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February 26, 2014

VIA HAND DELIVERY

Information Quality Guidelines Staff
Ronald Reagan Building
Room M1200
U.S. Environmental Protection Agency
1300 Pennsylvania Avenue, N.W.
Washington, DC 20460

Re: Information Quality Act Request for Correction Regarding the Libby Amphibole Asbestos IRIS Assessment

Dear Sir or Madam:

This Request for Correction regarding the August 2011 External Review Draft "Toxicological Review of Libby Amphibole Asbestos In Support of Summary Information on the Integrated Risk Information System," EPA/635/R-11/002A, is submitted pursuant to the Information Quality Act guidelines of the Office of Management and Budget and the U.S. Environmental Protection Agency. An electronic copy of this petition, together with all its appendices, is enclosed for your convenience.

Questions related to this Request for Correction and responses hereto may be directed to the undersigned.

Sincerely yours,

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On behalf of Requester W.R. Grace & Co.-Conn.

cc: Kenneth Olden, Director, NCEA, EPA
Vincent Cogliano, Director, IRIS Program, NCEA, EPA
David Bussard, Director, Washington Division, NCEA, EPA

Enclosures:

Information Quality Act Request for Correction Regarding the Libby Amphibole Asbestos IRIS Assessment

Appendix A - Summary of Information Quality Act Requests for Correction Regarding the Libby Amphibole Asbestos IRIS Assessment

Appendix B - Select Comments to EPA's Science Advisory Board Incorporated by Reference Into Information Quality Act Requests For Correction

Appendix C - Exhibits Incorporated by Reference Into Information Quality Act Requests for Correction

INFORMATION QUALITY ACT REQUEST FOR CORRECTION

REGARDING THE LIBBY AMPHIBOLE ASBESTOS IRIS ASSESSMENT

February 26, 2014

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INFORMATION QUALITY ACT REQUEST FOR CORRECTION

REGARDING THE LIBBY AMPHIBOLE ASBESTOS IRIS ASSESSMENT

Submitted to U.S. Environmental Protection Agency Information Quality Guidelines Staff

February 26, 2014

INTRODUCTION

This Request for Correction regarding the August 2011 External Review Draft "Toxicological Review of Libby Amphibole Asbestos In Support of Summary Information on the Integrated Risk Information System ("IRIS")," EPA/635/R-11/002A ("Draft Assessment"), is submitted pursuant to the Information Quality Act ("IQA") guidelines of the Office of Management and Budget ("OMB")[1] and the U.S. Environmental Protection Agency ("EPA" or the "Agency")[2] (collectively, the "IQA Guidelines"). For the reasons set forth in this request, the Draft Assessment fails to comport with a number of the objectivity and utility information quality standards in the IQA Guidelines. Given the pervasive nature of these deficiencies that call into question the scientific validity of the Draft Assessment, and the likely significant impact on public and private resources if the Draft Assessment continues to be disseminated in this or a similar form, we request that the Draft Assessment be removed from the Agency's IRIS website and not be further disseminated or used in its current or a revised form until the fundamental shortcomings identified herein have been corrected. As set forth in Section VI of this Request for Correction and consistent with the EPA Guidelines, we seek a response to this request no later than when EPA responds to peer review and public comments on the Draft Assessment.

[1] Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies; Republication, 67 Fed. Reg. 8452 (Feb. 22, 2002) ("OMB Guidelines") (Exhibit 1).

[2] Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency, EPA, EPA/260R-02-008 October 2002 ("EPA Guidelines") (Excerpts at Exhibit 2).

EXECUTIVE SUMMARY

EPA's Draft Assessment, broadly disseminated[3] by EPA in August 2011 for public and peer review, proposes both cancer and noncancer IRIS toxicity values for Libby Amphibole Asbestos ("LAA"). EPA describes IRIS as:

> a human health assessment program that evaluates information on health effects that may result from exposure to environmental contaminants. Through the IRIS Program, EPA provides ***the highest quality science-based human health assessments*** to support the Agency's regulatory activities.[4]

IRIS assessments are relied upon for risk evaluations and other purposes by local, state and federal governments, as well as private entities throughout the country, making the quality of this information especially important.

EPA's LAA Draft Assessment falls well short of the "highest quality" because it reflects significant scientific methodological flaws. It also fails to meet the important standards that EPA has set for itself to ensure the quality of influential scientific information that the Agency disseminates. Key flaws include: 1) a noncancer draft toxicity value based on an effect that has not been demonstrated to be toxic, or "adverse"; and 2) toxicity calculations (cancer and noncancer) characterized by underlying database weakness, confounders, unsound modeling choices, missing or insufficient analytical steps, and insufficient transparency. As a result of these shortcomings, the Draft Assessment is not scientifically sound and does not disseminate information that "maximizes" quality, as required by the IQA. Through this request for

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[3] As stated by OMB, "dissemination" means "agency initiated or sponsored distribution of information to the public," or "essentially to share with, or give access to, the public." OMB Guidelines, Preamble, 67 Fed. Reg. at 8454 and § V.8. Neither the OMB nor EPA IQA Guidelines exclude draft IRIS assessments from the definition of "information" or "dissemination" for IQA purposes. In fact, EPA has indicated that any information issued in connection with a "process involving a structured opportunity for public comment on a draft or proposed document before a final document is issued" - including a "draft . . . risk assessment" - has been disseminated and that IQA requests for correction regarding such a draft document will typically be addressed in the public comment process established for that information. See EPA Guidelines § 8.5. Consistent with these IQA Guidelines, EPA stated, in its response to IQA Requests for Correction regarding draft IRIS assessments for arsenic and methanol, that information quality contentions raised in those petitions would be addressed through the IRIS public and peer review comment response process. As further evidence of the Draft Assessment's dissemination, EPA has already sought to apply the draft LAA IRIS toxicity value. See, e.g., Phase V Sampling and Analysis Plan for Operable Unit 3, Libby Asbestos Superfund Site, Working Draft, March 20, 2012, p. 49 (Excerpts at Exhibit 28).

Accordingly, the Draft Assessment has been disseminated within the meaning of the IQA Guidelines and EPA's form disclaimer language on the cover page of the document asserting that the document "has not been formally disseminated" is inconsistent with those Guidelines. The same cover page disclaimer was present on the aforementioned arsenic and methanol draft IRIS assessments and yet in each case EPA considered the IQA petitions filed. However, even if EPA were to assert that this one draft LAA IRIS assessment has not been "disseminated," the IQA Guidelines would still call for EPA's careful and cogent evaluation of, and response to, the IQA contentions set forth in this petition. See EPA Guidelines, §§ 2.2, 7.1 (indicating that EPA will incorporate the information quality principles of its IQA Guidelines into its pre-dissemination review procedures to provide additional assurances that the information the Agency disseminates is consistent with its Guidelines).

[4] EPA website, *available at* http://www.epa.gov/IRIS/ (emphasis added) (Exhibit 3).

correction, the Agency is urged to satisfy its own standards and thereby improve the quality of the information contained in the Draft Assessment.

This request for correction specifies deficiencies under each of the relevant IQA standards. Sections I and II of this request provide background information, a summary of the impact of the Draft Assessment, and a short overview of the IQA standards. Section III explains the Draft Assessment's failure to comply with the base objectivity "substantive" and "presentation" standards. In particular, the Draft Assessment is substantively unreliable, inaccurate and biased as a result of the:

- Failure to apply EPA IRIS guidance when selecting pleural plaques, also known as localized pleural thickening ("LPT"), as its noncancer "toxic" or "adverse" critical effect. LPT is a term for non-malignant discrete plaques that can slowly develop on the parietal (outer) lung tissue, and LPT is often viewed as a marker of asbestos exposure. As discussed below, authoritative sources view LPT as asymptomatic and not on a pathway to any functional impairment; consequently, LPT has not been shown to meet EPA's definition of "adverse" or to be upstream of an adverse effect, and cannot serve as the basis for a toxicity assessment;

- Failure to rigorously identify and separately evaluate the relevant scientific literature regarding LPT, and the flawed conflating by EPA of LPT with an entirely distinct condition that in contrast is widely acknowledged to be adverse: the similarly named diffuse pleural thickening ("DPT") and "pleural thickening" of the visceral (inner) lung tissue;

- Reliance on extremely small data sets, rendering the assessment incomplete and biased when calculating toxicity values; and

- Failure to apply sound scientific statistical and modeling methods.

The Draft Assessment fails to meet the base objectivity presentation standards due to the:

- Failure to provide full, accurate, and transparent documentation of data, policies, and models relied upon; and

- Failure to identify the uncertainty and error sources affecting data quality.

Section IV addresses the Draft Assessment's failure to meet the heightened objectivity standards for influential scientific information. The Draft Assessment fails to meet these standards for many of the above reasons and because of the:

- Failure to apply a rigorous "weight-of-evidence" evaluation when selecting the noncancer critical effect;

- Failure to reflect best available science by not applying longstanding EPA methodological guidance and National Academy of Sciences ("NAS")

recommendations deemed by both NAS and EPA to be essential to high quality IRIS assessments; and

- Failure to make available to the public certain methods and data underlying the assessment, thereby unduly limiting data transparency and reproducibility.

As discussed in Section V, the Draft Assessment also fails to meet the IQA "utility" standard because it is not useful for the public, municipalities, or federal or state agency staff that will use the assessment to evaluate and manage risk. Among other things, it:

- Proposes toxicity values below background levels that are of limited usefulness in making risk management decisions and will create public confusion as to what levels of LAA are "safe"; and

- Otherwise fails to provide risk assessors with the transparent and complete information needed to make sound judgments, for instance by not reflecting the range of uncertainty associated with the toxicity of LAA.

Given the fundamental and pervasive nature of these IQA shortcomings and the importance of ensuring the quality of influential scientific information of this nature, EPA should correct the Draft Assessment to conform to the Agency's own IQA Guidelines. The appropriate overarching corrective action under the IQA Guidelines is: (i) prompt notice to the public that the Draft Assessment has been withdrawn pending further review; (ii) prompt removal of the Draft Assessment and related information from EPA's IRIS website and other Agency public dissemination sources; and (iii) no further dissemination of an IRIS assessment for LAA in any form until EPA corrects the deficiencies identified herein.[5]

I. BACKGROUND AND SUMMARY OF IMPACT OF THE LIBBY AMPHIBOLE ASBESTOS DRAFT ASSESSMENT

In its April, 2011 Peer Review Report regarding a draft IRIS assessment of formaldehyde, a panel of the National Research Council ("NRC") of the National Academy of Sciences noted recurring scientific analytical and methodological flaws in EPA's IRIS assessments.[6] Finding this recurring pattern of flaws to be unacceptable as a matter of scientific and information quality, the NAS Formaldehyde Peer Review Report (Chapter 7) issued concrete recommendations for improvement. The NAS also pointedly referenced pre-existing

[5] Precedent exists for this type of correction in response to IQA Requests for Correction regarding other seriously deficient draft IRIS assessments, though based on separate grounds. See, e.g., Feb. 21, 2012 and Oct. 24, 2012 letters from Monica Jones, Director, Quality Staff, Office of Environmental Information, EPA, to Gregory Dolan, Executive Director-Americas/Europe, Methanol Institute (regarding IRIS Toxicological Review of Methanol); and Oct. 24, 2012 letter from Monica Jones, EPA, to Lynn Bergeson, Managing Director, Bergeson & Campbell, P.C. (regarding IRIS Toxicological Review of Inorganic Arsenic) (Exhibit 4).

[6] "Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde," National Research Council of the National Academies, Apr. 2011 ("NAS Formaldehyde Peer Review Report") (Excerpts at Exhibit 5).

Agency guidance that EPA had been failing to apply rigorously to its IRIS assessments, and that could be used immediately to remedy fundamental scientific shortcomings.

In August 2011, without applying the NAS recommendations that EPA subsequently embraced, EPA disseminated the LAA Draft Assessment. In addition to ignoring the NAS recommendations now being applied by the Agency to other ongoing IRIS assessments, the LAA Assessment does not address comments by federal agencies[7] and fails to apply key EPA IRIS guidance and IQA Guidelines. EPA nonetheless has moved forward with the flawed Draft Assessment. By the end of December 2011, EPA had formed and issued charge questions to a Science Advisory Board ("SAB") panel to conduct peer review of the Draft Assessment. Peer review formally commenced in February 2012, yielding a first draft report in two months and a completed SAB report in January 2013. The SAB report recommended that EPA conduct substantial additional analysis and modeling. However, that report failed to address fundamental information quality flaws. Despite its significant scientific and IQA shortcomings, the Draft Assessment remains in the public domain today.

As noted above, EPA has committed to providing "***the highest quality science-based human health assessments"*** to support its activities.[8] Clearly EPA intends to rely upon the results of this particular toxicity assessment.[9] Impacts from the LAA Draft Assessment will broadly extend beyond EPA to other governmental agencies and to members of the public who will rely upon this assessment in making risk assessment and risk management decisions[10] about LAA and, in all likelihood, other forms of asbestos.[11] However, the ramifications are broader still. At issue are the integrity of EPA's IRIS program and the public's confidence that the Agency will objectively consider and weigh all relevant data, apply its controlling guidance, transparently reveal information, and apply the best available science to generate information of the "highest quality."

Correction of IQA deficiencies in the Draft Assessment is an important matter of public policy for the following reasons as well:

- The Draft Assessment's choice of LPT as the "adverse effect" (or "critical effect") for noncancer toxicity value ("reference concentration" or "RfC") derivation will cause confusion, because EPA's choice conflicts with scientific and medical

[7] See Elizabeth Anderson, Comments on the EPA Document, "Draft Toxicological Review of Libby Amphibole Asbestos" Feb. 7, 2012, p. 5 (App. B) (summarizing the types of comments from ATSDR, DOD, OMB, and NIEHS to EPA that mirror scientific concerns discussed in this petition).

[8] EPA Website, *available at* http://www.epa.gov/IRIS/ (emphasis added) (Exhibit 3).

[9] Draft Assessment, pp. 1-1 thru 1-4 (Excerpts at Exhibit 6).

[10] IRIS assessments are used in a number of ways, including in the first two steps of the multi-step risk assessment process: 1) identification of whether there is a hazard, and 2) assessing potential health problems at different exposures. A short summary of that process is found at http://www.epa.gov/risk/health-risk.htm and http://epa.gov/riskassessment/basicinformation.htm#arisk (Exhibit 7).

[11] The components of LAA are not specific to LAA but instead similar amphiboles naturally are found in other locations. See footnote 13 and Section IV.E, below.

literature that treats LPT as non-impairing and at most is inconclusive as to whether LPT might be adverse. Moreover, if EPA selects LPT as adverse "in itself" (without a showing of any impairment from LPT), EPA would establish a controversial precedent that could also drive future IRIS assessments to be based on markers of exposure that lack any adverse effect.

- The proposed RfC of 0.00002 fibers per cubic centimeter ("f/cc") is at or below ambient background levels of asbestos.[12] Amphiboles are ubiquitous, composing about 5% of the Earth's crust and appearing in 13% of U.S. soil samples.[13] Setting a toxicity value at or below background levels that have caused no demonstrable adverse effects calls into question the value's accuracy. Unless the value is accurate, the RfC will cause confusion as to whether background levels in communities are safe, and could misinform decisions on how to allocate scarce resources in rural and urban locations nationwide for completed and future remedial activities.[14]

- The Draft Assessment creates the first noncancer toxicity value for a mineral fiber, and its methodologies may be applied to other fiber toxicity assessments.

Application of the best available science and compliance with the other IQA standards should help ensure that these important policy questions are addressed in a scientifically defensible manner and instill confidence in the scientific integrity of IRIS decision-making.

II. OVERVIEW OF THE INFORMATION QUALITY ACT

The Information Quality Act requires OMB and EPA to establish information quality guidelines "for ***ensuring and maximizing the quality, objectivity, utility, and integrity of***

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[12] SRC, Inc., Denver, CO, "Summary of Published Measurements of Asbestos Levels in Ambient Air." pp. 3-4, 6 and 9 (2013) (prepared for USEPA Region 8) ("Average concentrations in outdoor ambient air tend to range between about 1E-05 and 4E-04 f/cc > 5 um, with an overall mean of about 1E-05 to 3E-05 f/cc > 5 um. In general, concentrations in rural and remote areas tend to be lower than urban areas"); Lee, R.J.; Van Orden, D.R. "Airborne asbestos in buildings," Regul. Toxicol. Pharmacol. 50:218-225 (2008); Agency for Toxic Substances and Disease Registry (ATSDR), Atlanta: U.S. Department of Health and Human Services, Public Health Service, "Toxicological Profile for Asbestos." p. 149 (2001).

[13] Thompson, BD; Gunter, ME; Wilson, MA, (2011). Amphibole asbestos soil contamination in the U.S.A.: A matter of definition. Am. Mineralogist, 96: 690–693 ("Thompson, BD, 2011"); Blum, D, Landscapes Tainted by Asbestos, N. Y. Times, Jan. 17, 2014, http://well.blogs.nytimes.com/2014/01/17/landscapes-tainted-by-asbestos/? (example of press discussing widespread presence of natural asbestos fibers and citing information from New York and California, and a recent study of naturally occurring asbestos similar to LAA in Nevada about which authors cautioned that risk associated with any land use projects should be assessed: Buck, BJ, et al. (2013). Naturally Occurring Asbestos: Potential for Human Exposure, Southern Nevada, USA, Soi Sci. Soc.Am. J., 77:2192-2204).

[14] Elizabeth Anderson, Comments on the EPA Draft Risk Assessment For Libby Amphibole, Apr. 9, 2012, p. 3 ("E. Anderson, Apr. 9, 2012") (App. B) ("From a practical standpoint, the resulting non-cancer RfC, 0.00002 f/cc, is so low that use of this level will frustrate cleanup efforts and confuse the public. This is because distinguishing the incremental contribution of the source contamination over background will be difficult, time consuming and costly.").

information . . . disseminated by Federal agencies."[15] It further requires that the guidelines provide "administrative mechanisms allowing affected persons to seek and obtain correction of information maintained and disseminated by the agency that does not comply with the guidelines…."[16]

The resulting IQA standards established by OMB impose both "substantive" and "presentation" requirements, and set more rigorous standards for "influential scientific information" such as EPA IRIS assessments. EPA's IQA Guidelines expand on the OMB Guidelines in a number of ways, including to require scientific determinations (such as hazard assessments) to apply "careful consideration of all [relevant] information" under a weight-of-evidence approach.[17] Both the OMB and EPA Guidelines are binding on the Agency.[18]

A. The Base "Objectivity" and "Utility" Standards

The IQA Guidelines require that information disseminated by EPA meet base standards of "objectivity" and "utility" to ensure that information is accurate, reliable, and unbiased. The IQA base "objectivity" standard has both a "substantive" and "presentation" component. The substantive component requires that information be substantively accurate, reliable, and unbiased and be generated by sound statistical and research methods. The utility component requires that information be useful for the intended users, including the public, and that it be presented in a clear, complete, accurate, and unbiased manner. Supporting data and potential sources of error also must be transparent so that the public can assess for itself the objectivity of the sources and resulting information.[19]

B. Heightened IQA Standards for Influential Scientific Information

In addition to the base standards, IRIS assessments are subject to the heightened and more rigorous objectivity standards for "influential scientific information."[20] For example, the relevant heightened "substantive" standards require where practicable the use of best available peer-reviewed science and a weight-of-evidence approach that considers all relevant

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[15] Treasury and General Government Appropriations Act for Fiscal Year 2001, Public Law 106–554, H.R. 5658, Section 515(a) (Exhibit 9).

[16] *Id.* at (b)2(B).

[17] EPA Guidelines, p. 26.

[18] See *Prime Time Int'l Co. v. Vilsack*, 599 F.3d 678, 685 (D.C. Cir. 2010).

[19] See, e.g., OMB Guidelines, § V.2; EPA Guidelines, § 5.1.

[20] "Influential scientific information" includes information whose dissemination does or will have a clear and substantial impact on important public policies or important private sector decisions. OMB Guidelines, § V.9; EPA Guidelines, §§ 6.2, 6.3. EPA has categorically identified as "influential scientific" information those "[m]ajor work products undergoing peer review as called for under the Agency's Peer Review Policy," i.e., those scientific work products that have a major impact and/or involve precedential, novel, and/or controversial issues and are subjected to external peer review. EPA Guidelines, § 6.2. The Draft Assessment clearly meets this definition. *See, e.g., id*., Appendix A, § A.3.4 at 44 (providing the example of "IRIS Documentation: Reference Dose for Methylmercury" as a major peer-reviewed work product constituting influential scientific information).

information and its quality. In addition, EPA must follow its own agency guidance relating to hazard and risk assessments.[21] Also under these heightened standards, in order to ensure that information on human health hazards is "comprehensive, informative and understandable," EPA is to specify: (i) the expected risk or central estimate of human health risk for the specific populations affected, (ii) each appropriate upper-bound or lower-bound estimate of risk, (iii) each significant uncertainty identified in assessing the risk, together with studies that would assist in resolving all such uncertainties, and (iv) peer-reviewed studies known to EPA that support, are directly relevant to, or *fail to support* any estimate of risk disseminated, and (v) the methodology used to reconcile inconsistencies in the scientific data.[22] The relevant heightened "process" standards require a high degree of transparency to facilitate reproducibility of the information by third parties.[23]

As the EPA Administrator recently attested, environmental decisions "must be grounded, at a most fundamental level, in sound, high quality, transparent science . . . conducted in ways that are . . . free from bias, . . . and of the highest quality, integrity, and credibility." She noted as well that "a strong, scientifically rigorous IRIS program is of critical importance." If those ends are to be achieved, then IRIS assessments must adhere to the EPA Guidelines that set out EPA's own standards for transparent, unbiased, and high quality scientific information.[24]

III. THE DRAFT ASSESSMENT FAILS TO MEET THE BASE IQA OBJECTIVITY STANDARDS

The Draft Assessment fails to meet the base substantive IQA element for its inaccurate, unreliable, and biased choice of the noncancer critical effect (Section IIIA.1), its undue reliance on severely restricted subcohorts (Section IIIA.2), and its failure to use sound statistical methods through flawed modeling (Section IIIB). It also falls short of the presentation element because the Draft Assessment is incomplete and inaccurate, lacks transparency, and is biased (Section IIIC). For a presentation consistent with the IQA Guidelines, EPA should identify and quantify the potential sources of error in its selection of the critical endpoint, reassess and explain clearly its determinations as to whether that endpoint is truly adverse and has a causal relationship with the asserted symptoms, and provide the scientific basis for its ultimate choice of models.[25]

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[21] EPA has bound itself to implement its IQA Guidelines "in conjunction with [its] existing guidelines and policies," including those for dissemination of comprehensive scientific assessments of potential health risks, such as the Draft Assessment. EPA Guidelines, §§ 4 at 10, 6.4 at 23.

[22] OMB Guidelines, § V.3.b.ii.C, Preamble, 67 Fed. Reg. at 8457-58; EPA Guidelines, § 6.4.

[23] OMB Guidelines, § V.3.b.ii; EPA Guidelines, § 6.3. *See also* OMB Guidelines, Preamble, 67 Fed. Reg. at 8455-57.

[24] Testimony of EPA Administrator McCarthy Before the House Committee on Science, Space, and Technology, Nov. 14, 2013 (Exhibit 10).

[25] See, e.g., OMB Guidelines, §§ V.3.a, b; EPA Guidelines, § 5.1.

A. 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 LPT as the Critical Effect is Unreliable, Inaccurate, and Biased

The scientific foundation of the RfC is selection of an "adverse effect" to serve as the "critical effect" for all subsequent analyses.[26] In the Draft Assessment, this foundational analysis conflicts with longstanding EPA IRIS guidance, has unexplained inconsistencies, and conflicts with the scientific and medical consensus. These flaws violate IQA requirements that the Agency only distribute information that is reliable, accurate and unbiased.

The Draft Assessment selected LPT as "adverse" on the basis of the assertion that it "is an irreversible pathological change associated with constricting chest pain, dyspnea, and decreased pulmonary function."[27] The Draft Assessment fails to provide scientific support for these assertions because it: (a) lacks a demonstration that LPT is adverse as defined by EPA's own guidance; (b) fails to demonstrate a "causal" association 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.

a. The Draft Assessment Does Not Satisfy EPA's Own Definition of Adverse Effect and, as a Result, Fails to Meet the Agency's IQA Commitment to Apply Its IRIS Policies and Procedures to Ensure and Maximize Quality

Despite the IQA commitment to do so, the Draft Assessment does not apply EPA's own policies regarding selection of a critical effect for derivation of an RfC. EPA has bound itself to implement its IQA Guidelines "in conjunction with [its] existing guidelines and policies."[28]

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[26] *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry, EPA,* EPA/600/8-90/066F, Oct. 1994, p. xxvii (glossary) and p. 1-5 ("RfC Derivation Methodology, EPA 1994") (Exhibit 11) (determination of the "critical effect represents the first scientific evaluation required by the RfC dose-response assessment").

[27] Draft Assessment, Section 6.2.1, citing Section 5.2.1.4 (Exhibit 6). However, EPA's actual discussion of this point is in Section 5.2.2.3.

[28] EPA Guidelines, §§ 4, 4.7, 4.8, 4.9, 6.4. EPA has also reaffirmed its "commitment to [its] existing policies and procedures that ensure and maximize quality" and stated that it "will continue to work to ensure that our many policies and procedures are appropriately implemented." EPA's hazard identification and policies for toxicity assessment are among those that EPA committed to follow under the EPA IQA Guidelines. *See also* Risk Characterization Policy and Handbook, 100-B-00-002, Washington, DC: U.S. EPA Dec. 2000 (Incorporating information quality principles into EPA's risk assessment procedures). In addition to EPA's obligation under the "base" IQA Guidelines to follow its own relevant policies, the "heightened" IQA Guidelines for influential scientific information also mandate that EPA do so.

This section discusses EPA policy concerning the definition of the critical effect and several ways that the Draft Assessment's analysis fails to implement EPA policy.

For an IRIS toxicity assessment, EPA's prerequisite to selecting a "critical effect" is that it must be toxic or "adverse."[29] EPA defines an "adverse effect" as "[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."[30] As further explained by EPA, an "adverse effect" is more than a physical change and requires biological significance such that it:

> is likely to ***impair*** the performance or ***reduce the ability*** of an individual ***to function*** or to respond to additional challenge from the agent. Biological significance is also attributed to effects that are consistent with steps in a known mode of action. Statistical significance quantifies the likelihood that the observed effect is not due to chance alone. Precedence is given to biological significance, and a ***statistically significant change that lacks biological significance is not considered an adverse response.***[31]

Consistent with these principles, a structural change or irreversibility is not, by itself, adverse. Likewise a biomarker of exposure is not enough. Instead, there must be a showing that any change likely is accompanied by or results in functional impairment.

For respiratory tract effects in humans, EPA guidance more specifically describes how to apply these principles. Adverse respiratory health effects are:

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[29] RfC Derivation Methodology, EPA 1994, p. 1-1 ("Noncancer toxicity refers to adverse health effects other than cancer and gene mutations.") and p. xxvii (glossary defining critical effect) (Exhibit 11). At minimum, EPA has required critical effects to be biologically and clearly on the pathway to, or "upstream" of, an established adverse effect. See EPA website describing perchlorate IRIS assessment, http://www.epa.gov/iris/subst/1007.htm. That "upstream" basis for establishing a "critical effect" does not apply to LPT, which is not viewed as on the pathway to other disease. Therefore, the perchlorate IRIS assessment and any similar analysis do not provide precedent for selecting LPT as the LAA critical effect.

[30] Risk Assessment Guidance for Superfund, Volume I: Human Health Evaluation Manual, Part F (Supplemental Guidance for Inhalation Risk Assessment) Final ("EPA RAGS for Inhalation Risk Assessment"), EPA/540/R/070/002 Jan. 2009 at 9, fn.18, *available at* www.epa.gov/oswer/riskassessment/ragsf/pdf/partf_200901_final.pdf (Exhibit 12) (emphasis added).

[31] A Review of the Reference Dose and Reference Concentration Processes, Final Report, EPA/630/P-02/002F, Dec. 2002, at 4-11, *available at* http://www.epa.gov/raf/publications/review-reference-dose.htm (emphasis added) (Exhibit 13). *See also* RfC Derivation Methodology, EPA 1994, pp. 4-13 through 4-15 (Exhibit 11) (illustrating that structural alteration without functional impairment is not adverse: "In some cases, ***structural alteration can occur, but normal function can continue in target tissues with functional reserve such as the lung***, liver, and kidney. Not all tissues demonstrate this high reserve. The central nervous system can compensate to only a limited degree and where the damage occurs is vitally important for the function of the system. Therefore, "focal" damage may be adverse in some but not all target tissues. . . In general, ***effects that may be considered marginal are designated as adverse only to the extent that they are consistent with other structural and functional data suggesting the same toxicity***. For example, altered liver enzymes (statistically out of normal range) would only be considered adverse in context with altered structure (pathology) and liver weight changes.") (emphasis added).

medically significant physiologic or pathologic changes generally evidenced by one or more of the following (American Thoracic Society, 1985):

- ***Interference with the normal activity*** of the affected person or persons
- Episodic ***respiratory illness***
- ***Incapacitating illness***
- Permanent ***respiratory injury*** or
- Progressive ***respiratory dysfunction***.[32]

This list does not include merely a structural change, but instead illustrates that there must be a medically (clinically) significant impairment in order to be an "adverse effect." The list does not allow a biological marker *of exposure* to serve as a stand-alone "effect" for deriving an RfC. Because the respiratory tract is at issue in the Draft Assessment, this guidance applies. Therefore, LPT *cannot* be selected as the critical effect unless the science establishes a likely resulting "medically significant" interference, illness, injury, or dysfunction.

The Draft Assessment fails to satisfy this EPA guidance because the Draft Assessment's analysis reveals that no biological or medically significant impairment was determined for LPT, the selected critical effect. Instead, the language of the Draft Assessment illustrates that the science is, at most, inconclusive in this regard. For this key question of whether LPT is adverse, the Draft Assessment states the following as it sums up various studies:

- "although the ***evidence is mixed***, pleural plaques ***may*** be independently associated with reduced pulmonary function."[33]
- "an independent effect of plaques ***cannot be ruled out*** by these data."[34]
- pleural plaques were "***not statistically correlated*** with decreased pulmonary function."[35]

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[32] RfC Derivation Methodology, EPA 1994, pp. 2-18 to 2-19 (citing the ATS guidelines and adding details in its Appendix D) (Exhibit 11) (emphasis added).

[33] Draft Assessment, Section 5.2.2.3, *Health Effects of Localized Pleural Thickening (LPT) Viewed on Standard Radiographs,* p. 5-20 (emphasis added) (Exhibit 6). The Draft Assessment noted that the relevant studies used the out-of-date guidelines for reading radiographs. This approach calls into question the consistency of what EPA is identifying as LPT because the terminology has changed over time, as discussed below.

[34] *Id.* (referring to Kilburn and Warshaw (1991)) (emphasis added).

[35] *Id.* (citing Swartz et al., 1993; Copley et al., 2001 and appropriately distinguishing between visceral thickening and pleural plaques) (emphasis added).

The Draft Assessment never reconciles these observations with its ultimate unsupported assertion that LPT is adverse. On its face, the Draft Assessment lacks a well-supported determination that the selected critical effect meets the definition of "adverse," a necessary element under EPA guidance. Absent application of the correct standard based on a sufficient evidentiary foundation and reasoned analysis, the Draft Assessment is neither accurate nor reliable.

Moreover the Draft Assessment is unreliable, inaccurate, and biased (and as a result does not satisfy IQA requirements) due to the absence of a weight-of-evidence analysis and significant data gaps. These deficiencies further undermine the reliability of any conclusions as to whether LPT is "adverse" as follows:

- The Draft Assessment never integrates the evidence about LPT across studies to truly assess the strengths and weaknesses of studies. Absent a logical framework for analyzing studies' quality and a weight-of-evidence analysis,[36] the Draft Assessment's conclusions about LPT are unreliable and unclear. Also, a weight-of-evidence analysis explicitly is required under EPA's heightened IQA Guidelines (discussed below).

- The Draft Assessment lacks evaluation of data that specifically address LPT. LPT has been defined in different ways over time, and the definition informs whether a finding on an x-ray will be labeled as LPT or something else. The Draft Assessment ostensibly uses the ILO 2000 Guidelines to define LPT,[37] but it appears that none of the studies relied upon used that ILO 2000 definition. As stated by EPA, ***"[n]o studies*** correlating pulmonary function to radiographic signs of localized pleural thickening (LPT) using the [ILO] Guidelines could be located."[38] The Draft Assessment identifies this major data gap but fails to analyze its implications. It also fails to analyze the extent to which the inconsistent definitions of LPT muddy the analysis of whether LPT is adverse.

Overall, the failure to apply established guidance, the failure to pursue a logical analysis and to acknowledge and reconcile conflicting information, inconsistencies and data gaps, along with other deficiencies described elsewhere in this request, render the Draft Assessment unreliable and inaccurate.

The review of the Draft Assessment by the Science Advisory Board ("SAB") Review Panel did not cure these deficiencies because the SAB failed to apply the correct standard as to

[36] RfC Derivation Methodology, EPA 1994, p. 2-1 (Exhibit 11) (requiring a weight-of-evidence analysis).

[37] As discussed below, the Draft Assessment also incorrectly construes and applies the ILO 2000 Guidelines. See International Labour Office, Geneva, Guidelines for the Use of the ILO International Classification of Radiographs of Pneumoconioses, Revised Ed. 2000 ("ILO 2000"), Section 3.3 (for convenience this request uses the term ILO 2000 to refer to identical ILO 2000 and 2002).

[38] Draft Assessment, Section 5.2.2.3, p. 5-20 (emphasis added) (Exhibit 6).

what is "adverse." On this point alone, the SAB and its Report contained the following analytical deficiencies:

- The SAB Report's key basis for agreeing with the selection of LPT - that it is a physical change[39] - conflicts with EPA guidance on what constitutes an "adverse effect." The SAB Panel's underlying deliberations also reflect the incorrect view that physical change, without demonstrated causation of functional impairment, was enough for a finding of adversity.[40] LPT cannot be "adverse in its own right" under EPA's guidance if it is no more than a marker of exposure.

- Moreover, during deliberations, instead of properly focusing on whether LPT causes clinical impairment, key SAB clinicians discounted their own clinical experience in which LPT is understood as "no big deal" and not "necessarily associated with decreased lung function," departing further from EPA's standard under which the adverse effect must likely have medical significance.[41]

- Little of this confusion or disregard of EPA guidance was revealed in a highly edited final SAB Report. In fact, a key drafter of the LPT section eliminated certain phrases just to avoid a critical review under a 'less is more' principle.[42]

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[39] Science Advisory Board Review of EPA's Draft Assessment entitled *Toxicological Review of Libby Amphibole Asbestos,* Jan. 30, 2013 ("SAB Report"), cover letter and pp. 2, 15 ("LPT is a permanent, structural, pathological alteration of the pleura") (Exhibit 14).

[40] May 1, 2012 transcript of SAB panel, p. 56 (Exhibit 15) ("DR. SALMON: This is Andy Salmon here. I think it's probably worth just putting in a very small side comment to the effect that we are looking at ***these radiographic changes*** as an ***adverse effect in their own right. We are not necessarily arguing whether or not they progress to some other disease entity***. And that it needs to be considered as an adverse in its own right. DR. KANE: I think that is clearly stated but I will make sure that that is clear." (emphasis added)). *See also* June 27, 2012, SAB email (Exhibit 16) (explanation by Dr. Salmon that an observable change "in and of itself" and ***regardless of whether functional changes are observed***" would be an appropriate adverse effect (emphasis added)). See also July 25, 2012 transcript of SAB panel, p. 32-32 (Exhibit 19) (pulmonologist Dr. Redlich agreed with Dr. Salmon that all that is needed is an observable physical change). The SAB panel authors of the LPT portions of the SAB Report clearly did not apply EPA guidance as to what constitutes an "adverse effect."

[41] See July 28, 2012, Dr. Redlich SAB email (Exhibit 17) ("It may be helpful for the EPA to more fully explain RfC version of health effect vs clinical disease. ATS document focused on clinical asbestos-related disease. ***Clinicians / others are so used to reassuring patients that plaques are no big deal, don't affect lung function*** (esp as typically past exposure can't do anything about), that they may need an extra reminder as far as RfC / the public health perspective. It took me a while to remember this after "minimizing" plaques with individual patients for so long.") (emphasis added). *See also* February 6, 2012 transcript of SAB panel, p. 208-209 (Dr. Balmes) (Exhibit 18) (**"**The advantage of diffuse pleural thickening or asbestos[is] is those are clearly linked to decreased lung function ***where localized or pleural thickening has been brought up isn't necessarily associated with decreased lung function***.") (emphasis added). *See also* Exhibit 19 (disregarding importance of both clinical and scientific points of view and focusing only on the physical change).

[42] "I have made some additional minor edits (see attached) mainly deleting a few phrases per the 'less is more' principle, wanting to avoid statements that critics may attack." July 8, 2012, Dr. Redlich SAB email, (Edited Response to Question 2 on Noncancer Health Effects) (Exhibit 16). The SAB panel drafts progressively became more vague regarding the basis for supporting LPT selection. In April 2012, the Draft SAB report, pp. ii, 2, 18

Continued

- To the extent that the SAB Report may appear to base its support for LPT as a critical effect on a relationship with lung decrements, a close reading demonstrates that the SAB Report largely sidesteps any analysis of the issue.

    - The SAB reported a "general" association between LPT and lung decrements, rather than the required causal relationship (see below). A "general" association could refer to merely a weak correlation, not causation.

    - The SAB Report showed that the Draft Assessment's LPT literature review was insufficient, and that "[i]t is important to provide a more detailed review of the literature to support the use of LPT as the appropriate endpoint. . ."[43] But the SAB Report contradicted itself by also endorsing the endpoint selection even absent the vital literature review the SAB sought. This result is illogical.

    - The SAB's own review of the literature was superficial and biased, and therefore unreliable. For instance, the SAB Report selectively cited a portion of an American Thoracic Society ("ATS") Report out of context. When read in full, the ATS Report does not support the SAB's recommendation.[44] Also, it cited a letter to the editor critiquing a study, but failed to consider the response by study authors.[45] Furthermore, the SAB's review missed important studies and cited others that were not relevant.

The SAB Report's review of LPT was unreliable, inaccurate, and biased. It is internally inconsistent, failed to reflect the clinical experience of its pulmonologists, applied the wrong standards in developing its recommendations, and lacked transparency. As a result, SAB Report assertions regarding the selection of LPT as the critical effect should carry no weight in the present IQA review of the Draft Assessment.

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continued
(Exhibit 20) stated that LPT had a "***measurable relationship*** to altered lung function" (emphasis added). This "measurable" language reflected that this relationship was considered minimal, and avoids suggesting biological or clinical significance. The final SAB Report (cover letter and page 2) uses less descriptive language: LPT is "***generally associated*** with reduced lung function." (Exhibit 14) (emphasis added).

[43] SAB Report, pp. 2, 15 (Exhibit 14). Note that the SAB formed its conclusions without the benefit of a weight-of-evidence analysis required by the EPA Guidelines. Though the SAB cited literature, its Report did not reflect review and analysis of the literature, but merely pointed EPA to literature for it to assess.

[44] The cited ATS report observed that the literature does ***not*** yield consistent findings and that lung function "[d]ecrements, when they occur, are probably related to ***early subclinical fibrosis***." (emphasis added). However the SAB report omitted the full ATS conclusion or any reference to the conflicting evidence that the ATS found persuasive when the SAB asserted, "[c]onsistent with that ATS Statement, the SAB concludes that cohort studies have shown significant reduction in lung function, including diminished diffusing capacity and vital capacity associated with LPT." SAB Report, p. 15 (Exhibit 14) (Referencing American Thoracic Society, Diagnosis and Initial Management of Nonmalignant Diseases Related to Asbestos, 170 Am. J. Respir. Crit. Care Med. 691-715 (2004) ("American Thoracic Society, 2004"). This SAB statement is misleading.

[45] Albert Miller, Letter to the Editor, Am. J. Respiratory and Critical Care Med. (2002), Vol. 165, 305-306.

Overall, on this foundational issue of whether the noncancer toxicity assessment is based on a toxic ("adverse") effect as defined by EPA guidance, the Draft Assessment is unreliable and inaccurate, and does not satisfy substantive IQA requirements for objectivity.

b. The Draft Assessment Does Not Find A Causal Relationship Between the Selected Critical Effect and Any Impairment

A causal relationship (not just a general association or correlation) is needed to demonstrate an adverse effect. Under IQA Guidelines EPA must follow its relevant RfC derivation guidance that provides:

> Qualitative evaluation of the data base, also known as the hazard identification component of risk assessment, involves integrating a diverse array of data into a cohesive, biologically plausible toxicity "picture" or weight-of-the-evidence relationship to establish that the agent ***causes*** an effect (or effects) and is of potential human hazard. Questions addressed by this process include whether the agent associated with an effect ***is responsible for the effect***, if the effect is biologically significant, and what the potential public health implications might be. Answering such questions requires ascertaining the validity and meaning of the toxicity data, determining whether the experimental results as a whole suggest or show ***causality between the agent and the effect***, and evaluating whether or not the causal relationship is applicable under other sets of circumstances (e.g., in extrapolating from test animals to humans).[46]

The Draft Assessment selected LPT as "adverse" on the basis of the assertion that it "is an irreversible pathological change ***associated*** with constricting chest pain, dyspnea, and decreased pulmonary function."[47] The Draft Assessment assertion of an "association" and the underlying analysis fail to reflect a determination of the needed causation and therefore is inconsistent with EPA guidance. This is particularly important for an analysis of LPT because some of the underlying literature suggests that, where a statistical correlation between LPT and lung decrements is found, that finding may be due to confounders (and due to something other than LPT).[48] Also, as noted above, the Draft Assessment commented that at least some of the data shows that LPT was "***not statistically correlated with decreased pulmonary function.***"[49] The Draft Assessment should have corrected this analytical deficiency by scrutinizing and weighing the literature and assessing causation as required by EPA guidance. This failure to apply EPA guidance results in inaccuracy and unreliability and allows for bias.

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[46] RfC Derivation Methodology, EPA 1994, p. 2-1 (Exhibit 11) (emphasis added). *See also* NAS Formaldehyde Peer Review Report, pp. 157-159 (Exhibit 5) ("Hazard identification involves answering the question, Does the agent cause the adverse effect?" and reiterating criteria for determining causality).

[47] Draft Assessment, Section 6.2.1, p. 6-10 citing Section 5.2.1.4 (though the correct citation may be Section 5.2.2.3) (Exhibit 6) (emphasis added).

[48] American Thoracic Society, 2004, pp. 691-715 (decrements may be due to early subclinical fibrosis).

[49] Draft Assessment, Section 5.2.2.3, p. 5-21 (Exhibit 6) (emphasis added).

A well-established way to assess causation is by use of the "Hill" factors that look at the strength, consistency, and specificity of an association and other important factors such as biologic plausibility.[50] Applied here, the Hill factors are unlikely to support a finding of "causation" because the Draft Assessment describes "mixed" scientific evidence. The evidence is neither strong nor consistent, as required by the Hill factors. Also, as described above, much of the evidence is not specific to LPT. Regarding the important consideration of "biologic plausibility" under the Hill factors, the Draft Assessment fails to explain how LPT could plausibly cause, or be on a pathway to, impairment.[51] Indeed, no mode of action has been established.[52]

If the exposure to asbestos causes lung decrements, and if the exposure to asbestos causes LPT, hypothetically one might find a correlation between LPT and lung decrements. But this is insufficient to show that LPT itself causes lung decrements.

The SAB Report does not cure this deficiency. On the assertion that LPT is "associated" with lung decrements, the SAB Report points out that it found a "general" association[53] (i.e., a correlation). The SAB did not find or consider causation with regard to whether LPT can serve as a critical effect.[54] Because SAB did not apply EPA guidance that requires causation, the SAB finding of a general association between LPT and lung decrements does not support the selection of LPT as a critical effect.

In sum, the Draft Assessment is inaccurate, unreliable, and incomplete and thus fails to satisfy the IQA Guidelines due to the failure to apply required guidance regarding causation when assessing any relationship between LPT and the asserted impairments.

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[50] EPA Materials Submitted to the National Research Council Part I: Status of Implementation of Recommendations, Jan. 30, 2013 ("EPA Submittal to NRC, Jan. 31, 2013"), Appendix B-5, B-6 (Exhibit 21). This document shows that EPA has had well-established methods for establishing causation.

[51] For example, The British Industrial Injuries Advisory Council found that the "nature and anatomical location of pleural plaques means that they do not alter the structure of the lungs or restrict their expansion." Position Paper 23, Pleural Plaques, p. 5, June 2009, www.iiac.org.uk. See also "Pleural Plaques Information for Health Care Professionals," British Thoracic Society, 2011 ("British Thoracic Society, 2011"), p. 6 ("The fact that plaques are present on the parietal pleura means that they have little effect on lung expansion.").

[52] Draft Assessment, Section 4.5.1.1, pp. 4-71, 4-72, Section 4.5.5, pp. 4-76 thru 4-77, ("the data are not sufficient to establish a mode of action for the pleura-pulmonary effects of exposure to Libby Amphibole asbestos") (Exhibit 6). See E. Anderson, Apr. 9, 2012, pp. 1-2, 5-7 (App. B).

[53] SAB Report, cover letter and p. 2 ("generally associated with reduced lung function") (Exhibit 14).

[54] For example, the following SAB panelist explanation reveals that correlation rather than causation was the focus of the SAB analysis: ". . . [i]t appears that LPT findings are not invariably associated with observable lung function changes, or vice versa: how much of this is due to relative insensitivity and imprecision of these clinical evaluations, or merely to the fact that they are seldom done simultaneously on the same subject, is unclear. However, the risk assessment conclusions are simpler: ***both LPT and lung function changes are separately demonstrable effects of exposure to amphiboles, which may be considered independently in determining dose response relationships for adverse effects***." June 27, 2012, Dr. Salmon SAB email (Exhibit 16) (emphasis added). This description of a correlation (not causation) shows flawed reasoning and inconsistency with EPA guidance.

c. The Draft Assessment Conflates Diffuse Pleural Thickening with Localized Pleural Thickening, Leading to Error, Bias and Inaccuracy

The Draft Assessment's discussion of the literature is also hampered by shifting terminology that merges LPT and a distinctly different structure called "diffuse pleural thickening" or "DPT." LPT rarely occurs anywhere except in the parietal pleura. DPT appears in a different lung tissue (visceral pleura) and, in contrast to LPT, DPT is widely acknowledged to impact lung function.[55] Even so, the Draft Assessment merges discussion of LPT and DPT. This is inaccurate and likely biases the evaluation.[56] The following examples illustrate the merging of DPT into the LPT:

- In its summary of conclusions regarding LPT, the Draft Assessment uses an all-inclusive term ("pleural thickening") that includes DPT: "[p]leural thickening in general is associated with reduced lung function parameters with increased effect correlating with increased severity of the pleural thickening."[57]

- The Draft Assessment then switches terms again, referring to the "visceral thickening" as impairing lung function.[58] Use of the term "visceral thickening" suggests DPT, so the statement is not probative regarding LPT.[59] Indeed, after this confusing statement, the Draft Assessment concedes that the findings for DPT do not apply to LPT or "parietal plaques," stating, "when evaluated independently, parietal plaques [LPT] were ***not statistically correlated with decreased pulmonary function***."[60]

[55] American Thoracic Society, 2004, pp. 691, 707.

[56] Despite the confusing and inaccurate language in the Draft Assessment, EPA has shown that it does understand the difference between LPT and DPT: EPA Presentation, Feb. 5, 2012 (App. B, Slides 7, 11, 12). Also, the EPA bullets on slide 12 of that presentation contain unsupported conclusions, as explained in this petition.

[57] Draft Assessment, Section 5.2.2.3, pp. 5-19, 5-23 (Exhibit 6) (citations omitted).

[58] *Id*. at Section 5.2.2.3, p. 5-21 (Exhibit 6) (emphasis added).

[59] Importantly, the two references cited to support this statement (Schwartz, et al., 1993; Copley et al., 2001) do not use the term "visceral thickening." They use the more commonly used term "diffuse pleural thickening." Diffuse pleural thickening is an abnormality of the visceral pleura (not the parietal pleura) and typically results as a consequence of a previous benign asbestos pleural effusion (BAPE). Thus, by "visceral thickening" EPA is referring to diffuse pleural thickening, and the finding does not pertain to LPT. See, L. Mohr, Clinical Background Information and Comments On Recent Scientific Publications and the Draft EPA Report (Aug. 2011) Pertaining to the Libby Amphibole Asbestos, Apr. 8, 2012, p. 4. ("L. Mohr, Apr. 2012") (App. B).

[60] Draft Assessment, Section 5.2.2.3, p. 5-21 (Exhibit 6) (emphasis added) (as mentioned above, ILO 2000 and ILO 2002 refer to the same guidelines so this petition refers to ILO 2000 for convenience).

- The Draft Assessment asserts that LPT is an umbrella term that includes pleural plaques (LPT) and also a non-classified type of pleural changes akin to DPT,[61] citing the ILO (2000) Guidelines.[62] This assertion is incorrect and biases the analysis. The ILO (2000) Guidelines do not include the non-classified observations in the visceral pleura as "LPT."[63]

- When discussing LPT, the Draft Assessment incorrectly relied upon data that included DPT, such as two studies that the Draft Assessment references as "*somewhat applicable* to the current classification of LPT [citations omitted]."[64]

The Draft Assessment's LPT findings relied on irrelevant and non-probative DPT and visceral pleura data, and the Draft Assessment was inaccurate in how it applied an ILO classification. Because of the merging of the analysis of DPT (with known adverse effects) with LPT (which has not been shown to cause adverse effects), the Draft Assessment's analysis is unreliable, inaccurate, and biased.

d. The Draft Assessment Fails to Identify or Consider Influential and Relevant Scientific Literature Regarding Adversity

The Draft Assessment fails to consider all of the relevant literature.[65] For example, it fails to analyze and weigh the vast majority of important findings that use the most sensitive diagnostic tool, HRCT. The Draft Assessment relies almost solely on studies that use x-rays to identify LPT, even though x-rays cannot identify other lung abnormalities that may affect lung

[61] *Id*. The Draft Assessment refers to "pleural thickening that does not involve blunting of the costophrenic angle." *Id*. at Section 5.2.2.3, p. 5-18 (Exhibit 6). That "thickening" refers to the visceral (inner) rather than parietal (outer) pleura. LPT is ordinarily in the parietal pleura.

[62] *Id*. at Section 5.2.2.3.

[63] ILO 2000, Section 3.3 (using the terms LPT and "pleural plaques" co-extensively and not supporting the Draft Assessment definition). See J. DeSesso, Statement for Public Teleconference for the SAB Review of "Draft Toxicological Review of Libby Amphibole Asbestos" Anatomical Considerations of Localized Pleural Thickenings (Pleural Plaques), May 1, 2012 (App. B) (explaining that ILO 2000 does not have a category for diffuse pleural thickening (in the visceral pleura) without costophrenic angle blunting, and it is incorrect to lump that observation in with LPT). An EPA contractor for the RfC noted in an email of May 30, 2013 that there are really three categories of pleural thickening: LPT, DPT and "other" in the context of addressing the fact that the Rohs data from 1980 does not clearly differentiate between LPT and DPT. (Exhibit 29). EPA has long known that LPT and "diffuse pleural changes occur in different anatomical locations" and that it is not appropriate to combine them. (Exhibit 30).

[64] Draft Assessment, Section 5.2.2.3, p. 5-21 (Exhibit 6) (emphasis added).

[65] See E. Anderson, Apr. 9, 2012, p. 5 (App. B). For example, neither the Draft Assessment nor the SAB Report considered Rui, F; De Zotti, R; Negro, C; Bovenzi, M. 2004. "A follow-up study of lung function among ex-asbestos workers with and without pleural plaques." *Med. Lav.* 95(3):171-179 (lung function differences not related to presence or extent of LPT). Also, an example of recent literature that should be considered is "Chest imaging and lung function impairment after long-term occupational exposure to low concentrations of chrysotile." Spyratos, D; Chloros, D; Haidich, B; Dagdilelis, L; Markou, S; Sichletidis, L. *Arch.of Environ. & Occup. Health,* 2012, 67(2):84-90 ("lung function impairment (TCL and DLco) was related to parenchymal and visceral pleural but not to parietal pleural HRCT abnormalities."). See also next footnote.

function. In a recent analysis of available literature that used HRCT to assess LPT and also evaluated lung function, researchers identified eleven such studies that pre-dated, or were roughly contemporaneous with, the Draft Assessment but that the Draft Assessment fails to consider.[66] These HRCT-based studies, when viewed overall (and when persons who had non-LPT lung abnormalities appropriately were excluded from the analysis), do not show a consistent causal association between LPT and impairment, as discussed more thoroughly below. The SAB Report also failed to fill this gap, mentioning only one of these HRCT-based studies in its recommendations to EPA.

Other important literature cited in the Draft Assessment did not receive objective and full consideration. For instance, it cites an influential American Thoracic Society study but relegates it to a footnote. This important ATS paper concluded that the literature does not show a consistent finding regarding any LPT health impacts, and that "most people with pleural plaques have ***well preserved lung function***." Regarding any asserted association between LPT and lung function decrements, the ATS concludes that they are likely not causally related: "[d]ecrements, when they occur, are probably related to ***early subclinical fibrosis***." [67] In other words, ATS finds that LPT ***probably does not*** cause decrements. The Draft Assessment cites the finding (that reduced lung function "may be reflecting the effects of subradiographic parenchymal changes, rather than a direct effect of DPP"),[68] but drops it into a footnote without analysis. In doing so, the Draft Assessment downplays the ATS paper, resulting in bias.

The Draft Assessment also fails to consider other authoritative sources that, similar to ATS, have concluded that LPT is asymptomatic. For example, the British Thoracic Society has concluded that LPT is "nearly always asymptomatic." This prestigious British body also cautioned that while "[a]sbestos exposure is linked to a number of other conditions that may have serious implications on health [, i]t is important not to confuse these conditions with pleural plaques."[69] Other influential medical and scientific assessments of this issue that the Draft Assessment fails to consider include the following publications.

- The United States Agency for Toxic Substances and Disease Registry (ATSDR) *Public Health Assessment of the Libby Asbestos Site* (April 22, 2010) stated that "[n]o direct causal relationship between pleural abnormalities and asbestos-related

[66] LE Kerper, HN Lynch, LC Mohr, JE Goodman, "Do Asbestos-Induced Pleural Plaques Cause Lung Function Deficits?" Society of Toxicology Poster to be presented in 2014 (Exhibit 23) (an analysis of whether LPT causes lung function deficits based only on studies that used HRCT to diagnose plaques).

[67] American Thoracic Society, 2004, pp. 691-715 (emphasis added). See also L. Mohr, Scientific Review and Professional Commentary Pertaining to the Association Between Asbestos-Related Localized Pleural Thickening (Pleural Plaques) and Lung Infection, Nov. 2, 2012, p. 15 ("L. Mohr, Nov. 2012") (App. B) (discussing ATS Report).

[68] Draft Assessment, Section 5.2.2.3, p. 5-20, fn 28 (Exhibit 6).

[69] British Thoracic Society, 2011, pp. 1 and 5.

diseases has ever been demonstrated" though it speculated about possible associations.[70]

- In the American College of Chest Physicians *Consensus Statement on the Respiratory Health Effects of Asbestos,* a peer-reviewed study, "the experts concluded that the presence of pleural plaques did not decrease lung function to a significant extent." [71]

- The British Industrial Injuries Advisory Council found that the "nature and anatomical location of pleural plaques means that they do not alter the structure of the lungs or restrict their expansion. Therefore, they would not be expected to cause an important degree of impaired lung function or disability; and such studies as we have found and such experts as we have consulted agree that ***losses of lung function are likely to be either small or non-existent***. Some loss may arise coincidentally from minor degrees of underlying lung fibrosis . . . In other words, any increase in risk in those with pleural plaques arises because they ***have been exposed to asbestos***, not because they ***have pleural plaques***." [72]

Accordingly, the Draft Assessment fails to identify and consider all of the relevant literature, including authoritative papers and studies that contradict the Draft Assessment's position, and studies that use the most sensitive radiographic diagnostic tool. As a result, the Draft Assessment provides an inaccurate, unreliable, and biased analysis.

e. The Draft Assessment Fails to Consider Confounders

Despite EPA guidance requiring RfC assessments to consider potential confounders and effect modifiers, [73] the Draft Assessment also fails to consider and account for important

[70] The ATSDR report can be found at: http://www.atsdr.cdc.gov/HAC/pha/PHA.asp?docid=1224&pg=0#. The ATSDR statistical findings conflict with the Draft Assessment's assertions about LPT. See L. Mohr, Nov. 2012, p. 10. (App. B) (summarizing ATSDR findings as showing a very small 1.8% incidence of moderate to severe restriction in breathing capacity and not including LPT (pleural plaques) among the strongest risk factors for restrictive changes in pulmonary function in study participants).

[71] Banks DE, Shi R, McLarty J, et al., American College of Chest Physicians Consensus Statement on the Respiratory Health Effects of Asbestos: Results of a Delphi Study. Chest 2009; 135:1619-1627. *See also* L. Mohr, Nov. 2012, p. 10 (App. B) (discussing conclusion of experts).

[72] Position Paper 23, Pleural Plaques, June 2009, www.iiac.org.uk (italics in the last sentence are in original; other emphasis added), *see also* paragraphs 12 and 65, pages 6 and 27 ("Most authorities hold that pleural plaques rarely cause major symptoms, just as they rarely cause major impairment of lung function. . . Higher quality cohort studies, which allow for exposure history and (for lung cancer) smoking habits, suggest that the increases are a consequence of the degree of exposure to asbestos and that the presence of pleural plaques does not, of itself, independently affect risk levels.").

[73] RfC Derivation Methodology, EPA 1994, pp. 2-15 (Exhibit 11) ("There are essentially three areas of concern in assessing the quality of an epidemiologic study. These involve the design and methodological approaches used for: (1) exposure measures, (2) effect measures, and (3) the control of covariables and confounding variables."), and Appendix B-2 (Criteria for Assessing the Quality of Individual Epidemiological Studies). See EPA Submittal to NRC, Jan. 30, 2013, pp. F-21 through F-24 (Exhibit 21).

confounders identified in the literature and inherent biases that relate to any attempt to diagnose and quantify LPT. Potentially significant confounders in studies of LPT should have been addressed, including the following:

- Subpleural fat deposits can be easily mistaken for pleural plaques (LPT) on lung x-rays, "even by the most astute and experienced radiologists."[74] Even though pleural fat unquestionably can masquerade as pleural plaques on an x-ray, most of the studies relied upon by the Draft Assessment to evaluate pleural plaques rely on x-rays for diagnosis without uniformly addressing the possibility of subpleural fat being mistaken for LPT.[75]

- Some studies rely only on a single measure of pulmonary function that may not provide a reliable parameter for measuring impaired restrictive lung function.[76]

- Some studies may lack required comparisons with reference populations, making them deficient under EPA guidance and not reflective of best available science.[77]

- The Draft Assessment relies upon studies that do not uniformly document and control smoking and obesity (commonly measured by body mass index ("BMI")), pertinent risk factors for pulmonary decrements.

The Draft Assessment fails to address how these limitations apply to studies that it reviewed and how the study results are weighted in light of the limitations. As with the other deficiencies discussed, the SAB Report also failed to consider these important analyses. Unless it considers confounders, the Draft Assessment's evaluation of whether LPT causes adverse

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[74] L. Mohr, Apr. 8, 2012, p. 36 (App. B); Comments for EPA and SAB Regarding Libby Amphibole Asbestos, Dr. Jay Flynn, Apr. 17, 2012, pp. 3-4 (App. B). See also the following footnote, as a number of the authors cited there acknowledge the limitations of radiography.

[75] Examples of studies that relied upon x-rays and that could have failed to distinguish between LPT and fat include the following papers discussed in Dr. Mohr's Apr. 8, 2012 submittal to the SAB (App. B), and a number of the papers discussed in his Nov. 2, 2012 (App. B) submittal to the SAB: (i) Larson TC, Lewin M, Gottschall EB, et al. Associations between radiographic findings and spirometry in a community exposed to Libby amphibole. Occup Environ Med 2012; Published online, Mar. 1, 2012, doi:10.10.1136/oemed-2011-1000316; (ii) Larson TC, Antao VC, Bove FJ, Cusack C. Association between cumulative fiber exposure and respiratory outcomes among Libby vermiculite workers. Journ Occup Environ Med 2012; 54; 56-62; (iii) Rohs AM, Lockey JE, Dunning KK, et al. Low-level fiber-induced radiographic changes caused by Libby vermiculite. A 25-year follow-up study. Am J Respir Crit Care Med 2008; 177: 630-637; (iv) Weill D, Dhillon G, Freyder L, et al. Lung function, radiological changes and exposure: analysis of ATSDR data from Libby, MT, USA. Eur Respir J 2011; 38: 376-383; (v) Lilis, et al. (1991); (vi) Ohlson, et al. (1984); (vii) Jarvolm and Sanden (1986); (viii) Hjortsberg, et al. (1988); (ix) Oliver, et al. (1988); (x) Bourbeau, et al. (1990); and (xi) Schwartz, et al. (1990).

[76] L. Mohr, Nov. 2012, pp. 13-14 (App. B).

[77] RfC Derivation Methodology, EPA 1994, pp. 2-18 (Exhibit 11) ("For studies without internal control groups, reference populations are needed, particularly when evaluating spirometric data [citations omitted]. Each population used to predict 'normal' pulmonary function tests has its own characteristics, which should be considered when used for comparisons.").

health effects is inaccurate, unreliable, and biased, and does not apply best available scientific methods.

f. The Draft Assessment's Assertion That LPT is Associated with Chest Pain and Dyspnea is Likewise Unsupported

The Draft Assessment asserts that "parietal plaques have been associated with constricting pain in the thoracic cavity (Mukherjee et al., 2000; Bourbeau et al., 1990)," hypothesizing that pleural plaques' irregular edges irritate the sensitive parietal pleura. However, the cited studies do not support these assertions.[78] Moreover, the hypothesis of irritation from ragged edges contradicts medical literature that describes pleural plaques as "completely smooth surfaced and flat" or having "small rounded knobs."[79] In sum, there is no support for conjecture that LPT is associated with pain. Likewise, the Draft Assessment provides almost no information on dyspnea. Thus the Draft Assessment's assertions regarding chest pain and dyspnea are unreliable and inaccurate. As with the other errors, it is important that EPA remove from distribution the unsupported assertions that conflict with scientific and medical literature.

g. Requested Corrective Action

For the foregoing reasons, the Draft Assessment's conclusion that LPT is associated with impairment and that it is adverse is inaccurate, unreliable, and biased. Therefore, EPA should not disseminate the Draft Assessment or its conclusion. In order to address the multiple shortcomings underlying the base objectivity (and other) IQA standards as applied to the selection of the RfC critical effect, EPA should:

- Identify all Agency guidance relevant to determining "critical," or "adverse," effects and either apply that guidance or provide a reasoned justification 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;

[78] The cited Mukherjee study actually conflicts with Draft Assessment findings. The Mukherjee study found that non-anginal pain was associated with parenchymal disease only (not with LPT) and anginal pain was a cardiac issue. Thus, "the Mukherjee study results not only fail to support the assertion in the draft report, but actually conflict with the text of the report." J. Flynn, Comments to the SAB Panel, Jan. 27, 2012 (App. B). Likewise, the cited Bourbeau study does not support the Draft Assessment findings regarding pain.

[79] Pathology of Occupational Lung Disease: Andrew Churg, M.D. and Francis H.Y. Green, M.D. 1988, p. 241. Pathology of Asbestos — Associated Diseases: Victor L. Roggli, S. Donald Greenberg and Phillip C. Pratt 1992, p. 169.

- 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;"[80] and (ii) explain precisely the basis for the selection and how the critical effect satisfies EPA guidance;

- If LPT is the selected RfC critical effect, then set forth the reasoned justification for how LPT fully satisfies EPA guidance (including guidance cited herein in footnotes 30, 31 and 32), 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 herein), 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

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

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; 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 Data Sets, Thereby Rendering the Assessment Inaccurate, Unreliable and Biased When Calculating Toxicity Values

After EPA selects the critical effects for the RfC and IUR, a subsequent key decision is selection of the cohort for calculation of the toxicity values. For both its proposed noncancer and cancer values, the Draft Assessment derives its toxicity value from a very limited subset (or subcohort) of available data on workers exposed to LAA. EPA relies on severely and inappropriately restricted data sets that bias and undermine the reliability of the assessment.

a. Noncancer Toxicity Value

The Draft Assessment uses only a selected subcohort of the data from one study (Rohs et al., 2008) to calculate its proposed RfC. The full Rohs data set reports 68 cases of LPT among 280 individuals. The Draft Assessment disregards most of these data for purposes of the RfC calculation and derives its RfC from only **12** cases of LPT (eliminating more than 80% of the cases of LPT). Reliance on such a tiny data set renders a statistically weak conclusion, with little power to detect any confounding influence.[81] The small subcohort also contains little information to support a proper dose-response analysis, resulting in an inaccurate and biased analysis.[82] Finally, the use of such a small subcohort does not allow for (i) the exposure-response relationship to be adjusted for potential confounders such as weight and age (contrary

[81] Suresh Moolgavkar, Comments on the EPA Draft Risk Assessment For Libby Amphibole, Mar. 27, 2012 ("S. Moolgavkar, Mar. 27, 2012") (App. B).

[82] David Hoel and Suresh Moolgavkar, Comments to the SAB on the Panel Recommendations on the EPA Draft Risk Assessment for Libby Amphibole Asbestos, Sept. 18, 2012, pp. 3-4 ("Hoel and Moolgavkar, Sept. 18, 2012") (App. B).

to the Agency's own criteria),[83] or (ii) calculation of the range of uncertainty.[84] The Draft Assessment does not address the vast uncertainty regarding the reliability of the analysis that results from use of the small subcohort. Therefore, use of the small subcohort renders the Draft Assessment unreliable and creates extraordinary potential for bias.

The Draft Assessment concedes that there are disadvantages to discarding most of these data, such as limiting the amount and quality of data analyzed, making it impossible to identify uncertainty in the Draft's toxicity values and precluding consideration of whether better analytical approaches are available.[85] Also, "[a]lternative critical effects were not considered for the sub-cohort analysis given the limited number of cases (one case of DPT and no cases of small opacities)."[86] Thus the deficiencies in the subcohort pushed the Agency to select a scientifically unsupported critical effect, essentially compounding errors. In addition, by precluding informed evaluation and presentation of uncertainty in the toxicity values disseminated, use of the subcohort resulted in further inconsistency with the IQA Guidelines.

Although the Draft Assessment asserts that these subcohort weaknesses could not be prevented because the remaining cohort lacked sufficient exposure information, this attempted justification does not fully or fairly consider the analytical options, available data, or uncertainty. For instance, the Agency has access to non-monitoring data from a variety of plant records and updated exposure estimates that it did not use.[87] Also, the Draft Assessment fails to demonstrate that use of the full cohort (that would afford a bigger sample size, adjustment for confounders and a broader range of exposures) would yield more uncertainty than use of a statistically weak subcohort.[88]

Other issues presented by the subcohort selection are as follows:

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[83] RfC Derivation Methodology, EPA 1994, p. 2-15 (Exhibit 11) ("The study population and study design must adequately address the health effect in question in order to support a risk assessment. [citation omitted] In order to accomplish this goal, the exposure measures must be appropriate and of sufficient quality; the statistical analysis methods must be suitable to the study design and goals; the health effect measures must be reliable and valid; and the covariables and confounding variables need to be controlled or eliminated.").

[84] Hoel and Moolgavkar, Sept. 18, 2012, p. 4 (App. B).

[85] Draft Assessment, Section 5.2.1.3.2 (Exhibit 6).

[86] *Id*. at Section 5.2.3.3.

[87] *Id*. at Sections 5.2.1.3. and 5.2.3.1.

[88] Although it addressed this issue inconsistently, the SAB Report also commented on serious limitations in the analysis associated with use of such a small subcohort as follows: (i) "The SAB recommends additional analyses/cohorts to strengthen and support the RfC since *the size of the Marysville subcohort is small*." (Exec. Summary p. 1 (emphasis added)); (ii) "At a minimum, discuss the possible quantitative uncertainties associated with using the smaller subcohort." (p. 34); (iii) "The small Libby cohort only "*may be* reasonable . . ." (cover letter and p. 3); and (iv) "The SAB notes that in principle it may be preferable to base the RfC on an analysis of incidence rather than prevalence data. Because of the nature of the dataset, the Marysville cohort does not support a direct analysis of incidence. While it may be possible to fit an alternative model derived from integration of a plausible incidence model [citations omitted], this approach will require a number of untestable assumptions, ***particularly given the small size of the Marysville cohort***." pp. 24-25 (Exhibit 14).

- The full Rohs cohort is confounded significantly by age.[89] The Draft Assessment should have rejected the database because of the age confounder, just as the Agency rejected use of a different study on that basis.[90] Instead, the Draft Assessment inaccurately suggests that age is not a confounder.[91] As stated by one commenter, "[s]electing a small subcohort to get around the issue of confounding by age and BMI is not the appropriate way to address this issue."[92]

- Another data limitation concerns the absence of evidence of an association between dose and the probability of LPT for durations of exposure less than 25 years. As the median duration of exposure in the subcohort is only about 25 years, "there is no straight-forward way to estimate an RfC from these data." [93]

- The small subcohort cannot distinguish among models, a limitation that renders model selection unscientific.[94]

- Eliminating all of the older data eliminates data relating to the older workers, which biases the point of departure to a lower number.[95]

There is no question that reliance on a weak database severely limits the power of the analysis and forces the analysis to be conducted with methods inferior to those that could be used with an adequate data set. For the RfC, the use of such a small subcohort is inaccurate and unreliable, and does not protect against bias. This subcohort choice alone potentially introduces so much uncertainty[96] as to make the analysis meaningless and not useful for its intended purposes.

b. Cancer Toxicity Value

For deriving the cancer IUR, the Draft Assessment determines that the most relevant data are from the cohort of Libby vermiculite miners analyzed by Larson et al. (2010a and 2010b). Instead of using this full cohort, however, the Draft Assessment bases its proposed

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[89] Hoel and Moolgavkar, Sept. 18, 2012, p. 4 (App. B); Suresh Moolgavkar, Comments to the SAB on the EPA document EPA/635/R-002A, "Draft Toxicological Review of Libby Amphibole Asbestos", Jan. 27, 2012, pp. 16-18 ("S. Moolgavkar, Jan. 27, 2012") (App. B).

[90] The Agency rejected use of the Amandus study because there was an insufficient exposure response relationship when age was included as a covariate. Draft Assessment, Section 5.2.1.3.2. (Exhibit 6).

[91] *Id*. at 5.2.1.3.2, number 6. The full Rohs data set is confounded by age; selection of a tiny subcohort that does not and cannot have the power to detect age-confounding does not support any conclusion that the confounder is not present.

[92] S. Moolgavkar, Mar. 27, 2012, p. 2 (App. B).

[93] Hoel and Moolgavkar, Sept. 18, 2012, pp. 4-5 (App. B).

[94] *Id*. at p. 4.

[95] *Id*. at pp. 4-5.

[96] See discussions of uncertainty in Section IV.H., below, and other portions of this petition.

cancer IUR on a small, selected subcohort of this study, and thus utilizes only **32** cases of lung cancer deaths (from 111 in the full cohort) and **seven** cases of mesothelioma deaths (from 19 in the full cohort). The SAB recognized deficiencies from not using the full cohort,[97] recommending that EPA should "[e]valuate the feasibility of conducting an ancillary analysis of the full Libby data set, including hires before 1959 . . . At a minimum, discuss the possible quantitative uncertainties associated with using the smaller subcohort."[98]

As with the RfC, the Draft Assessment tries to justify use of small IUR subcohorts on the basis of better exposure data. That rationale ignores the feasibility of estimating exposure and using the full cohort. Moreover, use of the small subcohorts leads to bias. By discarding cancer data from older individuals, where the incidence of lung cancer and mesothelioma would be most common, the Assessment uses a biased data set and cannot detect effect modification by age.[99] As a result of the cohort weakness, the Draft Assessment has not been shown to be accurate, reliable or unbiased in its assessment of cancer toxicity and fails to reflect sound statistical methods.

c. Requested Corrective Action

For the RfC and IUR, in order to address the serious shortcomings resulting from its selective use of data, EPA should:

- 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

[97] As stated by an SAB panelist: "***I do not agree that the use of the subcohort post-1959 for quantification is "reasonable"*** due to the lack of exposure information for many of the workers in earlier years. ***It *may* be reasonable***, but I think it improper to say that it *is* reasonable. At best, it is a modeling choice that some but certainly not all people would make. In my estimation, the ***Agency has not sufficiently explored the question of whether or not the lack, or rather paucity, of exposure data from earlier years invalidates or inhibits inferences. Those statistical questions have not really been asked***. Thus, I cannot "support the selection of the Libby worker cohort" as stated in the bullet's main clause. I have no problem with the rest of the text of the bullet. As a way forward, it might suffice to simply change "is" to "may be" in the third verb of the first sentence. I understand that the explanatory text on this matter persists in the body of the submission. Sorry if this has been much ado about nothing, but the tone of the bullet seemed too much of a whitewash to accept as a reflection of what we had discussed in our meetings." October 12, 2012, Dr. Ferson SAB email (Exhibit 22). The SAB failed to apply the same level of scrutiny to the RfC subcohort, that is just as weak as the IUR subcohort.

[98] SAB Report, p. 34 (Exhibit 14).

[99] S. Moolgavkar, Jan. 27, 2012, pp. 8-15 (App. B) (EPA's Draft Assessment "chose a subcohort for analyses in which effect-modification by age had been eliminated. As a result, the Draft fails to evaluate the critical importance of effect modification thus biasing the IUR for lung cancer.").

- 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

As is evidenced by the attached comments submitted to the SAB on the Draft Assessment's selective use of available data, the Draft Assessment fails to address information central to evaluating and correcting fundamental flaws that violate IQA Guidelines. A final assessment that fails to address these comments would perpetuate an unreliable, inaccurate, and biased dissemination of information in violation of the IQA. In order to correct these deficiencies, EPA should address in full all comments submitted to it and to the SAB.

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

A second aspect of the objectivity standard of the IQA Guidelines is whether disseminated information is supported by sound scientific methods. As discussed above, the Draft Assessment fails to apply EPA's own guidance establishing what the Agency views as "sound science," and, as discussed below, fails to follow NAS recommendations regarding valid scientific approaches.[100] Unjustified departure from these procedures does not reflect the "best available science" required by the IQA guidelines and is arbitrary. Also, the Draft Assessment's reliance on such small subcohorts fails to reflect sound statistical methodology. The discussions above regarding these failures and the associated requests for correction (Sections III.A and IV.A, B and C) are incorporated by reference herein. This section describes additional methodological issues, including the failure to identify and justify unsound statistical models. For example, the modeling selected for use in the Draft Assessment provides a false sense of scientific credibility to a simple curve fitting activity that is neither valid nor scientific.[101] Also, the Draft Assessment neglects to identify the uncertainty associated with statistical and data weaknesses.

1. The Draft Assessment's Failure to Apply EPA's Own Guidance and National Research Council (NRC) Recommendations Departs From Sound Scientific Methods

As discussed above, the Draft Assessment has not demonstrated that LPT is an adverse effect as defined by EPA, because LPT has not been demonstrated to cause, or itself to present, a functional impairment. In departing from EPA guidance, the Draft Assessment uses unsound

[100] See Section IV.C.1, below.

[101] Comments from Dr. David Hoel, July 23, 2012 (App. B).

and biased methods to derive its adverse effect. To correct this shortcoming, EPA should apply and follow its relevant guidance.

2. The Draft Assessment's Statistical Methodology for Noncancer Risks is Scientifically Unsound

The Draft Assessment's modeling is scientifically unsound. Best available science requires that even if a model fits the data "suitably from a mathematical standpoint" it is "essential **that the user exercise appropriate scientific judgment** when determining what datasets are appropriate for Benchmark Dose (BMD) modeling from a risk assessment or biological basis."[102] To estimate the potential noncancer risk at low doses, the Draft Assessment selected a statistical model (the Michaelis-Menten model) that is not justified and lacks appropriate scientific judgment for the following reasons:

- Because the Michaelis-Menten model does not fit the data better than logistic regression models, there is no basis for rejecting use of logistic regression models.

- Use of different models generates markedly different results, yet the Draft never analyzes the uncertainty associated with this disparity.[103] Also, the disparity shows that the sparse data set (described above) has no power to discriminate among models, and therefore cannot support model selection.[104]

- The selected model is used for enzyme kinetics and receptor binding, a purpose entirely irrelevant and inapplicable to modeling dose-response from exposure to asbestos.[105] Instead of modifying for use a poorly suited biochemical model, the Draft Assessment should apply a simple and well understood dose-response model.[106]

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[102] Introduction to Benchmark Dose Methods and US EPA's Benchmark Dose Software (BMDS) version 2.1.1, Davis, Gift and Zhao (the authors are each with the US EPA National Center for Environmental Assessment), Toxicology and Applied Pharmacology, doi:10.1016/j.taap.2010.10.016, p. 4 (2010) (emphasis added).

[103] See SAB Report, p. 32 (Exhibit 14) (noting in the context of the cancer IUR that disparities among results of completing models should be discussed). Presumably the same care and consideration should apply to the RfC, though the SAB Report fails to make this point.

[104] Additional Comments on the Draft Risk Assessment for Libby Amphibole with Emphasis on Re-Analyses of the Restricted Rohs Cohort for Derivation of a Reference Concentration, Dr. Suresh Moolgavkar, Apr. 23, 2012, Section A., pp. 2-3 (App. B).

[105] Moolgavkar, Mar. 27, 2012, Section A., pp. 2-3 (App. B); Dr. David Hoel, Comments, July 23, 2012 ("The reference to biochemical models such as Michaelis-Menten and the Hill model is most inappropriate in that it gives a false sense of scientific credibility to a simple curve fitting activity. The formation of pleural plaques has nothing to do with these two biochemical reaction models and as such the impression that they do should not be given.") (App. B).

[106] Hoel, May 1, 2012, slide 9 and July 23, 2012 (App. B).

- The selected model is not shown to be consistent with the biological understanding of the relationship between LPT and asbestos exposure, making the model implausible. This model has a plateau and therefore use of this model fails to take into consideration exposure at higher levels. The selected model should be biologically plausible.[107]

For these reasons, and for the additional reasons set forth in the attached comments,[108] the Draft Assessment does not reflect the required exercise of judgment in selecting a model that represents sound scientific methods, and results in an inaccurate, unreliable, and therefore scientifically flawed assessment.

In order to address this scientific issue for the RfC, EPA should make the corrections described in Sections III.A, III.B.3 and IV.A, B and C, and also:

- Abandon use of the Michaelis-Menten model;

- 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;

- 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.

3. The Draft Assessment's Model for Cancer Risks is Scientifically Unsound

In evaluating cancer risks, the Draft Assessment inexplicably ignores the decades-old scientific consensus on the appropriate models for evaluating asbestos-related lung cancer and mesothelioma risk. Applying the Cox proportional hazards model to a small subcohort, the Draft Assessment estimates only cumulative exposures and fails to examine the role of pattern of exposure (including duration of exposure and time since exposure ended). As described in expert public comments on this central issue, a more rigorous and reproducible approach should have been adopted, including use of the full data set, use of flexible statistical methods, such as spline smoothers, to explore carefully effect modification by age in the data, and application of different models.[109]

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[107] Moolgavkar, Apr. 23, 2012, Section A., pp. 2-3 (App. B); Moolgavkar, Follow-up Written Comment to the SAB Panel after the July 25, 2012 Teleconference ("I would like to point out to the Panel that it is logically inconsistent to say that the Michaelis-Menten and dichotomous Hill models are simply mathematical descriptions of the pleural plaque data without any biological and epidemiological interpretation and then to use the probabilities for background and plateau from epidemiological data. You cannot have it both ways.") (App. B).

[108] Modeling and statistical issues are more thoroughly presented by S. Moolgavkar and D. Hoel in each of their public comments (App. B). Each of their points and the underlying reasoning is incorporated herein.

[109] See comments by S. Moolgavkar, and joint comments of S. Moolgavkar and D. Hoel (App. B).

For analyzing mesothelioma, the Draft Assessment abandons the well-accepted model used by EPA in 1986 that has accurately described mesothelioma risk (the Peto-Nicolson model). The Draft does so without explaining the results of its analysis using this model. Instead, the Draft Assessment adopts a poorly-justified Poisson regression model that inaccurately applies cumulative exposure. Among other flaws, all information about time-to-tumor is lost, and it is not clear how the modeling was performed. As described in expert public comments, a sound scientific approach would be to utilize the entire data set to reduce the bias in the subcohort and the infeasibility of modeling only seven cases of mesothelioma, and to use other improved scientific methods.[110]

In summary, as with the RfC, the IUR suffers from fundamental deficiencies in scientific methodology. To address these deficiencies, EPA should make the following corrections for all modeling (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 modeling 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.

[110] *Id*. Expert recommendations include the following: 1) properly incorporate pattern of exposure in the hazard function and to make other corrections, use a likelihood-based time-to-tumor analysis with the scientifically accepted Peto-Nicholson model or the two-stage clonal expansion model; 2) justify any adjustment for under-ascertainment, taking into consideration the extensive monitoring of the studied population; and 3) avoid estimating the half-life of amphibole in the pleura unless it can be scientifically justified, because the simple formulation used has no biological interpretation. See SAB Report at p. 32 (Exhibit 14) (noting that competing models "could have provided very different estimates of risk, but they were not discussed.").

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

As a matter of IQA "presentation" requirements, the Draft Assessment fails to present supporting data, models and other sources of information in a clear, complete, accurate, and unbiased manner. It also fails to present potential sources of error so that the public can assess for itself whether the analysis and resulting information disseminated are objective.

The presentation failures correspond to each of the substantive deficiencies described in greater detail above. For instance, the evaluation and presentation of evidence supporting the selection of LPT as the critical effect is not complete or accurate, because it does not reflect consideration of all of the literature. It also lacks a discussion of how the Draft Assessment fulfills the EPA policy requirement that an adverse effect be "[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."[111] Moreover, the discussion of causality and confounders is absent or incomplete. In addition, the Draft Assessment fails to identify potential error sources associated with its selection of LPT.

With regard to the subcohort selection and modeling, contrary to requirements of the IQA, the Draft Assessment does not discuss the extent of uncertainty and error associated with the subcohorts and models selected, or explain, as a matter of transparency to users, why those sources of uncertainty are not sufficiently serious to warrant a change in approach. Also, as stated above, the Draft Assessment fails to fully present information that demonstrates why other modeling choices were rejected.

As a result of these failures, the Draft Assessment is incomplete and inaccurate, lacks transparency and fails to identify sources of error, violating the IQA presentation requirements. To correct these deficiencies, EPA should identify and quantify the potential sources of error in: (i) its selection of the critical endpoint; (ii) its determinations as to whether that endpoint is truly adverse and has a causal relationship with the asserted symptoms; and (iii) its 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;

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

- 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;

- 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, including the range of toxicity values resulting from selection of different subcohorts/cohorts and models.

IV. THE DRAFT ASSESSMENT FAILS TO MEET THE HEIGHTENED OBJECTIVITY STANDARDS APPLICABLE TO "INFLUENTIAL" SCIENTIFIC INFORMATION

The Draft Assessment does not comply with the heightened standards that apply to IRIS assessments. OMB and EPA IQA Guidelines establish heightened "process" and "substantive" quality standards for "influential scientific information," i.e., information whose dissemination does or will have a clear and substantial impact on important public policies or important private sector decisions.[112] EPA has categorically identified as "influential scientific information" those "major work products undergoing peer review as called for under the Agency's Peer Review Policy," i.e., those scientific work products that have a major impact and/or involve precedential, novel, and/or controversial issues and are subjected to external peer review.[113] The Draft Assessment clearly meets this definition.[114] Therefore, the enhanced quality standards for such information, which EPA itself has characterized as demanding adherence to a "higher" and more "rigorous" standard of quality,[115] apply to it.

The relevant heightened "substantive" standards require EPA to reach decisions based on a "weight-of-evidence" approach considering all relevant information and its quality, including peer-reviewed and non-peer-reviewed studies.[116] Moreover, these heightened substantive standards require (i) where practicable, use of best available peer-reviewed science and supporting studies conducted in accordance with sound and objective scientific practices, and (ii) data collected by accepted methods or best available methods.[117] The relevant

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[112] OMB Guidelines, § V.9; EPA Guidelines, § 6.2.

[113] EPA Guidelines, § 6.2.

[114] E.g., EPA Guidelines, Appendix A, § A.3.4, at 44 (providing the example of "IRIS Documentation: Reference Dose for Methylmercury" as a "major work product [that has] undergone peer review" and constitutes influential scientific information).

[115] EPA Guidelines, §§ 6.2, 6.3.

[116] OMB Guidelines, § V.3.b.ii.C, 67 Fed. Reg. at 8457-58; EPA Guidelines, § 6.4.

[117] OMB Guidelines, § V.3.b.i and Preamble, 67 Fed. Reg. at 8455-57; EPA Guidelines, § 6.3.

heightened "process" standards for influential scientific information require: (i) a high degree of transparency as to data and methods applied to facilitate reproducibility of the information by third parties,[118] and (ii) the availability to the public of underlying data and quantitative methods (absent overriding confidentiality concerns).

In addition, in order to ensure that information on human health risks is "comprehensive, informative and understandable," EPA must specify: (i) the expected risk or central estimate of human health risk for the specific populations affected, (ii) each appropriate upper-bound or lower-bound estimate of risk,[119] (iii) each significant uncertainty identified, together with studies that would assist in resolving all such uncertainties, (iv) peer-reviewed studies known to EPA that support, are directly relevant to, or *fail to support* any estimate of risk disseminated, and (v) the methodology used to reconcile inconsistencies in the scientific data.

The Draft Assessment falls well short of the heightened IQA standards for "influential" scientific information. The failures under the base standards, such as the failure to apply EPA IRIS-related guidance and an absence of transparency, described in detail above, also violate these heightened standards and are incorporated herein. Also, the Assessment fails to provide the following required components of highly influential scientific information:

(i) Identification of relevant peer-reviewed studies, including all those that are directly relevant to or fail to support the toxicity values disseminated in the Draft Assessment;

(ii) A rigorous "weight-of-evidence" approach evaluating relevant studies;

(iii) Production to the public of data underlying the Draft Assessment for the high degree of transparency and reproducibility required by the IQA Guidelines;

(iv) A clear and complete description of the population likely to be affected by the assessment;

(v) A description of the expected "central tendency" risks to that population;

(vi) An explanation of what constitutes upper and lower bound estimates of the expected risks; and

(vii) A statement of each significant uncertainty associated with the assessment and identification of studies that would assist in resolving those uncertainties;

Each of these failures and corresponding requests for correction are briefly discussed below.

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[118] OMB Guidelines, § V.3.b.ii.B (applies to single studies or combined information).

[119] EPA has noted in particular that assessments of "central estimates" and upper and lower bounds of risks are useful in deciding whether to remediate very low levels of waste contamination. EPA Guidelines, Appendix A at 49. Because the LAA IRIS assessment would be used in deciding whether to remediate low levels of LAA, an assessment of the central estimate of human health risk is particularly warranted here.

A. The Draft Assessment Fails to Identify Relevant Studies That Address Inconsistencies in the Scientific Evidence

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.[120] The importance of identifying all relevant studies cannot be overstated because the subsequent analyses and critical rigorous weight-of-evidence analysis (more fully discussed below) flow from the identified literature. As stated by the NAS, "a state-of-the-art literature review is essential for ensuring that the process of gathering evidence is comprehensive, transparent, and balanced."[121]

For example, the Draft Assessment fails to identify the majority of the available literature that used the most sensitive radiographic diagnostic tool (HRCT rather than x-ray) to assess LPT and lung function.[122] Of sixteen HRCT-based studies that conducted analyses of individuals with LPT only (as distinct from individuals with both LPT and non-LPT lung abnormalities), EPA identified only four (and SAB only one more).[123] The Draft Assessment's failure to consider all of the pertinent literature led to a biased conclusion, and one not based on best available science. This is not only because literature was missed, but also because of the significance of the missed literature. These HRCT-based studies corrected for a potential confounder (additional non-LPT lung abnormalities) that x-ray-based studies did not. This set of HRCT-based studies, when viewed overall, does not show a consistent association between LPT and lung function impairment, and thus undercuts EPA's Draft assertion that LPT causes lung function impairment.[124]

The Draft Assessment also fails to explain its methodology for reconciling literature that it does identify. For instance, the Draft Assessment mentioned the ATS statement (in a footnote), but failed to explain how it can be reconciled with the Draft Assessment conclusions.[125] See Section III.A.1.d, above, for a discussion of this and other literature that was either not considered or not reconciled under an identified methodology. Therefore, the Draft Assessment fails to identify relevant studies and influential analyses and fails to methodically evaluate and reconcile inconsistencies presented by available scientific literature.[126] To address these issues, EPA should:

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[120] See Section III.A.1.d above, identifying literature that the Draft Assessment fails to identify or consider.

[121] NAS Formaldehyde Peer Review Report, p. 158 (Exhibit 5).

[122] LE Kerper, HN Lynch, LC Mohr, JE Goodman, "Do Asbestos-Induced Pleural Plaques Cause Lung Function Deficits?" Society of Toxicology Poster to be presented in 2014 (Exhibit 23).

[123] *Id*.

[124] *Id*.

[125] American Thoracic Society, 2004, pp. 691-715.

[126] One identified HRCT-based study post-dated the Draft Assessment: Spyratos, D; Chloros, D; Haidich, B; Dagdilelis, L; Markou, S; Sichletidis, L. Chest imaging and lung function impairment after long-term

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- Perform each of the literature identification and integration corrections set forth under Section III.A 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 integration of the totality of the evidence that accounts for 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. (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 inconsistencies in the literature.

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

EPA's Guidelines emphasize the importance of conducting robust "weight-of-evidence" analyses assessing all relevant peer-reviewed and non-peer-reviewed scientific studies.[127] Independent scientific experts have also stressed the importance of such analyses to information quality. The NAS critiqued the recurring failure of EPA to conduct such analyses and the resulting scientific methodological flaws in IRIS assessments, which the NAS found unacceptable as a matter of scientific and information quality.[128] The April 2011 NAS Formaldehyde Peer Review Report is discussed further in the next section.

EPA has agreed with the importance of conducting a weight-of-evidence analysis and states that current policy has long been available to guide these assessments. EPA states:

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occupational exposure to low concentrations of chrysotile. *Arch.of Environ. & Occup. Health,* 2012, 67(2):84-90. EPA should consider this study and the above-discussed HRCT study analysis in its further assessment of LAA.

[127] EPA Guidelines, § 6.4, at 21, 26, and note 29 (requiring "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."). EPA cites its Risk Characterization Handbook, as setting forth principles and methodologies applicable to performing vigorous weight-of-evidence analyses. *Science Policy Council Handbook: Risk Characterization*, EPA 100-B-00-002, Washington, DC: U.S. EPA Dec. 2000. See also RfC Derivation Methodology, EPA 1994, pp. 2-43 through 2-44, and 2-1 (Exhibit 11) ("Qualitative evaluation of the data base, also known as the hazard identification component of risk assessment, involves integrating a diverse array of data into a cohesive, biologically plausible toxicity 'picture' or weight-of-the-evidence relationship to establish that the agent causes an effect (or effects) and is of potential human hazard.").

[128] NAS Formaldehyde Peer Review Report, at 151-52, 162, 164, 165 (Exhibit 5) (stating that rigorous use of weight of evidence in hazard identification is "[o]ne major, overarching issue" in IRIS assessments and recommending that, "[a]s called for by others, EPA might direct effort at better understanding how weight-of-evidence determinations are made with a goal of improving the process").

> All results, both positive and negative, of potentially relevant studies that have been evaluated for quality are considered (U.S. EPA, 2002) to answer the fundamental question: "Does exposure to chemical X **cause** hazard Y?" **This requires a critical weighing of the available evidence** (U.S. EPA, 2005a; 1994), but is not to be interpreted as a simple tallying of the number of positive and negative studies (U.S. EPA, 2002). Hazards are identified by an informed, expert evaluation and integration of the human, animal, and mechanistic evidence streams.[129]

Furthermore, EPA states that in performing the weight-of-evidence review "the IRIS Program evaluates the data for the:

- strength of the **relationship between the exposure and response** and the presence of a dose-response relationship;
- specificity of the response to chemical exposure and whether the exposure precedes the effect;
- consistency of the association between the chemical exposure and response; and
- **biological plausibility** of the response or effect and its relevance to humans.

The IRIS Program ***uses this weight-of-evidence*** approach to identify the potential hazards associated with chemical exposure."[130] Therefore, regardless of any ongoing NAS mandated reform, there is no doubt that EPA already knows how to conduct a weight-of-evidence analysis, considers such an analysis of fundamental importance, and was capable of performing a rigorous analysis at the time of the Draft Assessment.[131] The NAS Formaldehyde Peer Review Report also recognized in 2011 that EPA already had weight-of-evidence guidance and could immediately apply it.[132] Nevertheless, the Draft Assessment fails to apply EPA's own principles, guidance, and IQA Guidelines.

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[129] EPA Submittal to NRC, Jan. 30, 2013, p. 14 (Exhibit 21) (emphasis added). These materials provide EPA's own representations about its IRIS program and principles important to its quality.

[130] *Id*. (emphasis added).

[131] Notably, for other ongoing IRIS assessments, EPA has identified new weight-of-evidence descriptions that rely on existing guidance. *Id*. at p. 6 and Appendix B (preamble for new assessments).

[132] NAS Formaldehyde Peer Review Report, Chapter 7, p. 164 (Exhibit 5) ("Guidelines and protocols for the conduct of evidence-based reviews are available, as are guidelines for inference as to the strength of evidence of association and causation. Thus, EPA may be able to make changes in the assessment process relatively quickly by drawing on appropriate experts and selecting and adapting existing approaches").

One notable example of the Draft Assessment's failure to employ a weight-of-evidence approach is its lack of identification, examination, and careful weighing of all relevant scientific information as to whether LPT is an adverse effect, as required to serve as a foundation for an RfC. The Draft Assessment fails to evaluate underlying studies to assess how their design and methods, as well as the strength of the conclusions reached, inform the weight they should be accorded. Some studies are overlooked entirely. Moreover, confounders, measurement error and bias are not fully assessed.[133] (See Section III.A and IV.A, above).

The need for a weight-of-evidence evaluation in the Draft Assessment is starkly highlighted by the Assessment's acknowledgment that "the ***evidence is mixed***" on whether LPT is independently associated with reduced pulmonary function. Others have made the same observation. For example, Lawrence C. Mohr, M.D., F.A.C.P., F.C.C.P. completed a critical assessment of studies cited by the SAB Report and found:

> conflicting results, inconclusive evidence, and considerable scientific uncertainty regarding a causal relationship between localized pleural thickening and pulmonary function deficits. Furthermore, there are other excellent studies, which were not considered by the SAB Panel, that show no statistically significant or clinically significant correlation association between pleural plaques and decreased pulmonary function.[134]

In spite of such conflicting information clearly necessitating a weighing of its relative scientific strength, the Draft Assessment fails to undertake a scientific weight-of-evidence evaluation on the central question of whether LPT is adverse.[135]

The following corrections are requested to ensure that EPA complies with its own IQA Guidelines and its hazard assessment guidance. EPA should:

- 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.[136]

- At minimum, ensure that its 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."

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[133] The importance and application of these elements are outlined in EPA Submittal to NRC, Jan. 30, 2013, Appendix B-4 (preamble for new assessments) (Exhibit 21).

[134] L. Mohr, Nov. 2012, cover letter and pp. 8-27 (App. B).

[135] *Id*. at p. 28. See also, EPA Submittal to NRC, Jan. 30, 2013, p. 14. (Exhibit 21) ("Does exposure to chemical X **cause** hazard Y? This requires a critical weighing of the available evidence (U.S. EPA, 2005a; 1994)").

[136] EPA Submittal to NRC, Jan. 30, 2013, p. 14 (Exhibit 21).

- 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.

- Disclose the weight-of-evidence evaluation, explaining the results and how the evidence from the literature is integrated in an unbiased manner.

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

1. NAS Recommendations For High Quality IRIS Assessments Represent "Best Available Science" and Should Be Applied

In its April 2011 Formaldehyde Peer Review Report, the NAS devoted an entire chapter to addressing persistent scientific methodological shortcomings in existing IRIS assessments that NAS was convinced would re-occur and undercut the quality of future IRIS assessments unless a number of improvements were made to the Agency's methodological approach.[137] Because it believed that future IRIS assessments would suffer from the same scientific methodological deficiencies, NAS set forth recommendations for reforms of the assessment development process that it "consider[ed] ***critical*** for the development of a scientifically sound IRIS assessment."[138] NAS made these recommendations, in part, to ensure that development of IRIS assessments "would better reflect current practices" in "light of the continued evolution of risk-assessment methods."[139]

EPA agrees with the NAS recommendations.[140] Inexplicably, however, EPA has failed to implement *any* of these reforms for purposes of the Draft Assessment, even though the Agency is applying its new reforms to other ongoing IRIS assessments. NAS' critical reforms can and should be implemented based on Agency knowledge and experience on an *ad hoc* basis

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[137] See generally NAS Formaldehyde Peer Review Report, Chapter 7 (Exhibit 5). Noting that multiple groups had previously raised the need for improvements in the IRIS assessment development process, NAS stated in particular that the "persistence of limitations of the IRIS assessment methods and reports is of concern, particularly in light of the continued evolution of risk-assessment methods and the growing societal and legislative pressure to evaluate many more chemicals in an expedient manner." NAS Report at 152-153.

[138] *Id*. at 164 (emphasis added). As NAS noted, "[i]f the methodologic issues are not addressed, future assessments may still have the same general and *avoidable* problems that are highlighted here." *Id*. at 15 (emphasis added).

[139] *Id*. at 152, 163. NAS noted that although many of its recommendations were "basic and have [already] been addressed in the numerous EPA guidelines, implementation does not appear to be systematic or uniform in the development of IRIS assessments." In other words, NAS concluded that the systemic and serious flaws it had identified could be remedied by use of available scientific methodologies already set forth in various EPA guidance.

[140] EPA Submittal to NRC, Jan. 30, 2013, p. 3 (Exhibit 21).

to the present assessment while further systematic reforms are developed and implemented.[141] This approach is already being undertaken for new assessments and inconsistently for older assessments.[142] The accuracy and scientific integrity of the LAA Assessment is no less important than for other ongoing assessments. Congress has recognized as much, directing EPA to "include in *each draft and final IRIS assessment* released in fiscal year 2014, documentation describing how EPA has implemented or addressed NAS Chapter 7 recommendations."[143]

Given the scientific credentials of the NAS and its intimate knowledge of the IRIS development process, the NAS recommendations for the formaldehyde assessment clearly represent the "best available peer-reviewed science" and "sound and objective scientific practices" required by the IQA Guidelines. It would be contrary to those Guidelines, and otherwise arbitrary and capricious, for EPA to be implementing those recommendations for formaldehyde and other substances, but not to do so for purposes of the Draft Assessment that was issued after the NAS Formaldehyde Peer Review Report was released. Therefore, the following corrections are requested of EPA:

- 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."

[141] Even in the absence of ultimate IRIS reforms recommended by NAS, existing identified methods are available to EPA now to achieve the goals of IRIS reform that NAS has characterized as critical. NAS Formaldehyde Peer Review Report at pp. 151-52 (Exhibit 5) (setting forth "Critical Revisions of the Current Draft IRIS Assessment of Formaldehyde" that NAS concluded were necessary now for the formaldehyde assessment). NAS noted that existing "models for conducting IRIS assessments more effectively and efficiently are available, and the committee provides several examples in the present report." NAS Formaldehyde Peer Review Report at 15.

[142] For example, because the formaldehyde assessment had been under development for more than a decade when NAS issued its Peer Review Report on that substance, NAS did not recommend that that assessment await the development of a revised approach to IRIS assessments based on the NAS recommendations. Notably for purposes of this IQA Petition however, NAS recommended "critical overall changes" to the draft formaldehyde assessment based on recommendations similar to those that NAS was recommending EPA implement on a longer term basis. The application of reforms to the arsenic IRIS assessment is another such example.

[143] See 160 Cong. Rec. H475, H977-78 (Jan. 15, 2014) (Explanatory Statement of the House Committee on Appropriations Regarding the Consolidated Appropriations Act, 2014) (emphasis added) under which, if EPA decides not to incorporate any such recommendation, the Agency is to explain its rationale for not doing so.

2. The Draft Assessment Does Not Comply With Applicable EPA Guidance That Also Represents Best Available Science for IRIS Assessments

EPA guidance represents the Agency's position on the best available science, and therefore the IQA mandates application of that guidance.[144] EPA's guidance for conducting hazard assessments presumably should improve the objectivity and utility of influential scientific information and must be employed in concert with its IQA Guidelines to meet those IQA objectives.[145]

As discussed above, despite this clear mandate, the Draft Assessment fails to apply EPA guidance in material respects, such as guidance (i) requiring and describing a weight-of-evidence analysis, (ii) defining "adverse effect" as "[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,"[146] and (iii) for determining strength of evidence regarding "causation" and "association." In selecting a marker of exposure (as distinguished from a marker of effect) as the critical effect for derivation of the RfC and in failing to weigh critically the evidence, EPA has simply ignored established guidance. This violates the IQA.

In addition to being necessary for compliance with the IQA, EPA should at a minimum follow its own guidance in order to immediately address the NAS recommendations. The NAS determined not only that its recommendations reflect "basic" and sound current scientific practices, but also that many "have been addressed in numerous EPA guidelines."[147] As NAS observed, the shortcoming is not the absence of relevant EPA guidance, but that implementation of EPA's existing methodological approaches in such guidance has not been systematic or uniform in development of IRIS assessments.[148]

To correct these issues, EPA should:

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[144] EPA Guidelines, §§ 4 at 10, 6.4 at 23. Even if EPA were to view compliance with its own guidance as optional under the "base" IQA standards, under the "heightened" standards for influential scientific information, the Agency *must* apply its own policies that set forth best available science.

[145] *Id*. To the extent the Agency concludes that application of any such guidance is unwarranted in the context of the LAA IRIS Assessment, any such determination should clearly be set forth in the Assessment and a well-justified explanation for that determination, based on "best available science," provided therein.

[146] EPA RAGS for Inhalation Risk Assessment, 2009, at 9 (Exhibit 12).

[147] NAS Formaldehyde Peer Review Report, p. 164 (Exhibit 5) ("Guidelines and protocols for the conduct of evidence-based reviews are available, as are guidelines for inference as to the strength of evidence of association and causation"). That NAS Report also cites existing guidance at Appendix B, p. 178, such as RfC Derivation Methodology, EPA 1994. Also, NAS cites with favor the EPA approach now followed for reviewing and synthesizing evidence related to the Clean Air Act National Ambient Air Quality Standards as a potential model for IRIS assessments. *Id*. at 153-54, 162-63. That approach has already been implemented by one group in NCEA (which is also responsible for IRIS assessments). NCEA should evaluate it for purposes of applying the NAS recommendations to the Draft Assessment.

[148] *Id.,* at 14 - 15.

- Apply EPA's relevant IRIS and RfC guidance where EPA fails to follow it, including the examples provided in Sections III.A.1.a. and b. above 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 has 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 practices" and should not be followed, objective scientific reasons for this decision.

D. 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

The IQA Guidelines require that original and supporting data used to develop influential scientific information be made available to the public so that the basis for developing information is transparent.[149] Qualified parties must be able to determine independently whether the disseminated results are capable of being substantially reproduced.[150] The substantial reproducibility standard is imposed "above and beyond some peer review quality standards."[151] The purpose of this transparency standard is to cultivate a consistent agency commitment to reproducibility of results. Thus it is important to disclose the specific data used, underlying assumptions adopted, and analytic methods applied.[152] This approach ensures that qualified members of the public will be able to assess how much an agency's analytic result hinges on the specific analytic choices and judgments made by the agency and the implications of alternative technical choices.

The Draft Assessment fails to meet these transparency and reproducibility standards. As described above, the Draft Assessment lacks a transparent explanation as to how conflicting

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[149] *See* 67 Fed. Reg. at 8455 ("If an agency is responsible for disseminating influential scientific . . . information, agency guidelines shall include a high degree of transparency about data and methods to facilitate the reproducibility of such information to qualified third parties"), and OMB Guidelines § V.3.b.ii. *See also* EPA Guidelines, § 6.3 ("A higher degree of transparency about data and methods will facilitate the reproducibility of [influential] information by qualified third parties . . . . EPA intends to ensure reproducibility according to commonly accepted scientific . . . or statistical standards.").

[150] E.g., 67 Fed. Reg. at 8455.

[151] *Id* at 8455, 8457. *See also* 66 Fed. Reg. 49722 (Sept. 28. 2001) ("The substantial reproducibility standard is added as a quality standard above and beyond some peer review quality standards.").

[152] 67 Fed. Reg. at 8456. *See also* EPA Guidelines, § 6.3.

study results have been reconciled, and regarding the analytical method for selecting LPT as the critical effect.

The Draft Assessment also fails to openly evaluate data generated specifically for the RfC. For the cohort that EPA used to derive the RfC,[153] in 2009 EPA commissioned updated health information specifically to support the accuracy of the RfC. This information has been available to federally funded researchers for years,[154] but EPA has not been made it public. This information includes:

> follow-up worker interviews and [use of] more sensitive radiographic imaging and pulmonary function study techniques. Such additional information ***will ultimately be used*** by the EPA investigators to assess health effects in comparison to estimated worker exposure ***for development of the most accurate RfC*** for the Libby site.[155]

Consistent with both the EPA Guidelines and sound public policy, data generated with public funds specifically to support an IRIS assessment should be openly available to the public well before EPA issues the IRIS assessment. At a minimum, EPA's failure to discuss these data renders the Draft Assessment incomplete under the IQA.

A second set of such data is the ATSDR Libby Data, collected as part of a screening program conducted by ATSDR in Libby, Montana in 2000 and 2001. The Draft Assessment discusses these data and related studies.[156] Also, on a significant scientific issue an SAB panelist relied upon a new study that used these data, even though both the study and data were unavailable to the public.[157] These data (available only as of December 2013) contain serious data quality issues[158] undisclosed in the referenced papers or Draft Assessment.

These two sets of data were not made available to the public at the time that EPA disseminated the Draft Assessment in August 2011 or throughout the entire peer review and public comment process. Moreover, the Marysville updated health information remains

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[153] The Marysville, OH data (also referred to as the Rohs data) served as the basis for the RfC.

[154] Public Comments to SAB, Dr. James Lockey, University of Cincinnati, Jan. 31, 2012 (App. B).

[155] U.S. DOT/RITA/Volpe Center Contract, May 4, 2009, pp. 4 and 8 (Exhibit 24) (emphasis added).

[156] Draft Assessment, Section 4.1.2.4, p. 4-35, *Summary of Respiratory Health Effects* (Exhibit 6). Studies using these date are discussed on pages 2-22, 4-1, 4-17, 4-28 through 4-36, 4-59 through 4-61, and 4-72 through 4-74.

[157] Regarding the important issue of whether LPT should serve as the basis for the RfC derivation, an SAB peer reviewer noted, "[a]nd it's ***not yet published***, but it's going to be out in occupational environmental medicine as a lead pub soon, I hear. Dr. Larsen (sic) has done another analysis of the Libby cohort that actually shows the extent of plaques, how much of the pleural service (sic) is thickened, is associated with extent of decrease in lung function. So, again, I'm pretty comfortable ***now*** with the endpoint the EPA has chosen." Dr. Balmes, Feb. 7, 2012 transcript, p. 202-203 (emphasis added).

[158] In the ATSDR Libby Data (database produced Dec. 2013), 27% of the job history data contains conflicting and inconsistent information (Exhibit 8), raising fundamental data quality questions.

unavailable to the public. The incomplete disclosure of data and data deficiencies falls short of the IQA transparency requirements and prevents assessment of whether EPA's analysis and conclusions are reproducible.

To correct these deficiencies EPA should:

- 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 above-referenced 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 the 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. The Draft Assessment Lacks a Meaningful Discussion of the Population Likely to be Affected by the Assessment

Contrary to the IQA Guidelines, the Draft Assessment does not identify those populations that are likely to be affected by the LAA assessment. Libby Amphibole Asbestos has been described as a "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."[159] The components of LAA are not specific to LAA but instead are found in other locations.[160] Although the Draft Assessment focuses on LAA, no discussion has been provided as to whether this Assessment can or will be applied more broadly to populations

[159] Draft Assessment, p. 3-1, fn 8 (Exhibit 6).

[160] *Id*. at Section 4.1, p. 4-2; Thompson, BD, 2011.

exposed to other mineral fibers containing the LAA components (winchite, richterite, and tremolite) and other asbestos minerals, wherever located.

From a health perspective, EPA has stated that other asbestos types are associated with the same identified adverse effects as LAA. As stated in the Draft Assessment concerning the noncancer effect:

> . . . continued research demonstrates that the Libby Amphibole asbestos has biologic activity consistent with the inflammatory action and cytotoxic effects seen with other forms of asbestos. . .[161]

We are aware of no scientific, medical, or other credible evidence presented to demonstrate that LAA is more carcinogenic than other forms of amphibole or more toxic (from a noncancer perspective) than any other asbestos. Also, no IRIS toxicity value has been issued for any other type of asbestos so, if only by default, the non-cancer toxicity value for LAA is likely to be applied to other types of asbestos minerals. All of these factors suggest that toxicity values established for LAA could have broad influence and application where exposure to other forms of asbestos is at issue.[162]

Moreover, the potential for broad application of the Draft Assessment should be considered because, as noted above, the proposed RfC is likely below or at background levels of LAA and similar types of amphibole asbestos.[163] Any number of previously remediated properties (including both industrial sites and buildings that have been the subject of asbestos abatement[164]) may present exposure levels that are above the proposed RfC.

To correct this deficiency of failing to identify affected populations, EPA should address:

- Whether the RfC proposed would have implications for populations exposed to asbestos minerals other than LAA and, if not, why not; and

- 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.

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[161] Draft Assessment, p. 4-72 (Exhibit 6).

[162] Indeed, EPA's pursuit of an IRIS assessment rather than a site-specific assessment suggest an EPA intent to be able to apply the assessment broadly. The "RfC was originally begun as a site-specific toxicity value" but EPA later abandoned this site-specific approach. EPA Response to Draft Office of Inspector General Report, Sept. 5, 2012, p. 11 (Exhibit 25).

[163] Thompson, BD, 2011. See also Appendix (p. A-74) to EPA's Response to Selected Major Interagency Comments on the Interagency Science Consultation Draft IRIS Toxicological Review of Libby Amphibole Asbestos, August 25, 2011(Office of Management and Budget questions related to the proposed RfC being below background levels) (Exhibit 26).

[164] Federal, state, and local governments alone own and operate tens of thousands of buildings containing asbestos materials.

F. The Draft Assessment Does Not Address the Expected "Central Tendency" Risks to Affected Populations

EPA has explained that its exposure assessment policy requires consideration of a range of exposures, including not only the high end exposure, but also the effects of the "central tendency," which EPA describes as "an estimate of the average experienced by the affected population" that considers amount, frequency and duration of exposure.[165] These "central estimates" are useful in deciding whether to remediate very low levels of waste contamination.[166] Despite this relevant guidance, the Draft Assessment made no attempt to discuss the expected "central tendency" toxicity to populations anticipated to be affected by the cancer and noncancer toxicity values proposed (including populations referenced in Section IV.E above). We are aware of no methodological limitations that would prevent EPA from disseminating an evaluation of such "central tendency" toxicities for LAA consistent with relevant EPA guidance.

EPA should correct this failure by determining and issuing an expected risk or central tendency estimate of cancer and noncancer toxicities from exposure to LAA and should discuss the implications of this information on the usefulness and applicability of the assessment results.

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

Like the central tendency estimates, EPA's Guidelines refer to the usefulness of upper and lower bound estimates for deciding whether to remediate very low levels of waste contamination.[167] These estimates are absent from the Draft Assessment. The Assessment lacks any clear discussion of the upper and lower bound estimate of hazards that would be expected for populations exposed to LAA and like amphiboles (including the populations referenced in Section IV.E above). As with estimates of "central tendency" toxicity values, we are aware of no methodological limitations that would prevent EPA from developing and furnishing such estimates, consistent with applicable EPA guidance. Analyses of that type would help identify the likely range of LAA toxicity and the uncertainty associated with the toxicity values proposed by the Agency, thereby maximizing the utility of the Assessment consistent with EPA's Guidelines.

EPA should correct this failure by determining and issuing upper and lower bound hazard assessments of cancer and noncancer toxicities from exposure to LAA and should discuss the implications of this information on the usefulness and applicability of the assessment results.

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[165] http://www.epa.gov/risk/exposure.htm (Step 3) (Exhibit 27); EPA Guidelines, § 6.4 (B)(ii).

[166] EPA Guidelines, Appendix A (Discussion of Public Comments), at 49.

[167] EPA Guidelines, § 6.4 (B)(iii).

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

The Draft Assessment does not identify certain significant uncertainties associated with it and studies that would help resolve those uncertainties. As discussed above, the choice of LPT as the noncancer endpoint is highly uncertain. The statistical weakness of using the small subcohorts to derive the proposed toxicity values is another significant source of uncertainty. The relative scientific validity of the models evaluated and selected to model toxicity (such as the disparity among models that fit the data, and the biological plausibility of the models) presents further uncertainty.

The SAB Peer Review Report noted the deficiency in the uncertainty analysis and recommended correction with respect to the IUR discussion of uncertainty, but inappropriately failed to make a parallel recommendation for the RfC.[168] Uncertainty analysis should be applied to the entire Assessment, rather than selectively just to the IUR.

To address this deficiency for both the IUR and RfC (rather than selectively just for the IUR), EPA should:

- 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.

I. The Failure of the Draft Assessment to Comply With the IQA Standards for Influential Scientific Information Renders the Draft Assessment Neither Comprehensive Nor Informative as a Matter of Presentation

EPA's IQA's Guidelines require that presentation of influential scientific information on human health risks be comprehensive, informative, and understandable. By failing to comply with the IQA standards discussed in Sections IV A-H above, as a matter of substance the Draft Assessment fails to comport as well with this independent "presentation of information" requirement. In particular, the failure to disseminate the information called for by these substantive standards renders the Draft Assessment neither comprehensive nor sufficiently informative.

[168] SAB Report, p. 37 (Exhibit 14).

V. THE DRAFT ASSESSMENT DOES NOT MEET THE IQA "UTILITY" STANDARD

Under the IQA Guidelines' "utility" standard, information disseminated by EPA must be useful to the full range of intended users, including the general public. The potential users of the Draft Assessment include the public, federal, state, and local risk managers, municipalities, homeowners, and owners of urban and rural land where the RfC proposed in the Draft Assessment may be at or below background levels of asbestos. The Draft Assessment is not useful for these groups for the reasons briefly set forth below and discussed in more detail above.

First, the Draft Assessment does not adequately reflect the range of uncertainty associated with the cancer and noncancer toxicity values proposed for LAA, thereby depriving risk managers and other affected parties (including those exposed or potentially exposed to LAA and other similar forms of asbestos) of information they need to evaluate the likely range of human health risks posed by asbestos concentrations in a particular environment or at a given site. Also, other information that might explain the basis for the Draft Assessment's analysis and would allow interested parties to determine if the results of EPA's analysis are reproducible has not been transparently presented. When considering information's usefulness to the public, EPA must ensure the transparency of information disseminated and the data and analysis upon which that information is based.[169]

Second, the noncancer toxicity values in the Draft Assessment are below background levels. Because it is EPA's longstanding policy not to remediate sites to below background levels, the proposed values are not useful in making risk management decisions as they will subject communities to considerable, unresolved uncertainty as to whether EPA is leaving unsafe levels un-remediated. Moreover, toxicity values below background would suggest that soil disturbance in many situations may be unsafe, such as on farms and in the course of road construction. As a practical matter, if disturbance of background levels of asbestos caused LPT, with the ubiquitous presence of asbestos in soils the United States would be experiencing an epidemic of LPT.[170] EPA has not remotely suggested that to be the case. As such, the toxicity values will not aid rational decision-making and will not be useful to risk managers or the public. To the contrary, those values, not shown by EPA to cause functional impairment at any level, may result in extensive commitment of public resources to address unfounded health concerns not predicated on empirical evidence.

Third, for the assessment to be useful, values must be converted between two analytical methods, even though no broadly accepted and accurate conversion procedure exists. The RfC

[169] See OMB Guidelines, § V.2, 67 Fed. Reg. 8456; EPA Guidelines, § 2.2, at 7 and § 5.1 at 15.

[170] OMB also questioned whether the RfC value is "realistic" and pointed out that one would expect to see broad sectors of the population with pleural plaques if the RfC "background values" are accurate. Office of Management and Budget Comments to EPA, Appendix at p. A-74 to EPA's Response to Selected Major Interagency Comments on the Interagency Science Consultation Draft IRIS Toxicological Review of Libby Amphibole Asbestos, Aug. 25, 2011. EPA has not addressed this fundamental point in either the Draft Assessment or in other information disseminated to the public.

is expressed in units as measured by phase contrast microscopy ("PCM").[171] Today, more sophisticated transmission electron microscopy ("TEM") methods typically are used for sampling, as "[t]he PCM method cannot distinguish mineral fibers from other fibers."[172] However, the conversion from TEM to PCM has yet to be developed[173] and the correlation between the two measurements "is very poor."[174] For risk managers, this situation presents an obstacle, uncertainty, and potential inaccuracy. Before applying the Draft Assessment toxicity value, risk managers will need to collect data using TEM, develop site-specific conversions from TEM to PCM based on site conditions, and then apply that conversion factor to the data.[175] The absence of a uniform and scientifically accepted conversion method will yield variability and more uncertainty, and presents one more significant barrier to understanding, communicating to the public, and applying the toxicity value. This limits utility.

To correct the Draft Assessment's failure to comply with the IQA utility standard, EPA should:

- Implement the above requests (in Section IV. H) to calculate and explain the basis for the range of uncertainty associated with EPA's calculated 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 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;

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[171] Draft Assessment, p. 1-1 (Exhibit 6) ("the RfC is expressed in terms of the lifetime exposure in units of fibers per cubic centimeter of air (fibers/cc) in units of the fibers as measured by [PCM])."

[172] *Id*. at p. 2-10.

[173] This point was also noted by the SAB. SAB Report, p. 38 (Exhibit 14) ("EPA needs to develop a [TEM] method that provides equivalent data to [PCM]").

[174] EPA Office of Inspector General, Report No. 13-P-0221, Apr. 17, 2013, p. 12, fn 4.

[175] Draft Assessment, p. 6-27 (Exhibit 6) ("Different sampling environments and varied site conditions may pose the potential for airborne fibers from various materials. Because of that, it is expected that for many environmental risk assessments conducted now and in the near future, measures of exposure may be done with methods such as TEM and then adjusted through fiber-counting rules to estimate the number of PCM-countable asbestos fibers. Site-specific environmental conditions should be considered in determining how to best identify PCM-countable asbestos fibers in relevant air samples for exposure assessments used in conjunction with this health assessment to yield estimates of risk.").

- Explain how users should determine whether levels of LAA and like asbestos are the result of anthropogenic activities or are instead natural occurrences (background) and whether this determination informs remediation decisions;

- Explain 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.

VI. CONCLUSION AND REQUESTED CORRECTIONS

This petition identifies specific requested corrections that are believed necessary to ensure compliance with the IQA Guidelines, maximize the scientific quality of any IRIS assessment of LAA, and avoid arbitrary and capricious agency action in selecting and disseminating toxicity values for LAA. A summary of the corrections requested is included in Appendix A for EPA's convenience. If EPA concludes that no correction, or an alternative correction, is required or appropriate, we request that EPA provide an explanation of the specific bases for its decision in each case.

In addition to the above specific requested corrective actions, EPA should take the following actions:

- 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.

Consistent with EPA's IQA Guidelines, we understand that a response to this petition is due within 90 calendar days. Should EPA require additional time for a substantive response, we request the Agency's response as soon as possible thereafter, but in no event later than a

response to public comment on the Draft Assessment, as provided for in Section 8.5 of the EPA Guidelines and as EPA does with other disseminated information where a structured opportunity for public comment is provided.[176]

However, we note that public comments previously submitted with respect to certain issues addressed in this request for correction were not framed in the context of applicable IQA standards. Should EPA decide to respond to this IQA request for correction together with its response to public comments on the Draft Assessment, we request – consistent with Section 8.5 of the EPA Guidelines – the required separate EPA response for each IQA Guideline contention and request for correction.[177]

Under EPA Guidelines, this Request for Correction should include "an explanation as to how the alleged error affects or how a correction would benefit the requester."[178] The requester has in the past remediated, and anticipates that it will in the future remediate, sites containing amphibole asbestos, potentially including but not limited to LAA. For use in such activities, the requester would benefit from useful and high-quality toxicity assessments based on "best available science" to guide evaluations of risk and remedial decisions.

Questions related to this Request for Correction and EPA's response hereto may be directed as follows:

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[176] See EPA Guidelines, § 8.5. This is a procedure that EPA has followed before. See June 8, 2011 Letter from Monica D. Jones, Acting Director, Quality Staff, Office of Environmental Information, EPA to Lynn Bergeson (regarding the IRIS Toxicological Review of Inorganic Arsenic).

[177] See EPA Guidelines, § 8.5 ("EPA believes that the thorough consideration provided by the public comment process serves the purpose of the [IQA] Guidelines, *provides an opportunity for correction of any information that does not comply with the Guidelines*, and does not duplicate or interfere with the orderly conduct of the action.") (emphasis added).

[178] EPA Guidelines, § 8.2.