimates of Expected LAA Hazards to Affected Populations*

Overview: The Assessment lacks any clear discussion of the upper and lower bound estimates of hazards that would support remediation decisions for LAA and like amphiboles.

Requested Corrective Action:

- Develop and disseminate upper and lower bound hazard assessments of cancer and noncancer toxicities from exposure to LAA, and discuss the implications of this information on the usefulness and applicability of the assessment results.

H. *Heightened Process Standards: The Draft Assessment Fails to Identify Each Significant Uncertainty Associated With It and Studies That Would Help Resolve Those Uncertainties*

Overview: The Draft Assessment does not identify uncertainties associated with its choices of critical effect, subcohorts, and models, or identify studies that may resolve those uncertainties.

Requested Corrective Action:

- Conduct an integrated and comprehensive qualitative and quantitative uncertainty analysis;
- Evaluate and discuss the likely impact of each significant uncertainty, including, but not limited to, the uncertainty associated with EPA's choice of data sets, models, and LPT as a critical effect; and
- Explain what studies would help resolve those uncertainties.

SECTION 5 OF THE IQA REQUEST FOR CORRECTION: THE DRAFT ASSESSMENT DOES NOT MEET THE IQA "UTILITY" STANDARD

Overview: The Draft Assessment deprives risk managers and other affected parties of information they need to evaluate the likely range of human health risks posed by asbestos concentrations in the environment by failing to reflect the range of uncertainty associated with EPA's assessment. Also, because the noncancer toxicity value in the Draft Assessment is below background levels, it will likely confuse and complicate risk management decisions and leaves the public at a loss as to how to use the assessment to determine if background levels to which the public is routinely exposed are safe. Finally, the RfC requires conversion of TEM data to PCM, though the correlation between the two is poor and the conversion is not yet developed, yielding undue variability, uncertainty, and additional confusion as sampling, remediation, and risk management decisions are made.

Requested Corrective Action:

- Implement above requests (in Section IV. H of the main text) to calculate and explain the basis for the range of uncertainty associated with the proposed toxicity values;
- Explain EPA's analysis and conclusions regarding whether the LAA toxicity values are relevant for evaluating risks posed by other forms of amphibole asbestos that have compositions and characteristics comparable to that of LAA;

- Scientifically assess background levels of LPT and whether toxicity values at or below background levels of asbestos are scientifically sound, and identify whether there is any evidence of adverse human health effects from chronic exposure to levels at or approaching background at urban and rural locations throughout the United States;
- Explain how users should employ the Draft Assessment to make risk management decisions, and how they should communicate the level of risk present, when amphibole asbestos levels exceed the IRIS toxicity value but are below background;
- Explain how toxicity values in the Draft Assessment at or below typical background levels are useful in risk assessment given the difficulty in determining whether levels of LAA and like asbestos are the result of anthropogenic activities or are instead natural occurrences, and whether this determination informs remediation decisions;
- Identify how the public is to use the toxicity values in the Draft Assessment to determine whether the background levels of LAA to which various members of the public are routinely exposed are safe; and
- Identify how conversion from TEM to PCM measurements should be performed, what information needs to be collected to assess the accuracy of the conversion, and the uncertainty associated with this conversion.

GENERAL REQUESTS:

- Promptly remove the Draft Assessment and all related information from EPA's IRIS website and other Agency public dissemination sources, and notify the public that EPA is doing so;
- Promptly advise federal, state, and municipal risk managers not to rely on the Draft Assessment or the toxicity values proposed therein; and
- Refrain from disseminating a further LAA IRIS assessment, whether draft or final, or other information related to LAA cancer or noncancer toxicity, until:
 - The described IQA deficiencies have been corrected;
 - EPA provides a detailed and thorough response to the SAB peer review and public comments submitted on the Draft Assessment; and
 - EPA implements for the Draft Assessment the NAS recommendations set forth in Chapter 7 of the NAS Formaldehyde Peer Review Report and the current IRIS reforms that EPA is implementing for other ongoing IRIS assessments.