ASSISTANT ADMINISTRATOR FOR CHEMICAL SAFETY AND POLLUTION PREVENTION
WASHINGTON, D.C. 20460

December 26, 2023

MEMORANDUM

SUBJECT: Transmittal of Letter Peer Reviewer Comments on the White Paper: Quantitative Human Health Approach to be Applied in the Risk Evaluation for Asbestos Part 2—Supplemental Evaluation including Legacy Uses and Associated Disposals of Asbestos

FROM: Tamue Gibson, MS
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TO: Elisa Reaves, PhD
Director
Office of Pollution Prevention and Toxics

Please find the subject document attached. The letter peer review was initiated on October 25, 2023.

ATTACHMENT
1. Peer Reviewer Comments on the White Paper: Quantitative Human Health Approach to be Applied in the Risk Evaluation for Asbestos Part 2—Supplemental Evaluation including Legacy Uses and Associated Disposals of Asbestos

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Peer Reviewer Comments on the White Paper: Quantitative Human Health Approach to be Applied in the Risk Evaluation for Asbestos Part 2— Supplemental Evaluation including Legacy Uses and Associated Disposals of Asbestos

Docket No. EPA-HQ-OPPT-2023-0309

NOTICE

This document contains the individual comments and recommendations from experts participating in the letter peer review of the White Paper, "Quantitative Human Health Approach to be Applied in the Risk Evaluation for Asbestos Part 2—Supplemental Evaluation including Legacy Uses and Associated Disposals of Asbestos" under the Toxic Substance Control Act. The EPA sought a letter review to receive comments from independent experts on the White Paper. Each reviewer evaluated the draft technical work product independently without consultation with other reviewers. No collaborative or consensus peer review report was developed

This document contains the views and recommendations of the independent letter peer reviewers and does not necessarily represent the views and policies of the EPA, nor of other agencies in the Executive Branch of the federal government. Reviewers who provided comments beyond the scope of the charge questions were placed in the "Other Comments" section, following the guidelines in the review process. Any mention of trade names or commercial products does not constitute an endorsement or recommendation for use. This document does not create or confer legal rights or impose any legally binding requirements on the EPA or any party.

This document is publicly available in the public e-docket, Docket No. EPA-HQ-OPPT-2023-0309, accessible through the docket portal: https://www.regulations.gov. Further information about this document and the letter peer review can be obtained by contacting Tamue Gibson, MS, via e-mail at gibson.tamue@epa.gov.

CONTENTS

ABBREVIATIONS

ADAO	Asbestos Disease Awareness Organization
AI	Artificial Intelligence
BMR	Benchmark Response
CC	Cubic Centimeter
CT	Computerized Tomography
ELCR	Excess Lifetime Cancer Risk
EPA	Environmental Protection Agency
HBCD	Hexabromocyclododecane
IAFF	International Association of Fire Fighters
IUR	Inhalation Unit Risks
IRIS	Integrated Risk Information System
JEM	Job Exposure Matrix
LAA	Libby Amphibole Asbestos
LPT	Localized Pleural Thickening
mL	Milliliter
MPPCF	Million Particles per Cubic Foot
NHL	Non-Hodgkin Lymphoma
NOA	Naturally Occurring Asbestos
OM	O.M. Scott Marysville
OQD	Overall Quality Determination
OR	Odds Ratios
ORD	Office of Research and Development
OPPT	Office of Pollution Prevention and Toxics
PCE	Perchloroethylene
PCM	Phase Contrast Microscopy
PM	Particles per Milliliter
POD	Point of Departure

PECO	Population, Exposure, Comparator, and Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QC	Quality Control
RfC	Reference Concentration
RR	Relative Risks
SACC	Science Advisory Committee on Chemicals
SMR	Standard Mortality Ratios
STS	Soft Tissue Sarcoma
TCE	Trichloroethylene
TSCA	Toxic Substance Control Act
TSFE	Time Since First Exposure
TEM	Transmission Electron Microscopy
UF_D	Database Uncertainty Factor
UF_H	Intraspecies Uncertainty Factor
UF_S	Subchronic Uncertainty Factor
US	United States

BACKGROUND

The U.S. Environmental Protection Agency (EPA or Agency) programs have evaluated various aspects of asbestos hazard and exposure over many decades. Pursuant to the TSCA section 6(b)(2)(A), asbestos was designated as one of the first 10 chemical substances for the Office of Pollution Prevention and Toxics' (OPPT) initial risk evaluations in December 2016 (81 FR 91927). EPA's Integrated Risk Information System (IRIS) in the Office of Research and Development (ORD) completed an Asbestos Assessment and Libby Amphibole Asbestos (LAA) Assessment in 1988 and 2014, respectively, which are used by EPA program offices such as in risk assessments conducted under the Superfund program. OPPT's *Risk Evaluation for Asbestos Part 1: Chrysotile Asbestos* (hereafter "Part 1 of the Risk Evaluation" or "Part 1") was released in December 2020. Part 1 focused on inhalation exposures and mesothelioma and lung, laryngeal, and ovarian cancer and did not evaluate oral or dermal exposures or non-cancer effects. Part 1 also excluded consideration of all asbestos fiber types besides chrysotile asbestos and solely focused on ongoing uses.

The EPA is currently developing Part 2 of the Risk Evaluation for Asbestos (hereafter "Part 2 of the Risk Evaluation" or "Part 2"), which will provide a more comprehensive evaluation of the human health risks of asbestos, including all fiber types as well as cancer and non-cancer effects from all relevant routes of exposure. EPA agreed to consider these effects and routes of exposure as part of an agreement that was reached for the purpose of resolving a petition for review of Part 1 of the Risk Evaluation (see ADAO, et al. v. EPA, No. 21-70160 (9th Cir. Oct. 2021)). For the human health assessment in Part 2, OPPT has continued to focus on epidemiologic evidence and evaluated cancer and non-cancer evidence and conclusions from the existing EPA assessments in addition to other studies identified from a recently conducted systematic review approach.

The EPA requested letter peer review of the *White Paper: Quantitative Human Health Approach to be Applied in the Risk Evaluation for Asbestos Part 2 – Supplemental Evaluation including Legacy Uses and Associated Disposals of Asbestos.* The purpose of the White Paper is to describe the systematic review considerations and criteria for identifying studies for dose-response analysis, to evaluate and compare existing cancer inhalation unit risks (IURs) and the non-cancer point of departure (POD) with the results of the new systematic review, and to propose a cancer IUR and non-cancer POD for use in Part 2. It is important to emphasize that the White Paper does not describe all of the relevant evidence describing asbestos-related human health hazards as it is focused on the dose-response information. The draft Part 2 of the Risk Evaluation for Asbestos will address the broader hazard literature and will be available for public comment in early 2024.

The EPA requested that the peer reviewers specifically address charge questions provided below and to provide specific and detailed responses to the charge questions. In responding to charge questions, EPA also requested that the peer reviewers consider use of "reasonably available information" defined by statute in 40 CFR 702.33 as data that the EPA possesses or can reasonably generate, obtain, and synthesize for use in risk evaluations, considering the three-year deadlines specified in TSCA section 6(b)(4)(G) for completing such evaluations.

In summary, OPPT has made the following findings:

- OPPT conducted a systematic review to identify the reasonably available information relevant for consideration in the quantitative human health approach to be applied in Part 2 of the Risk

Evaluation for Asbestos. This included identification of cancer and non-cancer epidemiologic studies from oral, dermal, and inhalation routes of exposure.

- OPPT has not identified any cancer or non-cancer epidemiologic studies from oral or dermal exposures that support dose-response analysis; therefore, OPPT is not proposing cancer or non-cancer values for these routes.
- For inhalation exposures, OPPT has identified several inhalation epidemiologic studies (or cohorts) for non-cancer effects, including some that were considered in the IRIS LAA Assessment. However, none of those studies warranted an updated dose-response analysis for the non-cancer POD. OPPT is proposing to use the existing POD of 2.6×10^{-2} fiber/cubic centimeter (cc) from the IRIS LAA Assessment to assess non-cancer risks in Part 2 with application of appropriate uncertainty factors.
- OPPT did not identify any inhalation cancer cohorts beyond those considered by previous EPA assessments, including for cancers other than mesothelioma and lung cancer, which would warrant an updated dose-response assessment.
- The existing IURs derived by EPA, 0.23, 0.17, and 0.16 per fiber/cc, are based on lung cancer and mesothelioma with quantitative adjustment for laryngeal and ovarian cancers in the development of the IUR of 0.16 per fiber/cc in the Part 1 Risk Evaluation. Despite each value being derived from different information and epidemiologic cohorts, and therefore having different strengths and uncertainties, the values are notably similar and round to 0.2 per fiber/cc. OPPT is proposing to use an IUR of 0.2 per fiber/cc in Part 2 of the Risk Evaluation for Asbestos.

The EPA is solicited comment on these proposals and associated analyses. This White Paper is solely focused on the human hazard characterization and dose response to support Part 2 of the Risk Evaluation for Asbestos. OPPT will subsequently release a draft Part 2 Risk Evaluation, including a complete risk characterization and presentation of risk determination, which will be made available for public comment pursuant to TSCA section 6 (15 U.S.C. 2605(b)(4)(H)). OPPT will also release an accompanying Systematic Review Protocol for Asbestos at that time.

Charge Questions

Charge Question 1: *Proposed Approach to Identify Cohorts for Cancer and Non-cancer Dose-Response Assessment under TSCA*

Question 1. EPA's *White Paper: Quantitative Human Health Approach to be Applied in the Risk Evaluation for Asbestos Part 2 – Supplemental Evaluation including Legacy Uses and Associated Disposals of Asbestos*, in Section 3, describes details of the systematic review process used to identify the relevant epidemiologic literature for consideration in the dose-response assessment for Part 2 of the Risk Evaluation for Asbestos. Sections 3.1 and 3.2 describe the systematic review approach to literature searching and screening. Section 3.3 describes the fit-for-purpose approach to preliminarily identify epidemiologic studies that contain dose-response information. Section 3.4 describes the consideration of studies for applicability for dose-response analysis. Figure 3-1 in the White Paper is a schematic of this process.

a. Please comment on this approach and identification of cohorts for cancer dose-response assessment.
b. Please comment on this approach and identification of cohorts for non-cancer dose-response assessment.
c. Please comment on the extent to which the Agency's approach is complete and transparent.

Peer Reviewer Responses to Charge Question 1a:

Response 1

From the above perspective, I see the Agency's methodological approach and the identification of cohorts for both cancer and non-cancer dose-response to be outstanding. I see many man-months of concerted effort in this piece. I can find no issues with the logic. It appears to this reviewer to be both particularly well-thought-out and exhaustive.

I did note that the International Association of Fire Fighters (IAFF) has suggested including firefighters as an epidemiological cohort for the study. I believe this suggestion has merit if it can be shown that these folks could or could have incurred cumulative exposures that were comparable to those in the industrial facilities under consideration. I am unaware of any data for asbestos exposure during firefighting and lack of data could represent a nonstarter for inclusion of this group. I sense that by doing a good job of estimating the dose-response from the relatively data-rich industrial cohorts, the Agency will be able to estimate the risk to firefighters given data on their potential exposure.

Relative to whether the approach is complete and transparent, I have a few comments on one particular area for improvement. In section 3.3.2.1 we are advised that "Multiple measurements taken by phase contrast microscopy (PCM) or transmission electron microscopy (TEM) for a given exposure setting is preferred over a single measurement." Relative to the potential accuracy of any single monitored exposure value, I find this is a dramatic understatement. Most exposure monitoring of repeated or replicate measurements from airborne sources are reasonably well fit by a lognormal or other skewed distribution with a higher density of values closer to zero. Thus, the median and mean are typically

significantly higher than the mode or highest density value in the distribution. Simply stated, a single measured value is highly likely to significantly underestimate the median, mean or upper bound (e.g., 90 percentile) exposure. In industrial hygiene when sampling for compliance to an exposure limit, a rule of thumb is to take six replicate samples. I leave to statistical experts at the Agency to determine a reasonable number of replicates for this assessment. More importantly, I recommend this consideration and discussion for minimum sample size should be included within the document. A good place to put it is in the discussion of Domain 2, Metric 4 (Exposure Characterization). A minimum number of replicate samples should be included for a rating of HIGH confidence.

Concerning transparency, I could not find the number of exposure samples taken in either the main or the supplemental documents. Indeed, the specifics of the modeling relative to these critical numbers may be difficult to attain but extremely valuable in understanding the power and quality of the work.

Response 2

The quality evaluation process of the publications that EPA has undertaken is unusual, and overall is considered too qualitative. I wonder why the EPA did not use a standardized score, for example the Newcastle Ottawa Scale, which is very popular in systematic reviews found on high-impact, peer-reviewed journals (https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). This and/or other available quantitative assessments have the advantage of being reproducible, published, recommended by the National Institutes of Health, comparable across studies and measurable. I reviewed the original EPA document about the quality evaluation process that is referred to in the White Paper; the document sets the rules for the evaluation of publications considered for systematic review, and I have to admit that it raised several perplexities. For example, loss at follow-up is defined as "minimal," "moderate," etc., but there is no mention of what values define those cut-offs, what ranges are considered appropriate for each definition. It is important for the reviewer to know what makes a loss at follow-up so important to disqualify a study, and what is the definition of minimal, which seems to indicate a good study that will be included in the review.

When cohort studies are evaluated, the document defines "groups," and calls for them to be similar in basic characteristics such as age and sex, but a cohort does not have groups. A cohort is a defined population (could be workers in a certain factory) that is followed-up for disease occurrence; years later, disease rates are compared in those exposed versus those unexposed, at enrollment, to a certain factor of interest. Incidence rates are then calculated, compared to the rates in non-exposed, and adjusted for age and sex and whatever other covariates are deemed important.

It seems that the authors of the document were confused on the basics of study design, and should revise the premises on which they built this document, for what refers to study selection and evaluation.

Section 3.3.1: several statements here are imprecise. Dose-response estimates can be obtained through several approaches, not just standard mortality ratios (SMR) or regression analyses. Moreover, the distinction between how to calculate dose-response in cancer and non-cancer endpoints have no statistical or biological basis, at least for what I know. Any time there are various levels of exposure and a disease endpoint, one can build a dose-response curve using regression, odds ratios (ORs), relative risks (RRs), standard mortality ratios (SMRs), chi-square and perhaps many other statistical

approaches. The study design and the type of exposure define the statistical approach, certainly not the fact that the endpoint is cancer occurrence versus other non-cancer diseases occurrence.

Quality metrics: page 13, I am not in agreement with the quality metrics, as I have already mentioned in the paragraph above, or with the program used, Distiller SR. One suggestion I have is to add here a comparison of the results obtained with this program (Distiller SR) and with the methods used for quality scoring with the results obtained using standardized, published methods for quality evaluation in systematic review.

Assuming that the quality evaluation is conducted correctly, and the results are appropriate and reliable (something I cannot verify or confirm), in general, I can agree with selecting the "medium" and "high" quality studies, but I also suggest that a sensitivity analysis including the "low" quality studies be conducted. The reason behind my suggestion is that there is a serious risk that the effort of selecting the best quality studies will introduce selection bias and will deliver a result that has no external validity. The approach used in the past, including all the studies and correcting for an uncertainty factor, was in my view more appropriate and responsive to the need and the aims of the document. As a side note, the tables that include the various cohorts do not have a bibliographic reference attached to each study, thus it is hard to find the original papers for review and comments. On page 57, for example, where the Chongqing cohort is described in detail, there is no reference to the original publications, thus I cannot judge if the exclusion was appropriate by just reading the EPA description of it. Slovenia cohort: I am completely confused here, because the only two references are to case-control studies conducted on this cohort. Again, I don't know where the data discussed in this paragraph came from, and I am reluctant to believe that this cohort should be excluded but cannot judge further from the elements I was given.

I strongly agree with what is outlined on page 25 about selection bias and uncertainty and suggest to follow lead and conduct sensitivity analyses including all studies along with an uncertainty factor. This would better reflect the real-world experience of those who are still exposed to legacy asbestos.

Figure 3.1: this figure is very complex, and at the end, it is not informing more than what is actually written in the text. I personally don't see this as a helpful addition. It would be more informative to have a classic Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) graph of the inclusion/exclusion criteria, which includes references of the papers excluded and the reason why.

At the end of the selection, only nine cohorts are deemed suitable out of 43 (21%), or more extensively out of 105 (8.5%). These numbers are very small, somebody at the EPA should check the excluded publications to make sure that nothing important was left out of this document, something that could influence the final IUR.

Response 3

3.1 Literature Searching

Literature searches were conducted for Part 1 of the Risk Evaluation for Asbestos in 2016 and then updated in April 2021 for Part 2. The comprehensive literature search attempted to cast a broad net and included references for hazard (epidemiology, human health toxicology, and environmental hazard).

The literature search methodology was described in *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances Version 1.0, A Generic TSCA Systematic Review Protocol with Chemical-Specific Methodologies, dated December 2021.*

This search included the following general categories of sources:
1. Databases containing publicly available, peer-reviewed literature (*e.g.,* PubMed, Web of Science, ProQuest; "peer-reviewed literature").
2. "Gray literature," which is defined as the broad category of data/information sources not found in standard, peer-reviewed literature databases. Gray literature includes data/information sources such as White Papers, conference proceedings, technical reports, reference books, dissertations, information on various stakeholder websites and various databases.
3. Relevant data and information submitted under TSCA sections 4, 5, 6, 8(d), and 8(e), as well as for your information (FYI) submissions (a subset of gray literature).
4. Data/information sources generated from backward searches of existing documents containing data/information likely to be relevant to the risk evaluations.
5. Public comments that EPA receives during the risk evaluation process that include references or published or unpublished data proposed for consideration during risk evaluation. The search protocol as described above would seem to cast as wide a net as possible to identify all available peer reviewed, "gray" literature and other sources of data. I perused the selected literature in Systematic Review of Data Quality Evaluation Information for Human Health Hazard Epidemiology, and it seems to consist of peer reviewed literature and a few government reports. The literature searching method was clearly described and established a method for casting a wide net to capture all pertinent articles. The method is transparent (described in much detail) and worked well.

3.2 Literature Screening

EPA used two independent screeners (people) and two specialized web-based software programs DistillerSR10 and SWIFT-Active-Screener to assist with the screening process. The screening process and results for asbestos appear systematic and thorough.

3.3 Fit-for-purpose approach to preliminary identify epidemiologic studies that contain dose-response information.

In an effort to streamline the identification of studies relevant to dose-response assessment, EPA implemented modifications to the process described in the 2021 Draft Systematic Review Protocol. The modifications included conducting further screening of studies that met Population, Exposure, Comparator, and Outcome (PECO) criteria to identify the most relevant evidence prior to conducting data quality evaluation. The further screening was based on the data analysis method used in the study (regression and SMR studies were included), the method of exposure measurement (based on Data Quality Evaluation Metric 4), and the range, distribution, and levels of exposure in the analysis (based on Data Quality Evaluation Metric 5).

The studies were screened for those that use Standard Mortality Ratios (SMRs) and/or regression analyses to assess the dose-response relationship. This fit-for-purpose approach appeared to succeed at identifying the epidemiologic studies for dose-response. This procedure was clearly described and appropriate for this exercise.

3.4 Consideration of studies for applicability for dose-response analysis:
a. Please comment on this approach and identification of cohorts for cancer dose response assessment.

Each paper or cohort was evaluated by two epidemiologists: an initial evaluator and a quality control (QC) reviewer as to High, Medium, or Low. Crucial here was the methods of exposure measurement.

Studies were graded as to use of midget impinger, PCM and TEM, linkage to employment records, work histories, use of conversion factors, use of job exposure matrices, manner of dealing with missing years and other appropriate factors. The EPA exposure measurement analysis of the studies and grading system of studies and cohorts was appropriate and rigorous.

Studies and cohorts were assessed as to the method of measuring dose-response from continuous or categorical data. Quality analyses were done separately for lung cancer and mesothelioma, which led to elimination of some studies.

The steps of evaluating the studies for their applicability for dose-response analysis are transparent, thoughtful, logical, and appropriate. EPA did a good job here.

Response 4

The overall process including a comprehensive literature search, followed by successive steps to screen the studies, and consideration of the most relevant studies for cancer dose-response assessment, is clearly described. There are no concerns about the approach or the identification of the cohorts. Recognizing that the Part 2 of the Risk Evaluation on asbestos will include asbestos-specific updates for all disciplines, the following comments and suggestions are offered for that update.

First, a general comment on terminology. The terms “exposure” and “dose” are used interchangeably throughout the document. I’m aware that EPA, and everyone associated with these documents know these terms are not synonymous but refer to related concepts. The Glossary of the EPA Exposure Factors Handbook defines Exposure as contact between an agent and a target; while Dose is the amount of an agent that enters a target after crossing an exposure surface. If the exposure surface is an absorption barrier, the dose is an absorbed dose. If the exposure surface is not an absorption barrier, the dose is an intake dose.

Not to be pedantic about this, but almost all the human epidemiology studies that EPA reviewed considered exposure, not dose, the exceptions being a few that examined fibers in lung tissue. Recognizing that the literature on toxicology and risk assessment frequently uses the term “dose” when “exposure” would be more correct, what to do? Clearly EPA can’t rewrite the entire literature, but perhaps a statement could be crafted and included early in the White Paper explaining that exposure and dose are related concepts, and that the terms are used interchangeably throughout the document?

Response 5

The systematic review process that has been presented appears to be reasonable for identifying relevant studies. The “checklist” of characteristics which will eventually rank the studies as having high,

medium, or low quality is a good start. However, the checklist approach is overly complicated on some levels and inadequate on others. For example, I believe the process will identify virtually all of the individual studies, but it fails to consider the meta-analyses of the past 20 years. Some of those meta-analyses, such as Hodgson and Darnton (2000), Garabrant and Pastula (2018), and Darnton (2023) are not mentioned. That is not a trivial oversight. Those papers represent more than 15 years of focused research on the very papers that form the basis for the EPA's proposed approach. Those insights are missing from the EPA assessment. In my view, it is critical that they be evaluated and weighed.

Also, all of the comments (both published and unpublished) on the mechanisms of action and toxicology of the various types of asbestos are absent from the EPA analyses. One can't perform a well-informed risk assessment without these considerations (and a good understanding of the strength of the exposure assessment). Without understanding that the amphiboles cause cancer through repeated inflammation, a threshold mechanism, one cannot perform a scientifically valid low-dose extrapolation. Even if one chooses not to embrace this mechanism or DNA repair, this consideration still needs to be accounted for in the decisions regarding what to expect in the way of response in the low-dose region.

Overlooking the epidemiology meta-analyses and the mechanism/toxicology data are genuine deficiencies in EPA's work. Years were invested by those who conducted those studies in order to understand the many subtle aspects of the epidemiology studies which the EPA has identified. The primary shortcoming of the systematic approach described by EPA is that it focuses on a checklist for evaluating the quality of the studies. Checklists will never be adequate for identifying the key aspects of a study that determine whether it is solid and reliable, or if it is statistically weak or having other serious shortcomings.

Rating epidemiology studies as "high, medium or low quality," in part, is a challenge because "quality" depends on numerous factors. For example, the checklist approach that has been proposed places almost no emphasis on statistics. Indeed, in various places in the document the EPA says that statistics are not as important as other aspects of the studies. That is a major shortcoming of the approach. Ignoring the importance of statistics is one reason that the suggested cancer potency factors and non-cancer "acceptable intake" values are so far off-base.

The suggested EPA approach also places virtually no emphasis on evaluating the critiques of any of the studies that have been presented in the literature, the shortcomings of the original papers discussed in the various meta-analyses, or the many comments that EPA has received on the Chrysotile Risk Assessment (or this Legacy assessment). For that reason, I believe the suggested systematic review process needs additional "bells and whistles" that involve a very careful analysis of the design and quality of the various epidemiology studies. Only an experienced epidemiologist can do that. Indeed, to understand the 16 or more relevant asbestos epidemiology studies, the compilers and interpreters of the systematic review should have 10-20 years of experience at evaluating these studies. Since it is not feasible to expect EPA to have such persons on staff, "face-to-face" SACC reviews are necessary.

This brings up a critical aspect of this SACC review, which is now called "a letter peer review". I find this approach, which EPA has selected to evaluate this Legacy assessment to not meet the legal expectations of a "SACC review." The purpose of these reviews is to ensure that EPA's work is scientifically thorough and accurate. The design of this "letter peer review" process seems to be intended to avoid having the Agency receive a proper evaluation of their work.

That is the only way the EPA will have access to solid information for making decisions about "tolerable" or acceptable doses of the various forms of asbestos. It appears that EPA is trying to turn a systematic review into some activity that a computer, using artificial intelligence, might be able to accomplish. That would be an error. The past 40 years of evaluating this set of epidemiology studies have often identified improper statistical analyses, improper grouping (so-called "slicing and dicing"), and weak occupational histories. This has often resulted in incorrect conclusions by the authors. These studies simply can't be properly evaluated by professionals from a variety of fields who lack the 10-40 years of experience that is required to properly evaluate the studies.

One can readily understand the errors that can be introduced by an inadequate peer review by evaluating the history of EPA's assessment of 2,3,7,8-Tetrachlorodibenzodioxin (approximately 1985-2000). Over the course of ten years, the Agency embraced a different cancer epidemiology study every two years, and they identified a different disease as being "the most appropriate driver" of the assessment. The journey started by saying the Soft Tissue Sarcoma (STS) was the hallmark disease for dioxin. Later, it was NHL. Later, it was dysfunction of lipid metabolism leading to liver cancer. Some then believed the epidemiology could support a view that other tissues were the target organs for cancer. Eventually, the EPA said, "we believe it can increase the incidence of cancer in all tissues," …. saying that it acted like a hormone or non-ionizing radiation (the only two agents that many believe can increase cancer in many organs). But, of course, that isn't true either….as history has shown.

Because of the complexities of these studies, it is critical that the experts that are relied upon have a lively debate about the strengths and weaknesses of each study. If that had occurred, the EPA would never have suggested that they believe that the cancer potency factors for chrysotile, amosite, tremolite, and crocidolite are "essentially equal." For anyone who has studied these four types of asbestos, the flag should have been raised that "what we have done is fatally flawed." This is so because for 40 years or more, virtually everyone in toxicology and epidemiology has agreed that there are massive differences in the potency of these four fiber types for lung cancer and mesothelioma (often stated to be 1:100:500 for mesothelioma for chrysotile, amosite, and crocidolite, respectively). The recent Darnton (2023) paper is further support for these relative potencies.

As noted previously, to properly conduct a low-dose extrapolation (or even understand the dose-response in the observable range), one has to understand the toxicology of the various forms of asbestos. This is well illustrated in the papers by Cox (2021, 2022), where he describes how chronic inflammation is the mechanism through which both lung cancer and mesothelioma occur. This mechanism has been discussed for nearly 15 years (starting with the work of Brooke Mossman, 1993). Without a good understanding of this mechanism, which is generally embraced by those in the field, one cannot conduct a proper dose-response analysis (which is the basis for identifying acceptable intakes to prevent both cancer and non-cancer).

Lastly, there is far too much emphasis placed on the Marshville cohort in EPA's analysis. Questions about that site were raised by ten or more commenters to the Part I asbestos risk assessment by EPA on chrysotile (Paustenbach, et al., 2021). The Agency has claimed for at least 3-4 years that the Loomis and Dement papers are the strongest studies because they have relatively good work histories, a considerable amount of exposure data (with fiber lengths), good follow-up, and are statistically reasonable. The claim of the authors is that this was a "chrysotile only" cohort. Indeed, they recently published a paper in the American Journal of Industrial Medicine (2023) where they presented their

view of why their claim was valid.

What they didn't share with readers about their paper is that it appears it had considerable input by trial lawyers for the plaintiff in its production (which was not disclosed). That, in and of itself, is not troublesome to me. But, it is important for the EPA to do what is necessary to decide if these workers were exposed to substantial airborne concentrations of amosite before they finalize this Legacy assessment.

Last week, a presentation at a legal conference by Kurt Rasmussen (2023), who has studied the Marshville plant for more than ten years, offered what appeared to be a convincing rebuttal of the claims that Marshville was "chrysotile" only (paper is attached). An important paper, like this one, would not be found in a "search of the literature or systematic review" because it has not yet been published and because it is a critique rather than presenting original research. If there had been a face-to-face meeting of the SACC, with adequate time between meetings, then this analysis and others recently published (or in press) would have surfaced and been considered. Also, the systematic review does not include abstracts presented at conferences over the years. Those abstracts and the associated "posters or presentations" often contain important information.

As many commenters to Part I (the chrysotile analysis) indicated, if Marshville is a mixed fiber cohort, then the cancer potency factors which EPA is deriving can't be considered valid. I would suggest that this EPA document be reviewed by experts in toxicology, chemical/physical properties, statistics, and epidemiology for 20-40 years be on this panel and that they come from various stakeholder groups (academics, corporations, consultants, experts for plaintiffs and experts for defendants). This diversity of viewpoints is, in large measure, lacking in the current panel.

Response 6

I feel handicapped by not having a call or meeting with the White Paper and Part 2 authors and the selected reviewers. It is very difficult to comment on the appropriateness/utility of the EPA White Paper without a draft of the Part 2 assessment. The concept of "fit for purpose" that is frequently used in the White Paper is hard to apply to undescribed Part 2 exposure issues and "unreasonable risk" determinations (if any) without seeing and discussing the draft assessment.

The White Paper avoids a qualitative exposure and hazard initial step for identifying priorities for Part 2 approaches and needs. This may be in the Part 2 draft, but unavailable in the context of the White Paper. The 1988 assessment approach utilized all available data although the result is close to the other two single fiber approaches. Its broad base is closer to what I surmise are Part 2 legacy exposure groups.

It appears a critical decision has already been made that the only acceptable approach is a quantitative human health assessment which places emphasis on cohort studies that include data measuring air concentrations of asbestos. The literature search does that well but results in a quite narrow set of studies, nearly all used in previous analyses. Except for the community study, subsequently excluded, the types of legacy exposure circumstances (never described) do not appear to be represented in the "cohort" studies.

Focusing only on a quantitative approach needs to be justified considering the decision by over 60 countries that have banned all asbestos and the many scientific organizations such as IARC and scientific committees that have concluded there is no safe level of asbestos exposure.

I would suggest that there are different criteria that could be used in the literature search that would result in a more robust set of studies to utilize. One alternative would be to use "duration of exposure and time since first exposure" as the "quantitative" measure. Nearly all studies and case reports of legacy type exposures include information on duration of any identified asbestos exposure. Such "semi-quantitative" exposure data could be explored for exposure characterization in the Part 2 hazard assessment. The use of surrogate air concentration exposure data should be explored. There are data systems and publications such as those from the Australian Mesothelioma Registry and the Italian Mesothelioma Registry that would increase the available data.

Several of the papers in the literature review used surrogate exposure data. Utilizing data from a different but similar study in their analyses. The use of such surrogate data can be very useful when exposure data are lacking and using such data to expand and use other studies more "fit for purpose" for Part 2 than the traditional existing IUR's and POD's chosen by EPA.

Peer Reviewer Responses to Charge Question 1b:

Response 1

Many of the methodological perplexities I had for the cancer studies methods of selection and quality evaluation apply to the non-cancer endpoints as well. To reiterate, I suspect that the search for the perfect study that could give the exact estimate for asbestos exposure hampers the external validity of the results, and dismisses several important papers that could significantly contribute to finding the correct IUR.

Page 18: the two community-based cohorts are important, in my view, given the fact that most of the current exposure we are dealing with is community-based. I suggest to conduct a sensitivity analysis including these cohorts. Sometimes there should be a trade-off between the best, precise estimate and a more approximate estimate that reflects the reality of current exposure.

It seems to me that a large amount of data (in the format of articles and reports) was fed to the EPA program, and then the program selected a very small number of papers. The selected articles are all very old, and exposure conditions and metrics may not be applicable to the current exposure reality.

I also don't agree with giving less weight to mortality studies and to focus strictly on pleural thickening. There are so many chronic conditions associated with asbestos exposure; this makes mortality a good end-point that reflects the overall effects of exposure. Again, the tables that include the various cohorts do not have a bibliographic reference attached to each study, thus it is hard to find the original papers and data for appropriate review and pertinent comments.

In table Appendix B.2, I see that the non-cancer included cohorts are seven, three of which are overlapping with the cohorts included for cancer endpoints. The number seven is the result of the review of 43 cohorts (16%), or of the more extensive denominator of 105 cohorts (7%). The final

number is so low that it calls for an external reviewer to look carefully at all the excluded cohorts to make sure that nothing relevant has been left out.

I would love to see a table with each individual cohort considered for this White Paper, and the IUR obtained for each cohort. The missing part of this document is the lack of quantitative, summary tables that could guide the reader toward a meaningful conclusion.

Response 2

The outcomes assessed in the identified cohorts included non-cancer mortality (including asbestosis and pneumoconiosis), pleural changes/thickening, and lung function changes.

The two best cohorts for this exercise were picked by EPA from the Libby Amphibole Asbestos assessment: the Libby Montana mining and milling cohort (chest x-rays) ; and the O.M. Scott Marysville, Ohio plant workers (chest x-rays and interviews).

EPA deemed that the O.M. Scott Marysville, Plant Cohort provided the most robust data for dose-response assessment for non-cancer outcomes. This determination was based on reliable individual-level measurements of asbestos exposures and detection of pleural thickening, an early adverse effect.

Data from the O.M Scott Marysville Plant cohort was used exclusively. It would be wise to carry out calculations on other (maybe non-vermiculite) cohorts to see if similar POD's would be derived.

Response 3

Same comments as for Question 1a above.

Response 4

My comments on the approach to identifying studies of non-cancer endpoints are similar to what I have mentioned about the cancer endpoint. I am confident that the majority of published studies will be identified using the proposed approach, but that is not enough.

Papers commenting on those studies, meta-analyses, and toxicology studies, as well as the comments that have been submitted to the Agency, also deserve to be examined. For example, only one of the two major and relevant studies funded by EPA about 20 years ago were identified (the work of Crump and Berman).

Response 5

The literature search and grading system was poor at characterizing the utility of studies that did not have air exposure measurements but could be candidates for the application of surrogate data. The study chosen for POD while excellent is quite specific to a unique exposure circumstance. It is a good starting point but exploring applying surrogate data to other radiographic surveys should be explored and discussed.

The OSHA and State Programs have exposure measurements from site investigations that may collectively provide surrogate data appropriate to apply to other studies. This should be explored.

Peer Reviewer Responses to Charge Question 1c:

Response 1

The software and search engines that are indicated in the document and were used for studies identification and selection seem very powerful, but all of them are in-house tools. Using home developed tools comes with several drawbacks and limitations: one of them is the lack of external validity, transparency, and repeatability of these searches. Another missing piece is how these internal EPA products (software, search engines) compared to the more classic academic approach when conducting a systematic review; for example, what papers would have come out of a Medline search versus the EPA search? How the PRISMA graph would reflect the search results produced by these engines? I strongly suggest that an external validation of the search be done, especially given the paucity of studies extracted with the EPA method.

Each sub-section in part 4 describes very detailed steps that were taken in order to build the articles list. However, no data are included on the results of such effort. For example, section 4.2.3 describes in very much detail the process to find and eliminate duplicates, but nowhere are we told how many duplicates were there, and what happened to them. Which paper was kept of the duplicates, which was discarded? This would allow a better judgment of the process, and would create some healthy discussion on the choices of papers.

Overall, I find the search method and selection criteria very qualitative, not well described, not easy to validate and reproduce. Most of the important information ended up being in the Appendixes, and this approach makes it hard to follow the process at the expense of transparency.

Although the training method used by SWIFT is appropriately described, it is hard to believe that a training conducted with seven positive seeds (as it happened for asbestos) is comparable to a training with 378 positive seeds (HBCD). There must be more precision in the latter than in the former, just by considering the variability associated with seven sources versus 378 sources.

Another aspect that needs some discussion is the seven positive articles are from 1980, 1986, 1987, 1988, 1989, 1999, and 2011. This represents a very large range of years, and includes several very old studies. I wonder if this is a meaningful system for searching relevant publications on this topic.

Section B.4, page 50: it is almost impossible to give an impartial evaluation of which cohorts are included, which are excluded. This paragraph talks of “some” cohorts excluded, “some” almost reaching the level for inclusion, but this reader doesn’t know how many cohorts fall into each of these categories, and most importantly which ones are the excluded, which ones almost made it but were at the end excluded. From figure_Apx B-2, it looks like 32 cohorts were excluded, but it is not detailed which are cancer, which are non-cancer cohorts, and what are the reasons for exclusion for each of those cohorts. By reading the publications on these excluded cohorts, this reader could have given suggestions on the next steps.

Figure. Appendix B.1: this figure is appalling. How could it be that there are 257 documents unavailable to the EPA? Am I reading this figure wrong? Why the EPA is dismissing the option of producing a classic PRISMA figure, which is commonly used in systematic reviews and meta analyses?

There is no sub-analysis of papers where competing interests are mentioned versus those where there is no competing interest. I think that this sensitivity analysis would increase the transparency and objectivity of the report. For example, there are authors who report having worked for the defendants (asbestos companies), some in particular have worked extensively as expert witnesses for the asbestos industry, and that should not be discounted in the evaluation of the published results.

Response 2

The Agency's approach to identifying epidemiologic studies that contain dose-response information is very detailed. I can think of nothing to add to the procedure, so I would call it complete. It is described in detail and transparent.

Response 3

Aside from the specific comments and suggestions mentioned in responses a and b above, some general comments on the approach:

Page 13, Line 379, refers to studies summarized in Appendix D.3, some of these studies described exposure assessments that were not part of a larger epidemiologic study, that is they reported exposure information but not health outcomes. These studies were useful in providing information that was included in epidemiologic studies in comparable scenarios, however. Studies that report exposure information only should, therefore be described in the forthcoming Part 2 of the Risk Evaluation for Asbestos and included in Tabl_Apx F-2. Major Categories of "Potentially Relevant Supplemental Material."

Page 13, Line 412, states that the assessment of each of the 22 metrics presented in the supplementary information contributes to an overall quality determination (OQD) of High, Medium, Low, or Uninformative for each study. The details of the procedure for determining the OQD should be briefly described here. It seems from the overall study ranking is determined by summing the individual metric rankings and dividing by the total number of metrics to obtain an overall study ranking between 1 and 3 (page 643 of A Generic TSCA Systematic Review Protocol with Chemical-Specific Methodologies), but the readers of the White Paper shouldn't have to track this down when it could be included here.

Page 14, Line 437, mentions that the job exposure matrix (JEM) was used because the table provides estimated exposure levels in air (fibers/cc) for workers in each job for each year. The term JEM is applied to the Job Exposure Matrices that are commonly used in occupational epidemiology, and the JEM acronym is used elsewhere in the White Paper referring to job exposure matrices, but Appendix A (Glossary) defines it as job exposure metric. There is no need to (inaccurately) redefine the term here.

Page 14, Line 449, item 4 mentions Models that used individual-level exposure assignment methods. The models this refers to should be clarified. Are these the exposure-response models used in

epidemiologic analysis, or models used within the exposure assessment to estimate missing data?

Page 14, Line 450-452, I'm probably missing something here but I don't see what is different between items 6 and 7, they seem to refer to the same thing, maybe a little more explanation is needed here?

Page 45, Line 1358, states that the amount of asbestos dust in the air are reported as fibers or particles per milliliter (mL); it is customary that these concentrations are reported as fibers or particles per cubic centimeter or cm^3 for filter samples, and million particles per cubic foot (MPPCF) for impinger samples.

In Appendix G, Table Appendix G-1. Mesothelioma Criteria, Metric 4. Measurement of Exposure (detection/measurement/information, performance biases) should differentiate between the possible approaches to estimate data where direct measurements of exposure levels are not available. For example, a study in which measurements are available for only a portion of participant's work history of exposure (i.e., only early years or later years), such that extrapolation of the missing years is required would fall into the Medium Data Quality Rating. The method of extrapolation for the missing data should be considered, however. Some studies fill in the missing years by extrapolating values for adjacent cells in a matrix, this might be considered medium quality data. Other studies, however, employ mixed modeling approaches to develop estimates for cells without direct measurements, the North Carolina Textile cohorts are an example of this approach. Studies such as these should be considered as eligible for classification as High Data Quality, as the methods for addressing the missing data are more sophisticated.

Response 4

As noted, I don't think the terms "complete and transparent" are appropriate. The approach EPA has described will identify most studies but, clearly, it will miss critical work (such as statistical analyses not used by the original authors or the many meta-analyses).

I urge the Agency to reflect on the proposed approach, the adequacy of a "letter peer review" and how to genuinely understand the quality of each study. This can't be accomplished by an artificial intelligence (AI) approach. I would suggest that few persons want to rely exclusively on AI for the diagnosis or treatment of a medical condition that they might have developed. Evaluating an epidemiologic study is not much different.

Response 5

Without a draft Part 2 Risk Evaluation product it is hard to know if this limited approach is complete enough to meet robust "fit for purpose" assessments.

In Part 1, as part of its determination of "unreasonable risk" EPA applied a significant exposure reduction factor for assumed respirator use. That factor received considerable negative comments during the committee review. It would be inappropriate if EPA were to continue that practice for the legacy exposures.

Of considerable note would be that in the epidemiologic studies used in the IUR and POD development, studied workers may have used some type of respiratory protection. This would reduce

the actual fiber load to the lungs. A discussion of possible use of respiratory protection would be appropriate. If an exposure reduction factor were applied to the study used to develop the IUD or POD, the IUD or POD would be considerably higher. This issue just adds to the uncertainty in the derived values.

Charge Question 2: ***Consideration of the Existing IURs and POD for Asbestos and Proposed Application of an IUR and POD for Part 2 of the Risk Evaluation***

Question 2. As described in Section 5.5 of the White Paper, EPA is proposing an IUR of 0.2 per fiber/cc for application in Part 2 of the Risk Evaluation for Asbestos. Please comment on EPA's proposed selection and rationale for application of this IUR in Part 2 of the Risk Evaluation.

Peer Reviewer Responses to Charge Question 2:

Response 1

The discussion in this section is focused on two previous documents (EPA 2020 and IRIS LAA), but at least for the EPA 2020, the document referred to chrysotile, which is not the excess lifetime cancer risk (ELCR) theme of this White Paper. I am very reluctant to consider this as an advancement from EPA 2020, as it seems exactly the same analysis and discussion. Similarly, the whole calculation on page 30 refers to numbers obtained on chrysotile (EPA 2020).

Table 5.2: I am not sure if I interpret this correctly, but there is a clear difference in IUR per fiber/cc with mixed fibers than with chrysotile, as one number is 0.23, the others are around 0.16. On the same line, why not propose the more conservative value, under the precautionary principle? It seems like 0.2 is arbitrary, and does not appear in Table 5.2. I think that either 0.23 or 0.16 should be the choice, for different reasons. My choice would be 0.23, because it reflects the reality of legacy exposure, which is an exposure to mixed asbestos fibers.

Another topic that should be addressed in section 5.5 is possible differences of IUR with sex and race. We are very fortunate that some studies are focused on males, some on females. These studies seem to include the appropriate datasets for assessing at least any sex difference in IUR.

In relation to cancer end-points, the South Carolina and North Carolina textile cohorts have a great variety of participants, including males, females, whites, and other races. The analysis of the Chinese and US cohorts may allow further comparisons across races as well.

For what we know from the literature, it is also possible that females had lower exposures than males, and this would allow a better extrapolation of health effects at lower levels of exposure, a situation that is likely more reflective of the current exposure situation.

When estimating IUR, the community-based cohorts, such as the Wittenoom, are the most relevant, in my opinion, because they allow a refined look at lower levels of environmental exposure, and would probably generate a more precise IUR for exposures that resemble the current legacy exposures.

To summarize my comments on the selection criteria, I think they are too restrictive, narrow, based on old studies, not taking sufficiently into account the community base studies, which are instead more representative of the current non-legacy exposures.

In terms of rationale for the IUR choice, I don't see a clear rationale, and in my view EPA should either base its choice on the chrysotile studies, and pick 0.16 (I disagree with this choice, as legacy

asbestos in a more complex exposure that include several fibers, some of which are considered more dangerous than chrysotile), or stick with the old 0.23, with all its limitations (outdated number, based on old studies, not reflecting legacy exposure patterns).

A third way would be to consider and include newer studies, introduce an uncertainly factor in the calculations, and come up with an IUR number that reflects patterns of current legacy exposure.

Response 2

"Furthermore, the exposures that will be analyzed based on the conditions of use in Part 2 (U.S. EPA, 2022) will predominantly be for legacy uses of asbestos, or those uses for which there is no current manufacture, process, or distribution. These exposure scenarios will not pertain to specific fiber types (*e.g.,* chrysotile and LAA). Specifically, for asbestos-containing building materials, exposure to mixed fiber types is described."

This exercise Asbestos Part 2 is for "legacy uses" (*i.e.,* uses without ongoing or prospective manufacturing, processing, or distribution for use) or "associated disposals" (*i.e.,* future disposal of legacy uses) from the definition of conditions of use—although the court did uphold EPA's exclusion of "legacy 205 disposals" (*i.e.,* past disposals).

EPA uses three estimates of all cancer risk (inhalation unit risk, or IUR) taken from:

1988 IRIS Asbestos risk (largely based on EPA (Nicholson) 1986 Asbestos Update) = 0.23, (accounting for all asbestos fiber types); this is based on 14 epidemiologic studies that include occupational exposure to amphiboles, chrysotile, and mixed fibers, depending on the study.

2014 Libby-LAA Asbestos Risk = 0.17 (LAA);

2020 EPA PART 1 Asbestos Risk Assessment = 0.16 (for chrysotile only).

The EPA White Paper notes that these three estimates are quite similar and then settles on 0.2 as a proposed IUR by rounding.

Using 0.23 as the IUR would be the most justifiable method, because it would reflect a risk estimate for a significant number of people (workers and others) who have mixed fiber type legacy asbestos exposures, and is based on actual calculations, not "rounded."

The 2020 Chrysotile IUR of 0.16 is based on chrysotile only studies.

The Libby 2014 LAA of 0.17 is not based on commercial asbestos. From Rohs 2008: "The unprocessed vermiculite ore mined until 1990 in Libby, Montana, contained 0.1 to 26% naturally occurring amphibole fibers. Historically, these amphibole fibers were typically characterized as ''tremolite'' or ''soda-tremolite'' asbestos. Additional characterization with improved technology in conjunction with newer mineral classifications indicates that these fibers vary in chemical composition, including within a single fibrous particle, and are best described in decreasing order of abundance as winchite, richterite, and tremolite."

The 1988 IRIS asbestos risk based on 14 epidemiologic studies of occupational exposure to amphibole, chrysotile and mixed fibers which results in a IUR of 0.23 would appear closest to application for "legacy uses." Those uses include various fibers and mixes of fibers. The 2020 chrysotile and 2014 LAA do not cover mixed fiber types as completely as the 1988 IRIS exercise.

The procedures of the 1986 Airborne Asbestos Health Assessment Update and resulting 1988 IRIS Asbestos Assessment are well described on pages 25-26 of the White Paper. The IUR resulted from both an assessment using the studies with the best exposure data and a second approach, which used all the data from the 14 studies with estimates of the uncertainty of the data. For the dose response assessment 14 studies were used for lung cancer and four for mesothelioma. The 1986 assessment included an evaluation of the uncertainty introduced by the idea that crocidolite might have higher potency for mesothelioma, but quantitative investigation showed this idea had minimal impact. Cancer slope factors were done separately for lung cancer and mesothelioma and then statistically combined. Then a life table analysis using a relative risk model for lung cancer and an absolute risk model for mesothelioma with linear low dose extrapolation to arrive at an IUR of 0.23 per fiber/cc.

On page 30 of the White Paper, it justifies the rounding to 0.2. "When considering the strengths and uncertainties of each IUR, OPPT is proposing to use an IUR of 0.2 per fiber/cc in Part 2 of the Risk Evaluation for Asbestos based on the existing IURs. When considering standard practice of reporting IURs with precision to one significant digit, each of the existing IURs 871 would round to 0.2 per fiber/cc." The one significant digit justification for rounding is very weak.

It is reassuring that the three (2020 Chrysotile, LAA 2014, IRIS 1988) are so close (0.23, 0.17, 0.16). However, rounding to 0.20 is not adequately justified in the White Paper. Given that the IRIS 1988 is based on studies closest to the "legacy uses" covered in Asbestos Part 2, until a more current revision of the IRIS 1988 process is done, it should be judged the most complete for the purpose of Asbestos Part 2. I thus recommend using 0.23 as the IUR for Asbestos Part 2.

Response 3

Page 27, Line 764, and onward through Line 775 discusses the basis for the selection of the IUR. I think that the value for the IUR is well-founded in the studies that are mentioned in the White Paper.

Table 5-1. I suggest that the column Cohort Name include the links to the studies being referenced (as was done in Table 4-1).

Smoking is addressed on Page 29, Line 817–821, which discusses smoking as a strong confounder for lung cancer related to asbestos exposure. ("In addition to the factors mentioned confounding was deemed to be low because regression models accounted for birth cohort that would reflect changes in smoking rates over time. Additionally, it is likely that smoking rates among workers were similar across facilities and occupations"). I suggest the White Paper mention that the authors (Dement et al., 1982) addressed this and documented the smoking rates among the workers in the plants were virtually identical to the rates in the reference (US) population.

Page 29, Line 845, states the IUR of 0.17 per fiber/cc presented in the IRIS LAA Assessment (U.S. EPA, 2014b) has similar strengths and limitations as the chrysotile. As I mentioned in my comments on the non-cancer endpoints, I would consider the exposure assessment in the LAA to be subject to

much greater uncertainty than those for the North Carolina and South Carolina cohorts.

Response 4

As noted above, it is almost inconceivable that the Agency is suggesting a single IUR for all four fiber types (chrysotile, amosite, tremolite, and crocidolite). There are a myriad of epidemiology studies, toxicology studies, and evaluations of chemical/physical properties (e.g., the two papers by Korchevskiy, et al.) that clearly show that these different fiber types have dramatically different cancer potencies (both lung cancer and mesothelioma) (Hodgson and Darnton, 2020, and Darnton, 2023). These differences were recognized by Wagner, et al. as long ago as 1960 (60+ years ago).

As each year passes, these differences in potency become ever more apparent. Thus, my comment regarding this charge question is that EPA should "start over" with respect to identifying a potency factor for any of these fibers. A claim that they are virtually equivalent—long a tenet of many plaintiff lawyers—lacks a scientific foundation.

What the EPA has done is precisely what can occur when persons simply take what is published, attempt to combine the information in some manner, and then offer an opinion…. without really understanding the toxicology of the chemical or the epidemiology studies.

If EPA carefully reviews the comments that were submitted to the Chrysotile risk assessment, it is obvious that EPA either failed to appreciate the advice of dozens of commenters or it simply is not interested in conducting a proper scientific evaluation. I have long admired the role of EPA and its many accomplishments since 1970. For some reason, over the past 5-10 years, the rigor and openness to considering all scientific input when performing analyses and rulemaking seems to have been eroded.

I would urge that the scientists hired by EPA over the past 10 years go back and read the reports written by a dozen or so prior EPA Science Advisory Boards. They will readily see that a diversity of scientists with vast experience with the chemical were brought together and that they went back and forth in debating the quality of studies and the conclusions reached by the various authors. At the end of the day, I believe that most will agree that better decisions were reached than had that dialogue that has not occurred during this review.

The shortcomings of the current analyses are so numerous that it is impossible to attempt to identify in written comments within the timeframe provided. To do a good job which would require a "team" of experts days or weeks to conduct (with post-docs or other assistance). EPA deserves the benefit of listening to a serious dialogue among physicians, toxicologists, epidemiologists, statisticians, exposure scientists, and industrial hygienists, not to mention persons expert at low-dose modeling, before finalizing this initiative.

One might get the impression that the EPA is rushing this review because it gave only 20 business days and because they have set the DUE DATE for the day after Thanksgiving (when it was more reasonable to have it due on the Monday after Thanksgiving since that 3-day window is often available to many of us).

I urge that this evaluation of asbestos be taken as seriously as the EPA took the evaluation of the dioxins, TCE, PCE, formaldehyde, methylene chloride, and other complicated analyses. Those EPA reviews each took ten years to complete, and they probably required five or more SACC reviews. I am NOT suggesting that ten years be taken to deal with this challenge, and I recognize that TSCA requirements won't allow it. However, I am suggesting that asbestos is every bit as complicated as the chemicals that I have mentioned and that every possible safeguard of the scientific quality should be initiated so that society is given the best scientific information. To rush this to a conclusion in its present form is unfair to the Agency and the citizens it hopes to protect. During a week when national surveys have stated that the public trust in scientists is at its lowest in 40 years, all of us want EPA to help turn around this impression.

Response 5

The fact that the three IUR's reviewed are numerically quite similar underscores the fact that toxicity of the different fibers are the same. This supports not trying to separate the fiber types. I don't support the rounding and averaging of the three to arrive at a 0.2 per fiber approach.

Applying the "fit for purpose" concept, the 1988 IRIS IUR use purpose and derivation from a much more robust number of studies approach and set of study information is far more appropriate for the legacy exposures that are being evaluated. Thus, I find the 0.23 IUR to be most appropriate - unless a new comprehensive review were done using the 1988 type approach.

Charge Question 3: ***Consideration of the Existing IURs and POD for Asbestos and Proposed Application of an IUR and POD for Part 2 of the Risk Evaluation***

Question 3. As described in Section 4.3 of the White Paper, a non-cancer POD 2.6×10^{-2} per fiber/cc was established in the IRIS LAA Assessment. EPA is proposing to apply this POD in Part 2 of the Risk Evaluation for Asbestos to estimate non-cancer risks. Please comment specifically on the scientific reliability and robustness of this non-cancer POD for use in Part 2 of the Risk Evaluation.

Peer Reviewer Responses to Charge Question 3:

Response 1

Reliability and robustness of the approach: I don't see sufficient robustness and therefore reliability with the proposed approach, for the following reasons:

1) We cannot define "systematic review" something that starts from several hundred papers, narrows down to seven articles, and then consider only two of them, which by the way are not even on asbestos fibers but on specific sub-types. This is really a weak approach, and I don't see the premises for supporting it. Any reader would feel uncomfortable with the choices and would wonder why this happened.
2) It is unsettling that this document relies exactly on the numbers produced in the 2020 document on chrysotile, after so much discussion at that time on how the numbers defined for chrysotile are not transferrable to legacy asbestos exposure. After three years, EPA proposes to apply the chrysotile numbers to legacy asbestos exposure. I predict this will not go down well with any careful reader of the document.
3) To the best of my knowledge, there were no dose-response curves for non-cancer endpoints in Rohs 2008; curves are present in Loomis 2019, but those are for mesothelioma, for what I can tell. I don't see the calculations of how the POD was derived. I assume that the figures from EPA 2014A were used, for example figure 5.2 on page 5.33 and 5.4 on page 5.40. If this is the case, the results are not pertinent to the question that need to be addressed by this White Paper, which is asbestos legacy exposure.
   As a side comment, the links to the articles cited work only when I am in my office, when I can access my university library; the EPA should give easy access to the literature for the public and the reviewers.
4) It seems that the Anatolia study is the most informative, and has a large number of data points that could be used for the purpose of calculating a POD; the study has a modeling system that resembles more closely legacy exposure, as it includes sleeping time, household activity, etc. I am not sure why this publication didn't make it to the final line, as it seems the most pertinent. It shows, among other things, more plaques in males than females for the same duration of exposure, higher exposure matrix for males than females, all things that should be considered when estimating risks.
5) I suggest a separate sub-heading entitles POD in vulnerable populations, and include here POD estimates for children, females, and other sub-groups that could be identified. On the same line, the Wittenoom publications has a large number of results on females, with dose-response data, and the study was conducted in residential setting. Again, I can't figure out

why this study didn't make the finish line, especially in view of the complete lack of new data and new information contained in the present White Paper.

6) I suggest that a completely different approach be taken. I would start with publications on computerized tomography (CT) screening of previously exposed subjects and dose response analyses (here is one example I found on Medline: https://pubmed.ncbi.nlm.nih.gov/19129281/), and go from there in estimating POD.

In summary, I believe that a document that had taken into account the results of at least the seven cohorts that were originally selected as relevant would have proven to give results that are more reliable. Uncertainty factors could have been built in, as well as *ad-hoc* comments on the confidence that the EPA places on each of the results. The approach would have been better, in my view, than producing basically the same document as EPA2020, an approach that does not advance the field of asbestos risk assessment, since it referred to chrysotile exposure.

Response 2

EPA is proposing use of the IRIS LAA POD, 2.6x10-2, in Part 2 of the Risk Evaluation and will compare this value to MOEs that will take into account asbestos concentrations from the different exposure scenarios and a benchmark of 300 (UF_H = 10, UF_D = 3, UF_S = 10) based on the IRIS LAA Assessment.

A POD based on a 10 percent Benchmark Response (BMR) for Localized Pleural Thickening (LPT) was calculated to be 2.6•10−2 fiber/cc. This was calculated from a cohort of 109 workers at the O.M. Scott, Marysville, Ohio. Fertilizer Plant Workers in this cohort exposed to vermiculite were used to calculate the POD based on a 10% benchmark response for localized pleural thickening.

The O.M. Scott plant was a site that received vermiculite from Libby, Montana, by rail where it was processed into expanded form for use as an inert carrier for herbicides and fertilizers. A total of 512 workers participated in the 1980 investigation of pulmonary effects in Ohio plant workers (Lockey, et al., 1984). The initial study of this cohort utilized 505 air sample measurements collected in 1972 to assign cumulative worker exposures based on individual job histories. Outcomes were assessed by radiologist readings of chest x-ray films and spirometry for lung function measures. A follow-up of this cohort was conducted nearly 25 years later, providing more 508 robust exposure-response analyses (Rohs, et al., 2008).

In this follow-up analysis (Rohs, et al., 2008), the cohort was limited to men hired after 1972 as there was more certainty in the exposure estimates; post-1972 measurements were taken by industrial hygienists who followed employees during the course of their work with sampling devices. Sampling data were also collected within personal breathing zones beginning in 1977. Detailed employee records were used to construct exposure histories and estimate cumulative asbestos exposures for each individual. Health outcomes were assessed in 1980 and between 2002 and 2005; however, the use of different protocols was considered an uncertainty and the later film readings were deemed more reliable. In addition, the later radiographic films extended the follow-up time by roughly 25 years, which is important given the latency of effects. These considerations resulted in a sub-cohort of 119 men for which robust exposure and outcome data were available for dose-response modeling. With the data from the sub-cohort, a range of dose-response model forms were evaluated, but the most suitable model fitting results were obtained using the Dichotomous Hill model using the mean exposure and

pleural thickening. Various covariates were examined in model fitting; however, none appeared to be a confounder or a significant predictor of outcome risk in the model. One covariate examined, time since first exposure (TSFE), has been demonstrated to be an important predictor of asbestos-related effects (Loomis, et al., 2019). However, TSFE in the model did not improve model-fitting results, presumably due to the low variability across the dataset.

Given the known importance of TSFE, its impact on outcome was determined using the broader set of cohort data (including those hired prior to 1972), which was then incorporated as a fixed regression coefficient in the model. In the modeling, a BMR of 10 percent was used based on considerations of adversity for LPT. The benchmark concentration is the level of exposure expected to result in the excess risk defined by the BMR. A POD based on a 10 percent BMR for LPT was calculated to be 2.6•10−2 fiber/cc.

Basing the POD for LPT on modeling 109 men in one plant, with a specific exposure scenario for vermiculite, is a not necessarily a robust method for the calculation for pleural thickening, pleural plaques, and asbestosis. EPA says, "Also of note is that dose-response assessment for non-cancer effects is typically conducted for the most sensitive endpoint or the earliest observed adverse effect."

In looking at (Rohs, et al., 2008) there were 80 participants with radiographic pleural changes as seen in Table 2, Table 3, Table 4, (5 age 40-49, 28 age 50-59, and 47 age 60 or over). From Table 4, there were 109 workers equal to or over 60 years old, of which 47 had radiographic pleural changes (Crude OR 7.58, 95% CI 2.80-20.49, p <0.001). The POD seems to be based on the one line in this table.

Is a calculation based on one study of vermiculite in one small cohort (109) using the earliest observed adverse effect robust? At the very least, it would seem wise that some other cohorts should be tested by calculations to see if a generally similar POD would be derived. This procedure of doing calculations using different cohorts could be similar somewhat to looking at the three different IUR estimates for mesothelioma and lung cancer (0.23, 0.17, 0.16) and then judging that they were in the same ballpark.

I do agree with EPA that picking the most sensitive endpoint of the earliest observed adverse effect, which in this case is pleural thickening, is proper as it is a marker of noncancer disease and malignant asbestos disease.

Response 3

Page 15 Table 4.1 lists pulmonary function and mortality as the non-cancer outcomes of interest in the O.M. Scott Marysville, OH, Plant Cohort reported by Lockey, et al., 1984 and Rohs, et al., 2008. This is inconsistent with Page19, Line 593, which identifies LPT, as indicated by the presence of pleural plaques as the most effective endpoint.

Later in table 4-1. The cohorts named Libby, Montana, Vermiculite Mining and Milling Cohort, and the South Carolina Textiles Cohort need references.

Page 18, Line 537, describes the UFs to account for intraspecies variability (UF_H of 10), database uncertainty (UF_D of 3), and data-informed subchronic-to-chronic uncertainty (UF_S of 10) in the 2014 LAA Assessment. On Page 18, Line 546, the White Paper mentions that EPA has reevaluated the appropriateness of UF_D of 3 in light of the systematic review. Pages 5-42 of the EPA

TOXICOLOGICAL REVIEW OF LIBBY AMPHIBOLE ASBESTOS (ref 2014b) states that the uncertainty in the sequence of health effects (pleural or autoimmune) is the basis for selecting a UF_D of 3.

I realize that the EPA TOX REVIEW (ref 2014b) examined the entire question of exposure data quality and the associated uncertainty. I don't see in the White Paper, however, any accounting of the uncertainty associated with the exposure reconstruction in the LAA cohorts. Page A-36 of the TOX REVIEW states that "The uncertainty analyses pertaining to the derivation of the RfC are summarized in Table 5-17 and indicate that the uncertainty in the POD due to the factors examined (uncertainty in the exposure reconstruction, in the radiographic assessment of the critical effect, from potential confounding, in the effect of TSFE, in the endpoint definition, and in the choice of critical effect) is less than an order of magnitude."

My reading of the TOX REVIEW, and the references identified as 11. Atkinson GR, et al., and 12. Moatamed F, et al. in the 2007 Rohs article suggests that the forthcoming Part 2 of the Risk Evaluation for Asbestos should revisit the uncertainty around the exposure estimates for the Libby workers. Lockey suspected that exposure index before 1973 "…most likely underestimates prior employee fiber exposures" (the facility began using vermiculite in 1957). In the update by Rohs (2007), the unprocessed vermiculite ore mined until 1990 in Libby reportedly contained 0.1 to 26% naturally occurring amphibole fibers, with references to 11. Atkinson GR, et al., and 12. Moatamed F, et al. This variability in fiber content within the source material could introduce substantial variability in the airborne fiber levels in and around the mill.

Page 2-1 of the TOX Review states " Amphibole asbestos occurs in the Libby vermiculite ore body both in high concentration veins (>80%), as well as in lower concentrations (0.1 to 3%) within the layers of the vermiculite ore itself (Lowers, et al., 2012; U.S. EPA, 2000a; Boettcher, 1967; Pardee and Larsen, 1928). Analysis of historical ore samples from the Harvard and Smithsonian Museums (circa 1920s), the Butte Museum (circa 1960), and recent ore samples from the mine (circa 1999) indicate that the amphibole content of vermiculite ore from the mine has remained approximately constant over the 70-year mining history at the Rainy Creek complex (Sanchez, et al., 2008; Meeker, et al., 2003". My reading of Sanchez and Meeker is that they do not report the actual percent composition of fibers in the ore from the Libby mine. That is the characteristic that would be relevant to the airborne fiber concentrations that the workers experienced through time. I suggest, therefore, that uncertainty in the fiber exposure levels due to the variability in the fiber content in the ore be addressed in the forthcoming part 2 of the Risk Evaluation.

This is not to say that the exposure reconstructions in Lockey and Rohs are without merit. The most detailed presentation on the exposure measurement data in APPENDIX F. WORKER OCCUPATIONAL EXPOSURE RECONSTRUCTION FOR THE MARYSVILLE COHORT of the TOX REVIEW shows in Table F-2 that industrial hygiene fiber measurements by department and year were sparse with by far the greatest number of samples taken in 1976 and 1978. If the levels of fiber present in the vermiculite ore source material varied between 0.1 and 26%, there easily could have been variability in the fiber exposure levels that was not captured by the air sampling campaigns. This should be considered as a source of uncertainty in the upcoming Risk Evaluation.

The other source of uncertainty in the exposure reconstruction is the actual amount of time (hours per

workday, and workdays per year) that the study subjects performed. Lockey (1984) reported that the employees worked extensive overtime, so the actual duration of exposure hours/day is uncertain (8-hour days were assumed for calculation of the exposure indices). In the TOX Profile, section F.6.2.1 discusses adjustment factors to account for extended work shifts in some seasons. I suggest these also be considered as sources of uncertainty in the upcoming Risk Evaluation.

Response 4

With respect to the non-cancer POD, I don't have a comment on the scientific strength of the analysis supporting 2.6×10^{-2}.

I will note that Libby amphiboles are in no way similar to chrysotile, amosite, or crocidolite. Thus, without digging into the math and the approach, it is clear that what has been done is likely to be flawed because it is clear that the Agency doesn't fully understand the complexity of analyzing the Libby data.

The physical and chemical properties are much different among these various forms of asbestos. Also, not all Libby Amphibole exposures are equal. In fact, they are quite diverse due to the differences in the magnitude of exposure, as well as the analytical shortcomings inherent in many of the studies (which mask what can be drawn from the data).

To this day, there remains significant disagreement about the amphibole content of the various mined and processed materials from Libby. As the Agency is aware, although it is rarely, if ever, mentioned, e.g., there are different concentrations of asbestiform and non-asbestiform tremolite fibers in different mined and processed materials at Libby. These need to be understood in order to know which epidemiology studies are relevant for the question being posed.

The lack of sensitivity to the vast differences in the non-cancer and cancer risks posed by cleavage fragments vs. true amphibole fibers is a significant shortcoming in the non-cancer risk assessment. In my view, giving the impression that the Agency places Libby materials in the same box as chrysotile, amosite, and crocidolite is not appropriate. I believe a careful review of comments submitted to the Agency during the various reviews of asbestos over the past 20-30 years is worthwhile (especially the 2020 risk assessment) for the staff scientists to reread and consider. Also, please evaluate the papers by Garabrant and Pastula (2018) and Korchevskiy, et al. 2019, and Korchevskiy and Wiley (2021, 2022) and other papers in that edition of the journal which evaluate Libby amphiboles.

I would also ask that the Agency review the 15+ papers from the 2023 Monticello conference which were recently published.

Response 5

While using the one existing POD is certainly appealing, further investigation of studies that could use surrogate data should be investigated. Of the choices for non-cancer health measures the pleural abnormalities are the most reliable and reproducible. Given that current studies indicate that CAT scanning is more sensitive at identifying pleural abnormalities than the plain PA chest x-ray there may be a need to develop a modifying factor to apply if plain film x-ray studies were used. Using a single, though well done, study is not very robust. The uncertainty factors proposed remain appropriate.

Other Comments

Comment 1:

Let me close by saying that there is a reason why only a few scientists chose to volunteer to serve on this letter review (which was not posted in the Federal Register at a "letter review"). Genuinely serious experts in this area have lost confidence that the EPA has an open mind about weighing scientific information in an objective manner regarding asbestos.

I will remind the Agency that at one time, twenty or more scientists submitted their names to be considered to serve on these evaluations of asbestos. The Agency received only a few submissions to evaluate the Legacy assessment by EPA.

Much of the scientific community has concluded that, since several thousands of pages of comments were received on the Chrysotile Risk assessment of 2020, and the final document failed to consider nearly all of the substantial comments, the Agency has made up its mind and that input is not taken seriously. Thus, most of the serious scientists are not submitting comments on this Legacy initiative nor did they volunteer to serve on this panel. I urge the Agency to try to change this perception.

Comment 2:

The members of this panel, who are reviewing this document have specifically been told that we are not to talk with one another. We have been told that there will be no conference calls among members and that there will be no "face-to-face" meetings. This is entirely inconsistent with the 40-year history of EPA Science Advisory Panels and the actions of the past ten heads of this department within the EPA (going back to Don Barnes). In my view, it is particularly critical that true experts, who have spent one, two or three decades evaluating the 16 or more relevant epidemiology studies, meet with one another to discuss the strengths and weaknesses of each study. Much of what is needed to understand these studies is not presented in the published papers (often due to page limitations).

Comment 3:

I am in strong agreement with the following comment in the ADAO docket submission:

The White Paper is intended to support EPA's Part 2 evaluation of exposure to legacy asbestos, which is pervasive in buildings, products and other settings and is a significant source of ongoing asbestos risks to millions of workers and consumers. Unlike EPA's Part 1 risk evaluation, Part 2 will address all asbestos fiber types, not simply chrysotile, and many pathways of exposure, such as asbestos contamination of products, that were outside the scope of Part 1. The risk and exposure scenarios for legacy asbestos are both numerous and complex and will require close analysis. No comprehensive assessment of legacy asbestos risks has been conducted for over four decades. To fully protect public health, the Part 2 evaluation must be based on complete data and the best available science.

Legacy uses of asbestos must be part of the calculus and should include exposures associated with building demolition, asbestos abatement work, naturally occurring asbestos (NOA), Libby Amphibole

Asbestos and other similar exposures.

As a peer reviewer, the charge questions are deeply important to the risk evaluation and determination of asbestos risk management. More time and effort need to be devoted to this very important work.

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